

FULL TEXT

Environ Health Perspect. 2000 May; 108(Suppl 2): 161–176.

PMCID: PMC1637753

Research Article

Trichloroethylene and cancer: epidemiologic evidence.

[D Wartenberg](#), [D Reyner](#), and [C S Scott](#)

Environmental and Occupational Health Sciences Institute, UMDNJ--Robert Wood Johnson Medical School, Piscataway, NJ 08855, USA. dew@ehsi.rutgers.edu

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Trichloroethylene is an organic chemical that has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins. It has been shown to cause liver and kidney cancer in experimental animals. This article reviews over 80 published papers and letters on the cancer epidemiology of people exposed to trichloroethylene. Evidence of excess cancer incidence among occupational cohorts with the most rigorous exposure assessment is found for kidney cancer [relative risk (RR) = 1.7, 95% confidence interval (CI) 1.1–2.7], liver cancer (RR = 1.9, 95% CI 1.0–3.4), and non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9–2.3) as well as for cervical cancer, Hodgkin's disease, and multiple myeloma. However, since few studies isolate trichloroethylene exposure, results are likely confounded by exposure to other solvents and other risk factors. Although we believe that solvent exposure causes cancer in humans and that trichloroethylene likely is one of the active agents, we recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk. *Key words:* cancer, degreasers, dry cleaning, epidemiology, PERC, solvents, TCE, TCOH, tetrachloroethylene, trichloroethylene. — *Environ Health Perspect* 108(suppl 2):161–176 (2000).

<http://ehpnet1.niehs.nih.gov/docs/2000/suppl-2/161-176wartenberg/abstract.html>

From: (b) (6)
To: (b) (6)
Subject: Useful article-
Date: Tuesday, December 02, 2014 12:51:52 PM

Lancet. Aug 30, 2014; 384(9945): 755–765.

Published online Aug 30, 2014. doi: [10.1016/S0140-6736\(14\)60892-8](https://doi.org/10.1016/S0140-6736(14)60892-8)

PMCID: PMC4151483

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults

[Krishnan Bhaskaran](#), Dr, PhD,^{a,*} [Ian Douglas](#), PhD,^a [Harriet Forbes](#), MSc,^a [Isabel dos-Santos-Silva](#), Prof, PhD,^a [David A Leon](#), Prof, PhD,^a and

From: (b) (6)
To: (b) (6)
Subject: useful article on second malignancies caused by radiation therapy for prostate ca
Date: Tuesday, September 09, 2014 2:48:41 PM

Secondary malignancies following radiotherapy for prostate cancer
Petros Sountoulides, Nikolaos Koletsas, Dimitris Kikidakis, Konstantinos Paschalidis and
Nikolaos Sofikitis; Ther Adv Urol (2010) 2(3) 119[1]125



DEPARTMENT OF VETERANS AFFAIRS
Veterans Benefits Administration
Washington, D.C. 20420

November 29, 2011

Director (00/21)
All VA Regional Offices

In Reply Refer To:
Training Letter 11-03 (Revised)

SUBJ: Processing Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune

This updated training letter incorporates multiple recommendations provided by other interested organizations, including the Department of Defense, Department of Justice, and Office of Management and Budget. It also reflects the Environmental Protection Agency's revised assessment of trichloroethylene (TCE), now characterized as "carcinogenic to humans" by all routes of exposure.

Purpose

Veterans who served at U.S. Marine Corps Base Camp Lejeune, North Carolina, were potentially exposed to contaminants present in the base water supply prior to 1987. The chemical compounds involved have been associated by various scientific organizations with the possible development of certain chronic diseases. However, many unanswered questions remain regarding the extent of base water contamination, the type and duration of exposure experienced by base personnel, and the likelihood that contaminant levels in the water supply were high enough to result in a particular disease.

While these issues are being studied, the Department of Veterans Affairs (VA) has determined that disability claims from Veterans who served at Camp Lejeune during this period deserve special handling to ensure fairness and consistency in claims processing. As a result, adjudication of these claims has been centralized at the Louisville, Kentucky, Regional Office with tracking measures initiated. Technical aspects related to processing these claims are outlined in Fast Letter 11-03, *Consolidation and Processing of Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune, North Carolina*.

This training letter was developed to provide additional background information on the Camp Lejeune situation, as well as to provide specific guidance for issues related to claims development and adjudication. The current guidance supersedes the initial release and the Camp Lejeune section of Training Letter 10-03, *Environmental Hazards in Iraq, Afghanistan, and Other Military Installations*.

Questions

Questions should be e-mailed to VAVBAWAS/CO/211/ENVIRO.

/S/

(b) (6)

Director

Compensation Service

Enclosures

Processing Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune

I. Background

United States Marine Corps Base Camp Lejeune, NC, was established in 1941. In the early 1980s, it was discovered that two on-base water-supply systems were contaminated with the volatile organic compounds (VOCs) trichloroethylene (TCE), a metal degreaser, and perchloroethylene (PCE), a dry cleaning agent. The main source of TCE contamination was on-base industrial activities, while the main source of PCE was an off-base dry cleaning facility. Benzene, vinyl chloride, and other VOCs were also found to be contaminating the water-supply systems. These water systems served housing, administrative, and recreational facilities, as well as the base hospital. Department of the Navy estimates indicate that as many as 630,000 active duty personnel may have been exposed. The contaminated wells supplying the water systems were identified and shut down by February 1985. The Agency for Toxic Substances and Disease Registry (ATSDR), a branch of the Department of Health and Human Services, conducted a Public Health Assessment of Camp Lejeune in 1997, which did not determine whether base personnel experienced any long-term health effects from consumption of the contaminated water. However, the assessment indicated that the drinking water contaminants at Camp Lejeune created a “past public health hazard.” Follow up studies by ATSDR focused on potential birth defects experienced by mothers exposed to the drinking water. In 2008, as public awareness of Camp Lejeune increased, the Navy sent an informational outreach letter to those individuals who could be identified as having served there between 1957 and 1987. Apparently, the Navy felt that including individuals serving until 1987 would cover potential exposure from any residual contaminants present in the water beyond the well closings in 1985. The letter notified these former Servicemembers that “unregulated chemicals were discovered in some of the base drinking water systems” and encouraged them to participate in a registry so as to receive information from new health-related scientific studies initiated by the Navy. These studies involved the National Academy of Sciences’ National Research Council (NRC) and ATSDR.

Based on a congressional mandate, the Navy requested that NRC undertake a study to assess the potential long-term health effects for individuals who served at Camp Lejeune during the period of water contamination. In the resulting report, *Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects* (June 2009), NRC reviewed previous work done by ATSDR, including computerized water flow modeling, and concluded that additional studies may not produce definitive results because of the difficulties inherent in attempting to reconstruct past events and determine the amount of exposure experienced by any given individual. To address potential long-term health effects, NRC focused on diseases associated with TCE, PCE, and other VOCs. Based on analyses of scientific studies involving these chemicals, NRC provided an assessment of the potential association between certain diseases and exposure to the chemical contaminants.

The NRC analysis utilized categories of potential disease “health outcomes.” The categories included: (1) sufficient evidence of a causal relationship; (2) sufficient evidence of an association; (3) limited/suggestive evidence of an association; (4) inadequate/insufficient evidence to determine whether an association exists; and (5) limited suggestive evidence of no association. The analysis found that no diseases fell into the categories of sufficient evidence of a causal relationship or sufficient evidence of an association with the chemical contaminants. However, fourteen diseases were placed into the category of limited/suggestive evidence of an association. A number of diseases were also identified that fell into the category of inadequate/insufficient evidence to determine whether an association exists. NRC indicated that placement of diseases in these categories was based primarily on studies of highly exposed industrial workers, where the amount and duration of toxic chemical exposure greatly exceeded that experienced by individuals at Camp Lejeune.

The presentation of NRC’s disease list in this training letter is not meant to specifically associate these diseases with Veterans who served at Camp Lejeune. Rather, it reflects limited/suggestive evidence of an association between these diseases and the chemical compounds found to be in the Camp Lejeune water supply during the period of contamination. Limited/suggestive evidence of an association is defined as: “evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence.” U.S. and international scientific organizations have reviewed the available literature on the health effects of the identified chemical compounds found to be present in the water supply. These findings are summarized in Appendix B of this training letter. Disability compensation for any of these diseases under VA regulations must proceed under a case-by-case analysis, which requires evidence of a current disease, evidence of service at Camp Lejeune during the period of contamination, and a medical nexus between the two, justified with a rational scientific explanation.

ATSDR, with support from the Navy, is conducting additional studies to assess the human health risks associated with the Camp Lejeune water contamination. The suite of studies in progress and planned include: a continuation of water flow computer modeling studies to generate potential contaminant exposure rates and durations, a re-analysis of data collected on birth outcomes, studies on birth defects and childhood cancers, and further epidemiological studies based on mortality and health surveys that are in the process of being distributed to former Camp Lejeune residents. ATSDR’s pending studies, which include making use of computerized water flow modeling and the epidemiological mortality and health survey, have the potential to provide a higher level of exposure predictability and definable health outcomes than are possible at this time.

For additional information on the history of Camp Lejeune water contamination and the various governmental responses to it, see the Internet websites listed in Appendix A of this training letter.

II. Claims Processing

Evidence Development

Service connection for any disease alleged to have been caused by contaminated water at Camp Lejeune requires evidence of a current disease, evidence of service at Camp Lejeune during the period of contamination, and a medical nexus between the two, justified with a rational scientific explanation. Evidence development for water contaminant exposure requires obtaining verification of actual service at Camp Lejeune and as much detail as possible about that service, including the duration of that service. It also requires verifying, with medical evidence obtained through a VA medical examination or other authoritative medical source, whether a claimed current disease or disability is at least as likely as not the result of exposure to the chemical compounds present in the water at Camp Lejeune. A number of diseases are identified in Appendix B of this training letter that meet the limited/suggestive association criteria based on human and experimental animal studies. Manifestation of any of these diseases would be sufficient to initiate a VA medical examination and request an opinion regarding its relationship to Camp Lejeune service. However, this is not an exclusive list. Medical evidence provided by a Veteran indicating that some other disease may be related to the known water contaminants would also be sufficient to initiate a VA examination.

Verification of Service

Verification of service at Camp Lejeune will generally be available through military personnel and/or medical records. These can be obtained with standard development procedures, including a PIES O19 records request. When documents in the claims file do not provide sufficient information on Camp Lejeune service, it should be obtained through VCAA notification or direct contact with the Veteran. It is important to verify that service at Camp Lejeune occurred within the 1957 to 1987 timeframe. Additionally, when not specified in the records, efforts should be made to obtain the length of time served at Camp Lejeune, preferably the dates of arrival and departure. When feasible, it is also desirable to obtain the Veteran's work duty location and information regarding whether the Veteran resided on base or off base. There is some indication from ATSDR that certain base locations may have been associated with higher levels of water contamination. However, this has not yet been established with certainty. If the Veteran is claiming Camp Lejeune service but initial development does not show it, a PIES O18 request should be initiated to obtain complete service records, which might verify service through temporary duty orders or performance evaluations. Obtaining as complete a picture as possible of the Veteran's Camp Lejeune service will assist medical examiners with determining the likelihood of a nexus between water contaminant exposure and disease development.

Disease Manifestations

Scientific organizations, including NRC, have determined that some evidence is available that suggests the possible association between development of certain diseases and sufficiently high exposures to chemicals known to have contaminated the water at Camp Lejeune. However, where NRC recognizes associations, they are often based on experimental animal studies involving exposure dose rates generally considered to be in excess of the amount of exposure experienced by Camp Lejeune personnel. To date, there are no definitive scientific studies upon which to conclude that an individual who served at Camp Lejeune during the period of water contamination developed a particular disease as a result of that service. There are many unanswered questions regarding the levels of water contamination at various base locations, the amount and type of exposure experienced by any given Veteran who served there, and the probability that such contamination levels were sufficient to cause the health effects identified by NRC. Therefore, the question remains whether a Veteran's particular claimed disease resulted from the service at Camp Lejeune rather than from some other source. As a result, there are currently no "presumptive" diseases attributed to service at Camp Lejeune by statute, regulation, or VA policy. The listing of diseases in this training letter does not imply that any Camp Lejeune Veteran who is diagnosed with one of the listed diseases developed that disease as a result of the Camp Lejeune service. The listed diseases are only meant to serve as a guide for determining when a VA examination should be scheduled. It is the VA medical examination process that will determine, on a case-by-case basis, whether one of the listed diseases is at least as likely as not the result of Camp Lejeune service.

As noted above, each of the chemical compounds present in the contaminated water has been shown by toxicologic or epidemiologic studies to be associated with some form of negative health outcome. Appendix B of this training letter provides an overview of each contaminant and the diseases potentially associated with it. Appendix C of this training letter provides a list of Internet websites containing scientific analyses of the contaminants. Although certain disease manifestations may be associated with one of the specific contaminants found in the water and not associated with another, it is currently impossible to determine which contaminants, if any, were in the Camp Lejeune water consumed or used by a particular Veteran. Therefore, until scientific evidence shows otherwise, it will be assumed by VA that any given Veteran-claimant who served at Camp Lejeune was potentially exposed in some manner to the full range of chemicals known to have contaminated the water there between 1957 and 1987.

Requesting VA Medical Examinations

Service connection for any disability claimed to have resulted from contaminated water exposure at Camp Lejeune requires sufficient medical evidence that the disability is related to that exposure. This medical evidence will generally come from a competent and qualified medical examiner who provides an opinion, justified with a rational scientific explanation, establishing a medical nexus between the claimed disability and the exposure. NRC has determined that the diseases listed in Appendix B of this training letter are associated in a limited/suggestive manner with the chemical contaminants in the

water at Camp Lejeune. However, this does not mean that service connection can automatically be established for a Camp Lejeune Veteran claiming one of these diseases. It is up to a competent medical authority, based on each Veteran's individual case, to determine whether it is at least as likely as not that the claimed disease or disability has resulted from the contaminant exposure at Camp Lejeune. Sufficient medical evidence to establish the required nexus may come from a private physician or other competent private medical authority. In such cases, the claim may be adjudicated without further development if the level of disability can also be ascertained from the available evidence. If the level of disability cannot be ascertained, a VA medical examination is needed to establish the basis for a disability rating. However, in the majority of cases, an initial VA medical examination will be required to establish both service connection and the level of disability.

VA regulations at 38 C.F.R. § 3.159(c)(4) serve as the basis for requesting medical examinations and opinions in claims based on Camp Lejeune service. Under these regulations, an examination should be requested when the claim: (1) contains competent lay or medical evidence of a current diagnosed disability or persistent or recurrent symptoms of disability; (2) establishes that the veteran suffered an event, injury, or disease in service; and (3) indicates that the claimed disability or symptoms may be associated with the established event, injury, or disease in service. These requirements establish a relatively low threshold for requesting medical examinations for Camp Lejeune Veterans. The first requirement is met when a Veteran provides any credible lay or medical evidence showing a current diagnosis or symptoms of a disease or disability. The second is met when service at Camp Lejeune between 1957 and 1987 is verified. The third is met when the claimed disease or disability is included among, but not limited to, the diseases described in Appendix B of this training letter because these have a limited/suggestive association with exposure to the water contaminants. Other claimed diseases or disabilities may also trigger a VA examination request if they are supported by credible medical evidence or an opinion provided by a competent medical authority indicating a possible association with one of the known water contaminants. However, certain claimed conditions, such as those based on a musculoskeletal *injury*, may not be sufficiently reasonable, or as likely as not from a scientific standpoint, to justify requesting an examination for determining its relationship to a chemical compound. On the other hand, additional consideration would be required if a musculoskeletal *disease* was involved because the contaminants are linked to disease processes.

When examinations are requested, it should be kept in mind that these claims represent a unique situation for VA medical examiners. They must determine, on a case-by-case basis, whether a particular claimed condition is linked to contaminated water exposure. In order to assist them with their assessment and determination, the regional office must provide them with the Appendices to this training letter listed below. These replace the Camp Lejeune "Fact Sheet" intended for VA examiners found in Training Letter 10-03.

Appendix A, *Internet websites related to the issue of contaminated water at Camp Lejeune*,

Appendix B, *Diseases potentially associated with exposure to contaminants present in the Camp Lejeune water supply between 1957 and 1987,*

Appendix C, *Websites describing potential health effects of exposure to chemical contaminants present in the water supply of Camp Lejeune between 1957 and 1987, and*

Appendix D, *Notice to Examiners Evaluating Claims Based on Service at Camp Lejeune.*

This information is intended to provide the VA examiners with an adequate basis for providing a reasoned opinion. This opinion is a critical element for evaluating the claim. Therefore, if the examiner fails to provide a reasoned opinion and resorts to a statement such as “an opinion cannot be made without resort to mere speculation,” the examination should be returned as inadequate.

Rating Decisions

The VA medical examination report and opinion, or in some cases a private medical examination report and opinion, will serve as the basis for the rating decision. If the examiner determines that it is at least as likely as not that the claimed condition resulted from exposure to the known water contaminants, service connection can be granted and a disability percentage assigned based on the examiners assessment of symptom severity. The rating narrative should provide the Veteran with a clear explanation for all decisions made. Upon completion of the rating decision, it is important to ensure that all tracking procedures outlined in Fast Letter 11-03 have been followed.

Appendix A

Internet websites related to the issue of contaminated water at Camp Lejeune

US Marine Corps Site for Camp Lejeune Contaminated Water

<https://clnr.hqi.usmc.mil/clwater/index.html>

NRC Report on Water Contamination at Camp Lejeune

http://books.nap.edu/catalog.php?record_id=12618

US Navy Funding of ATSDR Camp Lejeune Studies

http://www.navy.mil/search/display.asp?story_id=51453

ATSDR Home Page for Camp Lejeune

<http://www.atsdr.cdc.gov/sites/lejeune/index.html>

ATSDR Feasibility Assessment for Future Studies of Camp Lejeune

http://www.atsdr.cdc.gov/sites/lejeune/docs/feasibility_assessment_Lejeune.pdf

Appendix B

Diseases potentially associated with exposure to contaminants present in the Camp Lejeune water supply between 1957 and 1987

I. National Research Council

The National Academy of Sciences' National Research Council (NRC) published its *Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects*, in 2009. This report included a review of studies addressing exposure to Trichloroethylene (TCE), and Tetrachloroethylene or Perchloroethylene (PCE), as well as a mixture of the two, and a discussion of disease manifestations potentially associated with such exposure. Fourteen disease conditions were identified as having limited/suggestive evidence of an association with TCE, PCE, or a solvent mixture exposure. They include:

- esophageal cancer
- lung cancer
- breast cancer
- bladder cancer
- kidney cancer
- adult leukemia
- multiple myeloma
- myelodysplastic syndromes
- renal toxicity
- hepatic steatosis
- female infertility
- miscarriage, with exposure during pregnancy
- scleroderma
- neurobehavioral effects

NRC uses the category “limited/suggestive evidence of an association” when the evidence is “limited by the inability to rule out chance and bias, including confounding, with confidence” [see online report page 6, Box 1]. More specifically, the NRC “concluded that the epidemiological studies give some reason to be concerned that sufficiently high levels of the chemical may cause the disease, but the studies do not provide strong evidence that they actually do so” [see page 7]. While the NRC noted that animal testing showed adverse health effects of TCE and PCE, it also noted that the “highest levels of either TCE or PCE measured in the mixed-water samples at Camp Lejeune were much lower than the lowest dose that caused adverse effects in the most sensitive strains and species of laboratory animals. The lower levels of exposure may be of some concern for effects on neurotoxicity and immunotoxicity, but further research is needed to evaluate the specific effects of TCE and PCE and whether they are relevant to humans” [see page 9].

The National Research Council's report also contained a listing of disease conditions classified as having inadequate/insufficient evidence to determine whether an association existed. This listing can be found in the report, which is available on the Internet and can be accessed in Appendix C of this training letter.

II. Other Scientific Organizations

Assessments of potential long-term health effects resulting from exposure to TCE and PCE, as well as benzene and vinyl chloride, are available from a number of scientific sources. Among the reliable sources are the Chemical Abstract Services (CAS) of the American Chemical Society, the Agency for Toxic Substances and Disease Registry (ATSDR), and the Environmental Protection Agency (EPA). Succinct "substance profiles" are available from CAS, each with a statement of "carcinogenicity" for the chemical compound evaluated. More extensive analyses of the compounds of interest are provided by ATSDR's "toxic substance portal" and EPA's "integrated risk information system" (IRIS).

Regarding the reliability of this group of assessments, a distinction is not always made between potential health effects due to inhalation versus ingestion and dermal contact. The contaminants involved are volatile organic compounds and are most commonly encountered by humans in the air rather than dissolved in water, as was the case at Camp Lejeune. However, any of the exposure routes may have occurred.

The health assessments provided by the scientific organizations are summarized below for each contaminant. Their Internet websites, which contain detailed analyses and explanations, are provided in Appendix C of this training letter.

Trichloroethylene (TCE), according to CAS, "is reasonably anticipated to be a human carcinogen" based on limited evidence from human studies and sufficient evidence from experimental animal studies. It has been associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma. According to ATSDR, drinking small amounts of trichloroethylene for long periods may cause liver and kidney damage, impaired immune system function, and impaired fetal development in pregnant women, although the extent of some of these effects is not yet clear. Additionally, animal studies suggest that high levels are associated with liver, kidney, and lung cancer.

EPA revised its assessment of TCE on September 28, 2011, and characterized it as "carcinogenic to humans" by all routes of exposure.

Tetrachloroethylene or Perchloroethylene (PCE), according to CAS, “is reasonably anticipated to be a human carcinogen” based on limited evidence from human studies and sufficient evidence from experimental animal studies. It has been associated with esophageal and cervical cancer and non-Hodgkin’s lymphoma. According to ATSDR, pregnant women may be affected, and the results of animal studies, conducted with amounts much higher than those to which most people are exposed, show that tetrachloroethylene can cause liver and kidney damage.

Benzene, according to CAS, “is known to be a human carcinogen” based on sufficient evidence from human studies. It is primarily associated with increased risk for lymphatic and hematopoietic cancers, total leukemia, and specific histologic types of leukemia, including chronic lymphocytic leukemia, as well as acute myelogenous leukemia. According to ATSDR, epidemiological studies and case reports provide clear evidence of a causal relationship between occupational exposure to benzene and the occurrence of acute nonlymphocytic leukemia, particularly the myeloid cell type or acute myelogenous leukemia. Some studies also provide suggestive evidence of an association with non-Hodgkin’s lymphoma and multiple myeloma. According to EPA’s current IRIS report, benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies. Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia and also suggest evidence for chronic nonlymphocytic leukemia and chronic lymphocytic leukemia. Other neoplastic conditions that are associated with an increased risk in humans include hematologic neoplasms, blood disorders such as preleukemia and aplastic anemia, Hodgkin's lymphoma, and myelodysplastic syndrome.

Vinyl Chloride, according to CAS, “is known to be a human carcinogen” based on sufficient evidence from human studies. It is primarily associated with liver cancer, especially angiosarcoma of the liver, as well as cancer to a lesser extent at other tissue sites including the brain, lung, lymphatic system, and hematopoietic system. According to ATSDR, vinyl chloride is a known human and animal carcinogen. It has been associated with both an increased incidence of hepatic angiosarcomas and hepatotoxicity. According to EPA’s current IRIS report, studies demonstrate a statistically significant elevated risk of liver cancer, specifically angiosarcomas, from vinyl chloride exposure. There is also a possible association with brain, soft tissue, and nervous system cancer, as well as cancers of the hematopoietic and lymphatic systems.

Appendix C

Internet websites describing potential health effects of exposure to chemical contaminants present in the water supply of Camp Lejeune between 1957 and 1987

Trichloroethylene (TCE)

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s180tce.pdf>

ATSDR

<http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=172&tid=30>

EPA

<http://www.epa.gov/iris/subst/0199.htm>

NRC

http://books.nap.edu/catalog.php?record_id=12618

Tetrachloroethylene or Perchloroethylene (PCE)

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s169tetr.pdf>

ATSDR

<http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=264&tid=48>

EPA

<http://www.epa.gov/iris/subst/0106.htm>

NRC

http://books.nap.edu/catalog.php?record_id=12618

Benzene

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s019benz.pdf>

ATSDR

<http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=40&tid=14>

EPA

<http://www.epa.gov/iris/subst/0276.htm#reforal>

Vinyl Chloride

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s186viny.pdf>

ATSDR

<http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=282&tid=51>

EPA

<http://www.epa.gov/iris/subst/1001.htm>

ATSDR Summary for all contaminants

http://www.atsdr.cdc.gov/sites/lejeune/tce_pce.html

Appendix D

Notice to Examiners Evaluating Claims Based on Service at Camp Lejeune

Examiner,

The water supply at Camp Lejeune, North Carolina, was contaminated between 1957 and 1987 with a number of chemical compounds that have been associated by scientific organizations with the potential for developing certain diseases. These include a limited/suggestive association for trichloroethylene (TCE) and tetrachloroethylene, also known as perchloroethylene (PCE), as well as benzene, and vinyl chloride. The Veteran you are examining has verified service at Camp Lejeune during that period and is claiming service connection for (specify disease or diseases claimed). Please evaluate the available evidence, determine whether it is at least as likely as not that the claimed disease is related to the Veteran's exposure to contaminated water while serving at Camp Lejeune, and provide a medical rationale for that determination.

For assistance, we are providing a document that identifies diseases which have a limited/suggestive association with exposure to the known contaminants in the Camp Lejeune water supply between 1957 and 1987. We are also providing a list of Internet websites from scientific organizations, which analyze the potential long-term health effects of exposure to the contaminants. The web addresses can be copied and pasted into a search engine such as Google in order to access them.

Please conduct any required tests and consider any evidence in the file, or obtained by you, which identifies the duration or extent of contaminated water exposure experienced by the Veteran. Information on how long the Veteran served at Camp Lejeune, and whether the Veteran lived off base, should be considered. Unfortunately, there are many unanswered questions regarding potential exposure to contaminants at Camp Lejeune. They include: the levels of water contamination at various base locations, the amount and duration of exposure experienced by any given Veteran who served there, and the scientific probability that a Veteran's particular claimed disease resulted from service at Camp Lejeune and not from some other source.

[Purchase IF](#), [Stafford J](#), [Paddle GM](#). Vinyl chloride: an assessment of the risk of occupational exposure. [Food Chem Toxicol](#). 1987 Feb;25(2):187-202.

Abstract

There is little doubt that exposure to high levels of VCM as a consequence of occupation can result in an increased incidence of ASL. A review of 20 epidemiological studies involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver showed an increase in incidence in the majority of studies. For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity, and pharynx, cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies. In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze et al. (1980), who did not confirm these findings in humans, are of importance. The register of ASL cases now contains records of 99 persons with confirmed ASL and occupational exposure to VCM. The average latent period between first exposure to VCM and death from ASL is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of exposure are not available for the periods of most interest, the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of ASL. For example, ASL cases tended to occur in larger numbers in some plants than in others, a finding that can be explained most easily by differences in exposure patterns. There is an extensive series of animal studies on the carcinogenicity of VCM. Some of these precede the epidemiological studies confirming the association between VCM exposure and ASL in man. ASL and neoplasms of a number of other organs have been induced in laboratory rodents by VCM. Estimation of the exposure levels likely to cause a lifetime risk of ASL of 10^{-6} on the basis of these data give extremely low levels (down to 3.9×10^{-7} ppb) which appear to be unrealistic estimates for man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolites chloroethylene oxide and chloroacetaldehyde. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response relationship.

[Paulu C](#), [Aschengrau A](#), [Ozonoff D](#). Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers. [Environ Health Perspect](#). 1999 Apr;107(4):265-71.

Full text: <http://web.ebscohost.com/ehost/detail?vid=3&sid=9c017e1b-41b2-4e27-ac9d-1938ec4a4bfd%40sessionmgr110&hid=108&bdata=JnNpdGU9ZWlhvc3QtbGl2ZQ%3d%3d#db=mnh&AN=10090704>

Abstract:

We conducted a population-based case-control study to evaluate the relationship between cancer of the colon-rectum (n = 326), lung (n = 252), brain (n = 37), and pancreas (n = 37), and exposure to tetrachloroethylene (PCE) from public drinking water. Subjects were exposed to PCE when it leached from the vinyl lining of drinking-water distribution pipes. Relative delivered dose of PCE was estimated using a model that took into account residential location, years of residence, water flow, and pipe characteristics. Adjusted odds ratios (ORs) for lung cancer were moderately elevated among subjects whose exposure level was above the 90th percentile whether or not a latent period was assumed [ORs and 95% confidence intervals (CIs), 3.7 (1.0-11.7), 3.3 (0.6-13.4), 6.2 (1.1-31.6), and 19.3 (2.5-141.7) for 0, 5, 7, and 9 years of latency, respectively]. The adjusted ORs for colon-rectum cancer were modestly elevated among ever-exposed subjects as more years of latency were assumed [OR and CI, 1.7 (0.8-3.8) and 2.0 (0.6-5.8) for 11 and 13 years of latency, respectively]. These elevated ORs stemmed mainly from associations with rectal cancer. Adjusted ORs for rectal cancer among ever-exposed subjects were more elevated [OR and CI, 2.6 (0.8-6.7) and 3.1 (0.7-10.9) for 11 and 13 years of latency, respectively] than were corresponding estimates for colon cancer [OR and CI, 1.3 (0.5-3.5) and 1.5 (0.3-5.8) for 11 and 13 years of latency, respectively]. These results provide evidence for an association between PCE-contaminated public drinking water and cancer of the lung and, possibly, cancer of the colon-rectum.

The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis.

[Cheungpasitporn W](#)¹, [Thongprayoon C](#)², [O'Corragain OA](#)², [Edmonds PJ](#)², [Ungprasert P](#)², [Kittanamongkolchai W](#)², [Erickson SB](#)².

Author information

Abstract

BACKGROUND:

The objective of this meta-analysis was to evaluate the association between a history of kidney stones and kidney cancer.

METHODS:

A literature search was performed from inception until June 2014. Studies that reported odds ratios or hazard ratios comparing the risk of renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of the upper urinary tract in patients with the history of kidney stones versus those without the history of kidney stones were included. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

RESULT:

Seven studies were included in our analysis to assess the association between a history of kidney stones and RCC. The pooled RR of RCC in patients with kidney stones was 1.76 (95% CI, 1.24-2.49). The subgroup analysis found that the history of kidney stones was associated with increased RCC risk only in males (RR, 1.41 [95% CI, 1.11-1.80]), but not in females (RR, 1.13 [95% CI, 0.86-1.49]). Five studies were selected to assess the association between a history of kidney stones and TCC. The pooled RR of TCC in patients with kidney stones was 2.14 (95% CI, 1.35-3.40).

CONCLUSION:

Our study demonstrates a significant increased risk of RCC and TCC in patients with prior kidney stones. However, the increased risk of RCC was noted only in male patients. This finding suggests that a history of kidney stones is associated with kidney cancer and may impact clinical management and cancer surveillance.

The Upper Midwest Health Study: gliomas and occupational exposure to chlorinated solvents.

[Ruder AM](#)¹, [Yiin JH](#), [Waters MA](#), [Carreón T](#), [Hein MJ](#), [Butler MA](#), [Calvert GM](#), [Davis-King KE](#), [Schulte PA](#), [Mandel JS](#), [Morton RF](#), [Reding DJ](#), [Rosenman KD](#), [Stewart PA](#); [Brain Cancer Collaborative Study Group](#).

Abstract

OBJECTIVES:

Occupational exposure to chlorinated aliphatic solvents has been associated with an increased cancer risk, including brain cancer. However, many of these solvents remain in active, large-volume use. We evaluated glioma risk from non-farm occupational exposure (ever/never and estimated cumulative exposure) to any of the six chlorinated solvents--carbon tetrachloride, chloroform, methylene chloride, trichloroethylene, tetrachloroethylene or 1,1,1--trichloroethane--among 798 cases and 1175 population-based controls, aged 18-80 years and non-metropolitan residents of Iowa, Michigan, Minnesota and Wisconsin. Methods Solvent use was estimated based on occupation, industry and era, using a bibliographic database of published exposure levels and exposure determinants. Unconditional logistic regression was used to calculate ORs adjusted for frequency matching variables age group and sex, and age and education. Additional analyses were limited to 904 participants who donated blood specimens (excluding controls reporting a previous diagnosis of cancer) genotyped for glutathione-S-transferases GSTP1, GSTM3 and GSTT1. Individuals with functional GST genes might convert chlorinated solvents crossing the blood-brain barrier into cytotoxic metabolites.

RESULTS:

Both estimated cumulative exposure (ppm-years) and ever exposure to chlorinated solvents were associated with decreased glioma risk and were statistically significant overall and for women. In analyses comparing participants with a high probability of exposure with the unexposed, no associations were statistically significant. Solvent-exposed participants with functional GST genes were not at increased risk of glioma.

CONCLUSIONS:

We observed no associations of glioma risk and chlorinated solvent exposure. Large pooled studies are needed to explore the interaction of genetic pathways and environmental and occupational exposures in glioma aetiology.

Temporal Variation in the Association between Benzene and Leukemia Mortality

David B. Richardson

Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina USA

BACKGROUND: Benzene is a human carcinogen. Exposure to benzene occurs in occupational and environmental settings.

OBJECTIVE: I evaluated variation in benzene-related leukemia with age at exposure and time since exposure.

METHODS: I evaluated data from a cohort of 1,845 rubber hydrochloride workers. Benzene exposure–leukemia mortality trends were estimated by applying proportional hazards regression methods. Temporal variation in the impact of benzene on leukemia rates was assessed via exposure time windows and fitting of a multistage cancer model.

RESULTS: The association between leukemia mortality and benzene exposures was of greatest magnitude in the 10 years immediately after exposure [relative rate (RR) at 10 ppm-years = 1.19; 95% confidence interval (CI), 1.10–1.29]; the association was of smaller magnitude in the period 10 to < 20 years after exposure (RR at 10 ppm-years = 1.05; 95% CI, 0.97–1.13); and there was no evidence of association \geq 20 years after exposure. Leukemia was more strongly associated with benzene exposures accrued at \geq 45 years of age (RR at 10 ppm-years = 1.11; 95% CI, 1.04–1.17) than with exposures accrued at younger ages (RR at 10 ppm-years = 1.01; 95% CI, 0.92–1.09). Jointly, these temporal effects can be efficiently modeled as a multistage process in which benzene exposure affects the penultimate stage in disease induction.

CONCLUSIONS: Further attention should be given to evaluating the susceptibility of older workers to benzene-induced leukemia.

KEY WORDS: benzene, cohort study, leukemia, mortality, Ohio. *Environ Health Perspect* 116:370–374 (2008). doi:10.1289/ehp.10841 available via <http://dx.doi.org/> [Online 2 January 2008]

In 1982 the International Agency for Research on Cancer (IARC) concluded there was sufficient evidence that benzene is carcinogenic to humans, with evidence predominantly related to associations between benzene and development of acute non-lymphocytic leukemia (IARC 1982). Subsequent epidemiologic studies have supported that conclusion (Hayes et al. 1997; Rinsky et al. 1987; Wong 1987; Yin et al. 1996). In addition, molecular and cytogenetic studies provide evidence of induction of chromosomal alterations by benzene that is likely to play a role in leukemogenesis (Smith and Zhang 1998; Zhang et al. 2007).

Despite its status as a recognized leukemogen, benzene exposure is common (IARC 1987). Benzene is an important raw material for the chemical industry and an occasional industrial solvent, as well as a component of gasoline (Hricko 1994). Smokers commonly experience protracted inhalation exposures to benzene as a component of cigarette smoke (Wallace et al. 1987). In addition, environmental exposures to benzene arise from sources such as gasoline vapor emissions and auto exhaust (Wallace 1996). Consequently, the identification of a factor that influences a person's susceptibility to benzene-induced leukemia has important public health implications, as does understanding the evolution over time of leukemia rates after benzene exposure.

Multistage theories of carcinogenesis predict that a person's susceptibility to benzene-induced leukemia will depend upon the age

at which exposure occurs, as the probability of transition through the stage (or stages) of the disease process unaffected by benzene exposure are assumed to be age dependent (Thomas 1988). Moreover, age-related physiologic changes might lead to changes in susceptibility to benzene's carcinogenic effects via changes in benzene uptake and its metabolism (Kim et al. 2006). Despite its plausibility as an effect measure modifier, the epidemiologic literature to date provides minimal information about whether susceptibility to benzene-induced leukemia varies with age at exposure.

Multistage cancer models also predict that effect of an increment of exposure on cancer risk may vary with time since exposure. Whereas some investigators have found that a simple metric of cumulative exposure adequately characterizes the exposure time–response relationship (Crump 1994, 1996), others have reported evidence of substantial variation in the impact of benzene exposure on leukemia risk with time since exposure (Finkelstein 2000; Hayes et al. 1997; Silver et al. 2002).

The analyses reported in the present article examine age at exposure and time since exposure as modifiers of the association between the leukemia mortality and occupational benzene exposure in a cohort of rubber hydrochloride workers. Previous analyses of these data have been used by the U.S. Occupational Safety and Health Administration (OSHA) to support the current permissible exposure limit for

benzene in the workplace and by the U.S. Environmental Protection Agency (EPA) as the basis for risk estimates for inhaled benzene (OSHA 1987; U.S. EPA 1985). The objective of these analyses was to use exposure time windows and a multistage model to evaluate temporal modifiers of the impact of benzene on leukemia rates.

Materials and Methods

This study is based upon the experience of workers employed in the manufacture of a natural rubber film (rubber hydrochloride) at two locations in Ohio. Natural rubber was dissolved in benzene and spread over a conveyor; the benzene was evaporated and recovered while the rubber film was stripped from the conveyor (Rinsky et al. 1987). Production at the first location commenced in 1939 and ceased in 1976; production at the second location began around 1937 and continued until 1965. All nonsalaried workers employed in a rubber hydrochloride department between 1 January 1940 and 31 December 1965 were included in these analyses.

Vital status was ascertained through 31 December 1996 via records of the Social Security Administration, Ohio Bureau of Motor Vehicles, and the National Death Index. If there was no death indication for a worker then they were assumed to be alive as of 31 December 1996. Information was obtained on underlying cause of death for deceased workers, coded according to the revision of the *International Classification of Diseases* (ICD) in effect at the time of death. These analyses focus on leukemia [ICD-6 and ICD-7 code 204 [World Health Organization

Address correspondence to D. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 USA. Telephone: (919) 966-2675. Fax: (919) 966-2089. E-mail: david.richardson@unc.edu

Supplemental Material is available online at <http://www.ehponline.org/docs/2008/10841/suppl.pdf>

I thank R. Rinsky, Cincinnati Children's Hospital Medical Center and S. Silver, National Institute for Occupational Safety and Health, for their support of these analyses, which make use of data derived from their previously published research.

This project was supported by grant K01-OH008635 from the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention.

The author declares he has no competing financial interests.

Received 4 September 2007; accepted 2 January 2008.

(WHO) 1948, 1957], ICD-8 codes 204-207 [U.S. Public Health Service 1968], ICD-9 codes 204-208 [WHO 1978]].

The exposure of interest was defined as cumulative benzene exposure, expressed in parts per million-year (ppm-year). Annual exposure rate estimates by plant, department, and job were developed by Rinsky et al. (2002, 1987) based on available air sampling data. Utterbach and Rinsky (1995) have reviewed the methods employed in this assessment of benzene exposure among rubber hydrochloride workers. The U.S. National Institute for Occupational Safety and Health provided a file that contained a plant, department, and job code, and start and finish dates, for each job held by each worker. Using this information, benzene exposure histories were computed for each worker as the product of the length of employment in each job in a year by the estimated benzene exposure rate for that job.

Statistical methods. Cox proportional hazards regression models were fitted to these data via the statistical program PECAN, with attained age as the primary time scale (Preston et al. 1993). Model covariates included a categorical indicator of birth cohort (classified as born before 1905, 1905 to < 1910, 1910 to < 1915, 1915 to < 1920, or after 1920), a binary indicator of sex, and a binary indicator of employment status (active employment status began when a person started employment and ended 1 week after the end of employment in order to allow for inaccuracies in personnel records regarding the day last employed) (Arrighi and Hertz-Picciotto 1994; Steenland and Stayner 1991; Steenland et al. 1996). The majority (99%) of workers of known race in this cohort was white, and no deaths due to leukemia were observed among nonwhite workers; therefore, race was not included as a covariate in these analyses. In analyses of cumulative exposure (expressed in 10-ppm-year increments) log-linear regression models were fitted, providing

an estimate of the log relative rate per 10 ppm-years; we report the anti-log of this estimate and discuss it as an estimate of the relative rate at 10 ppm-years. Ninety-five percent confidence intervals (CIs) were estimated via the likelihood method.

Cumulative exposure was treated as a time-varying explanatory variable that described the benzene exposures accrued prior to a person's entry into a risk set in the Cox regression analysis. The model with a single parameter for cumulative benzene exposure implies that the magnitude of the hazard ratio does not depend on when exposures occurred. Exposure time window analyses were conducted to assess whether the relationship between disease risk and benzene exposure depends on when exposures occurred (Checkoway et al. 1990; Richardson and Ashmore 2005; Thomas 1988). A model with three exposure time windows, defined *a priori*, described the association between leukemia rates and exposures accrued in the periods < 10 years, 10 to < 20 years, and ≥ 20 years prior to a person's entry into a risk set in the regression analysis (Rothman 1981). To assess variation in exposure effects with age at exposure, metrics of cumulative exposures accrued at < 45 and ≥ 45 years of age were examined (Richardson and Wing 1998). Each model was compared with a standard model of lifetime cumulative exposure by means of a likelihood ratio test (LRT); the difference between model deviances, described as an LRT statistic, can be interpreted using a chi-square distribution with degrees of freedom (df) equal to the difference in the numbers of model parameters.

Multistage models of carcinogenesis, of which the best known is the Armitage-Doll model, involve the mathematic expression of hypotheses about the process of carcinogenesis (Armitage and Doll 1954). Central to the Armitage-Doll model is the concept that cancer arises as the result of a single cell undergoing a series of transformations. The model

predicts that cancer incidence, I , will increase as an integer power of attained age, a , with the integer, depending on the number of stages, k , required for cancer induction. Specifically, the model posits the relationship $I = ca^{k-1}$, where c is a constant that is proportional to the product of the transition rates. When considering the effect of an environmental carcinogen, the transition rate from one rate-limiting step to the next is often assumed to be affected in a linear fashion by exposure. If exposure influences the transition rate for a single stage, $j < k$, this implies a linear relative rate model of the form RR (relative rate) = $1 + \delta_{j,k}Z$, where Z is a weighted cumulative exposure metric calculated for each person (Thomas 1988; Whittemore 1977). Specifically, if a denotes the attained age of members of a risk set enumerated for a Cox regression analysis, and a_0 is the age at which an increment of exposure occurs, then the weight assigned to that exposure increment is given by the expression, $w(a_0) = (1 + a^{k-1}) a_0^{j-1} (a-a_0)^{k-j-1}$. The weighted cumulative exposure metric Z represents the sum of weighted exposure increments accrued through age a .

Leukemia incidence rates increase approximately as a function of age to the fourth power, suggesting a process of carcinogenesis that involves five stages (Little et al. 1992; Ries et al. 2003). Therefore, a disease process that involves five stages was posited (i.e., $k = 5$) and weighted cumulative exposure metrics for each integer value of $j < k$ were calculated. Relationships between leukemia mortality and these weighted cumulative exposure metrics were evaluated, and fitted regression models were compared with reference to residual model deviance ($-2 \log$ likelihood). Alternative models with fewer than five stages and those with more than five stages were also evaluated. Regression analyses were conducted via the log-linear rate model as well as via the linear relative rate model.

Results

Table 1 shows the distribution of major characteristics among cases and noncases in the study cohort. A single leukemia death was observed among the females in the study cohort. Over one-third of the leukemia cases were ascertained among workers born before 1905, whereas nearly 60% of the noncases were born in the period 1920 or later. Leukemia cases were employed for a longer average duration than noncases, tended to start employment at older ages than noncases, and accrued higher average cumulative benzene exposures (144 ppm-years) than noncases (34 ppm-years). Two percent of the workers were hired before 1940, 19% were hired in the period 1940–1944, and the remainder were hired in 1945–1975.

Table 2 reports estimated RRs for categories of benzene exposure. The rate ratio for

Table 1. Characteristics [n (%)] of cohort of 1,845 rubber hydrochloride workers stratified by leukemia case status, Ohio, 1940–1996.

| Characteristic | Cases ($N = 17$) | Noncases ($N = 1,828$) |
|--|-----------------------|-----------------------------|
| Sex | | |
| Male | 16 (94) | 1,705 (93) |
| Female | 1 (6) | 123 (7) |
| Birth cohort | | |
| < 1905 | 6 (35) | 230 (13) |
| 1905 – < 1910 | 2 (12) | 131 (7) |
| 1910 – < 1915 | 3 (18) | 193 (11) |
| 1915 – < 1920 | 3 (18) | 226 (12) |
| < 1920 | 3 (18) | 1,048 (57) |
| Employment status | | |
| Employed | 2 (12) | 10 (1) |
| Terminated | 15 (88) | 1,818 (99) |
| Age at entry (years, mean \pm SD) | 41 \pm 11 | 32 \pm 11 |
| Age at exit (years, mean \pm SD) | 62 \pm 17 | 67 \pm 12 |
| Duration of employment (years, mean \pm SD) | 7 \pm 8 | 4 \pm 7 |
| Cumulative exposure (ppm-years, mean \pm SD) | 144 \pm 207 | 34 \pm 91 |

the contrast drawn between the categories 1 to < 50 ppm-years and < 1 ppm-year was below unity (Table 2). When considering contrasts drawn between 50 to < 250, 250 to < 500, and \geq 500 ppm-years and < 1 ppm-year, the rate ratios were greater than unity and increased in magnitude with increasing cumulative exposure level, although the associated 95% CIs were relatively wide for each exposure category, reflecting the small numbers of leukemia cases observed within each category.

There was a positive trend in the leukemia mortality rate with cumulative benzene exposure (Table 3). Table 3 also describes the association between leukemia and cumulative benzene exposure accrued in the periods < 10 years, 10 to < 20 years, and \geq 20 years prior. The largest magnitude of association was observed for benzene exposures accrued in the period < 10 years prior, whereas exposures received 10 to < 20 years previously exhibited a smaller, positive association with leukemia, and benzene exposures received \geq 20 years prior showed no association with leukemia. A model with three exposure time windows provided a substantially better fit to these data than a lifetime cumulative exposure model (LRT = 13.2, 2 df, p -value = 0.001).

Table 4 reports the association between cumulative benzene exposures accrued at younger (< 45 years) and older (\geq 45 years) ages and leukemia in the periods < 10 years, 10 to < 20 years, and \geq 20 years after exposure. When considering benzene exposures accrued at \geq 45 years of age, there was a positive association with leukemia mortality in the period shortly after exposure (< 10 years after exposure); there was minimal evidence of association within the period \geq 10 years after exposure. Benzene exposures accrued at younger ages exhibited little evidence of association with leukemia. The fit of this model with exposure time windows defined jointly by age at exposure and time since exposure was substantially better than the fit of a model for lifetime cumulative exposure (LRT = 16.9, 5 df, p -value = 0.005). Table 4 also reports estimates of the association between cumulative benzene exposures accrued at younger (< 45 years) and older (\geq 45 years) ages and leukemia, summarized over all periods of time since exposure. A model that included separate terms for two age-at-exposure time windows provided a slightly better fit to these data than the simpler, nested model that included a single parameter for cumulative benzene exposure accrued at all ages (LRT = 3.3, 1 df, p -value = 0.071).

Table 2. Estimated association between cumulative exposure to benzene and leukemia mortality among rubber hydrochloride workers, Ohio, 1940–1996.

| | Cumulative exposure to benzene (ppm-years) | | | | |
|--------------|--|---------------|----------------|-----------------|------------------|
| | < 1 | 1 to < 50 | 50 to < 250 | 250–500 | \geq 500 |
| RR (95% CI) | 1 | 0.8 (0.2–3.2) | 2.5 (0.6–10.2) | 10.5 (2.3–46.6) | 13.9 (0.7–116.1) |
| Deaths (no.) | 5 | 3 | 4 | 4 | 1 |

The results reported in Tables 3 and 4 are minimally impacted by inclusion of birth cohort, sex, or employment status as covariates; none of the parameter estimates on which the reported effect measures were based changed by > 10% on exclusion of these covariates. The linear relative rate model provided an equivalent fit to these data for analyses of lifetime cumulative exposure; however, the log-linear model fitted these data better for the exposure time window analyses. The cut point defining younger versus older age at exposure was chosen to broadly partition the ages at which exposures occur; there was minimal impact on relative rate estimates of selecting alternative cut points of 40 years or 50 years (results not shown).

In contrast to the exposure time window analyses presented above, which impose a piecewise constant model to describe temporal variation in exposure effects, the Armitage–Doll model implies a smooth time-varying exposure weighting function that jointly describes age at exposure and latency effects. Residual model deviances were compared for models in which benzene exposure acted upon the first, second, third, or fourth stage of a five-stage disease process (Table 5). A model under which the transition rate for the fourth stage was affected by benzene exposure resulted in the lowest residual deviance and therefore provided the best fit to these data. Figure 1A illustrates how the estimated effect of benzene exposure varies with time since exposure; the figure illustrates the natural log of the estimated relative rate of leukemia per 10 ppm-years for those 65 years of age (i.e., typical of the ages at which leukemia deaths occurred in this population). Consistent with observations from our exposure time window analyses, the modeled effect was largest for exposures that occurred in the prior decade and diminished rapidly with time since exposure. Figure 1B illustrates how the estimated effect of benzene exposure varies with age at exposure. As observed via time window analyses, the exposure effect was much smaller for exposures accrued prior to 45 years of age; the estimated effect of benzene exposure increased with age at exposure > 45 years of age. Multistage models were also fitted using a linear relative rate model; a model in which the transition rate for the penultimate stage was affected by benzene exposure provided the best fit to these data (Table 5). Evaluation of alternative models with as few as three stages, or as many as 15 stages, led to similar conclusions

(see Supplemental Material online at <http://www.ehponline.org/docs/2008/10841/suppl.pdf>); in all such models the best-fitting model is one in which benzene exposure acts at the penultimate stage.

Discussion

In the United States, the OSHA standard for benzene exposure is 1 ppm. The analyses in the present article suggest that accrual of benzene exposure at that level for a decade implies a modest increase in the relative rate of leukemia mortality, with the magnitude of the excess relative rate diminishing with time since exposure (Table 3). Because leukemia is a rare disease, this means that if a person is exposed to 1 ppm of benzene for a decade, it is still unlikely that they will develop leukemia. To understand the impact of benzene exposure on leukemia risk at a population level, however, the magnitude of the dose–response association and its variation over time must be accurately characterized. In this study population, the effect of benzene exposure on leukemia did not appear to persist indefinitely, but rather diminished with time since exposure. Of course, caution is warranted in drawing conclusions from an historical cohort study of a population in which working conditions differed substantially from those typical of contemporary work settings in the United States. Nonetheless, the findings of this historical cohort of U.S. workers may have substantial relevance for contemporary workers, both in the United States and abroad.

In prior analyses of this cohort, Crump (1994, 1996) investigated the hypothesis that the effect of benzene on leukemia risk diminishes with time since exposure by applying a set of time-dependent exposure weights with values informed *a priori* by latency patterns for leukemia after radiotherapy for ankylosing spondylitis. Crump reported that analyses using a simple metric of cumulative exposure fitted these data better than analyses using those exposure weights (Crump 1996). In the present paper, rather than assigning a set of

Table 3. Estimated relative rates (and associated 95% CIs) for leukemia mortality expressed as a trend with benzene exposure (10 ppm-years) and within time windows defined by time since exposure.

| | RR at 10 ppm-years (95% CI) |
|------------------------|-----------------------------|
| Cumulative exposure | 1.05 (1.02–1.08) |
| Time since exposure | |
| < 10 years prior | 1.19 (1.10–1.29) |
| 10 to < 20 years prior | 1.05 (0.97–1.13) |
| \geq 20 years prior | 1.00 (0.90–1.05) |
| Test of heterogeneity | |
| LRT, 2 df ^a | 13.1 |
| p -Value | 0.001 |

^aLRT comparing a model with terms for three exposure time windows to a model with one term for lifetime cumulative exposure.

exposure weights based on patterns observed in a study of radiation exposure effects, the method of exposure time–window analysis was used. The overall association between cumulative exposure and leukemia mortality (RR at 10 ppm-years = 1.05) is nearly identical to the estimate derived by Rinsky et al. (2002) via a log-linear Cox regression model; the evidence of heterogeneity of benzene exposure effects with time since exposure is consistent with previous observations reported by Silver et al. (2002) and Finkelstein (2000).

These findings suggest that the effect of benzene on leukemia mortality is jointly characterized as an effect of age at exposure and time since exposure. The temporal pattern is consistent with a multistage cancer model with benzene affecting a late stage in the induction of leukemia; the relative rate of leukemia per unit exposure increases with age at exposure and decreases with time since exposure (Thomas 1988). This conclusion is supported by analyses that involve fitting weighting expressions implied by the Armitage–Doll model. These weighted exposure metrics were evaluated via fittings of standard log-linear models as well as via fittings of linear relative rate models [the latter being the model form implied by the work of Whittemore (1977), whereas the former approach was consistent with the model form used in the exposure time–window analyses]. In these analyses a model with five stages was posited. Armitage and Doll intentionally used the word “stage” rather than mutation to allow for the possibility of nonmutational events leading to cancer induction (Doll 2004). They correctly maintained that the application of multistage models for cancer risk estimation offers a heuristic tool that allows an investigator to explore potentially complex dose–time–response patterns by imposing some relatively minor constraints based on biological expectations about the disease process. Although mutational events are clearly central to carcinogenesis, useful insights from these models may be obtained even if carcinogenesis is viewed more generally as resulting from a series of rate-limiting pathogenic events, with exposure influencing one or more transition rates (Hanahan and Weinberg 2000; Morrison 1979).

The validity of these findings depends, in part, on the validity of the benzene exposure estimates derived for this cohort. To the extent that the exposure measurement error conforms to a classical model, attenuation of the dose response would be expected. However, non-random measurement errors could lead to bias away from the null. Estimates of these historical benzene exposures used air monitoring results, which were relatively sparse for the early years of operation (Utterback and Rinsky 1995; Williams and Paustenbach 2003). In

theory, temporal variation in the magnitude of a benzene–leukemia association (e.g., diminished evidence of association with increasing time since exposure) could reflect increasing exposure misclassification for benzene exposure estimates for periods of employment further in the past. While it is difficult to assess such concerns, the observation in this cohort that the benzene–leukemia association diminished with time since exposure is consistent with patterns observed in other populations of benzene-exposed workers (Glass et al. 2004; Hayes et al. 1996), suggesting that the temporal patterns in this cohort are not simply an artifact of errors in exposure estimates.

Although the fitted models include a relatively small number of covariates, concerns about bias because of residual confounding are tempered by the fact that there are few leukemogens that are plausible strong confounders of the association under study. Cigarette smoking is a nonoccupational source of benzene exposure and could, in theory, confound our estimates of association between occupational benzene exposure and leukemia. However, given the relatively small

magnitude of association between smoking and leukemia mortality, high levels of correlation between occupational benzene exposure and smoking would be necessary to account for even modest dose–response trends for leukemia (Axelson and Steenland 1988; Siemiatycki et al. 1988).

The analyses in this article examined the broad category of all leukemia deaths. It is reasonable to posit that associations may vary in magnitude and temporal pattern by disease subtype. Although evaluation of heterogeneity in exposure–response analyses for different subtypes of leukemia is of interest because of small numbers of leukemia cases and the sparse information available from the death certificates, subtype-specific exposure–response analyses were not conducted. In addition, the use of mortality data in these analyses does not allow assessment of whether benzene exposure influences disease prognosis or incidence; therefore, it is possible that benzene exposures accrued proximate to death could influence mortality rates by reducing survival time rather than by increasing incidence rates. The relatively small number of

Table 4. Estimated association between leukemia mortality and cumulative exposure to benzene in exposure time windows cross-classified by age at exposure and time since exposure.

| | RR at 10 ppm-years (95% CI) | |
|------------------------|------------------------------|------------------------------|
| | Accrued at < 45 years of age | Accrued at ≥ 45 years of age |
| Cumulative exposure | 1.01 (0.92–1.09) | 1.11 (1.04–1.17) |
| Time since exposure | | |
| < 10 years prior | 0.78 (ND–1.23) | 1.22 (1.11–1.32) |
| 10 to < 20 years prior | 1.05 (0.89–1.22) | 1.03 (0.92–1.13) |
| ≥ 20 years prior | 1.01 (0.90–1.09) | 0.93 (0.55–1.10) |

ND, not determined (the 95% confidence bound was not determined via the likelihood method). LRT comparing model with six exposure time windows to the cumulative exposure model = 16.9, 5 df, *p*-value = 0.005.

Table 5. Residual deviances from fitting of log-linear and linear RR regression models.

| Stage affected by benzene (<i>j</i>) | Log-linear rate model | Linear RR model |
|--|-----------------------|-----------------|
| 1 | 211.23 | 209.5 |
| 2 | 209.76 | 206.9 |
| 3 | 204.74 | 203.4 |
| 4 | 193.60 | 200.1 |

Comparison of models in which a cumulative weighted benzene exposure metric was derived via a multistage model with five stages (i.e., *k* = 5), assuming a single stage, *j*, was affected by benzene exposure.

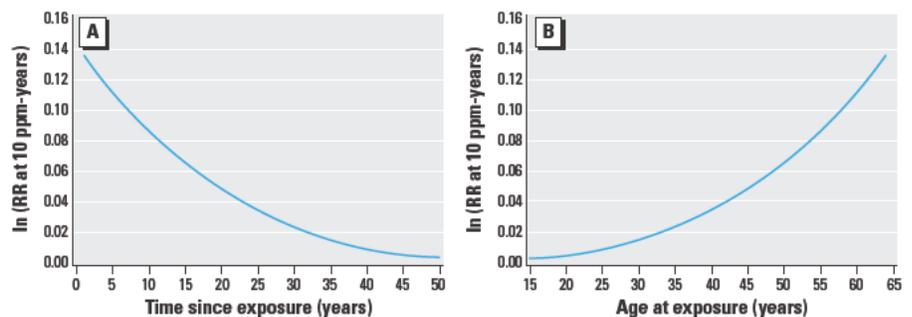


Figure 1. (A) Fitted time-varying exposure weighting function. Log relative rate (RR) of leukemia per 10 ppm-year benzene exposure by time since exposure for a person 65 years of age, rubber hydrochloride workers, Ohio, 1940–1996. (B) Fitted time-varying exposure weighting function. Log relative rate (RR) of leukemia per 10 ppm-year benzene exposure by age at exposure for a person 65 years of age, rubber hydrochloride workers, Ohio, 1940–1996.

leukemia deaths also suggests that model results are relatively sensitive to small changes in distribution of events; adding or subtracting a single case in the highest exposure category could lead to a substantial change in the estimates of the association between cumulative exposure and leukemia mortality. Last, the Armitage–Doll model, while often illustrated using mortality data (Armitage and Doll 1954), is posited as a model of disease incidence; it is likely that the conclusions obtained in these analyses would differ from those obtained via analyses of incidence data.

Since 1987, the Chinese Academy of Preventive Medicine has collaborated with the U.S. National Cancer Institute on a large-scale study of cancer among Chinese workers exposed to benzene (NCI-CAPM study) (Hayes et al. 1997). Although the NCI-CAPM study encompasses more leukemia cases than in this rubber hydrochloride cohort study, several concerns have been raised about the validity of the exposure estimates used in the previously reported analyses of the NCI-CAPM study (Hayes et al. 2001). Therefore, the rubber hydrochloride cohort examined in this article remains one of the important epidemiologic resources for benzene risk assessment.

The findings illustrate the importance of attention to dynamic changes in exposure–response patterns with temporal factors such as time since exposure and age at exposure. Failure to account for variation with time since exposure in the effect of an increment of benzene exposure on the relative rate of leukemia may lead to underestimation of the excess rate of leukemia in some risk periods (and overestimation of the excess rate of leukemia in other risk periods). In these analyses, the effect of an increment of benzene exposure on leukemia mortality appears promptly, diminishes with time since exposure, and is of greater magnitude for workers exposed at older ages than for those exposed at younger ages. These temporal patterns of association are consistent with a late-stage carcinogen and suggest that occupational protection efforts give particular consideration to the risks of benzene-induced leukemia faced by older workers. Further attention should be given to assessment of age at exposure in other benzene-exposed populations, specifically to the potentially greater susceptibility of older workers to benzene-induced leukemia.

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[Cancer](#). 1993 Aug 15;72(4):1369-75.

Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans.

[Mashberg A](#), [Boffetta P](#), [Winkelman R](#), [Garfinkel L](#).

Author information

Abstract

BACKGROUND:

Independent carcinogenic effects of alcohol drinking and tobacco smoking as well as their interaction can be usefully studied in a population of heavy drinkers and smokers.

METHODS:

A hospital-based case-control study was conducted during 1972 to 1983 in a large Veterans hospital in East Orange, New Jersey. A total of 359 oral cavity-oropharynx cancer cases and 2280 controls were interviewed according to tobacco smoking, use of smokeless tobacco, alcoholic beverage, coffee and tea drinking, race, family origin, religion, and occupation as bartender.

RESULTS:

Odds ratio of oral cancer increased up to the level of 35 cigarettes per day and 21 whiskey equivalents per day: no further increase was found for higher level of exposure to either factor. A protective effect of quitting smoking was found, but the number of former smokers was small. No difference occurred in oral cancer risk according to type of alcoholic beverage drunk. An interaction effect compatible with a multiplicative model was found between the two exposures. Blacks were at lower risk than whites, and, in the latter group, individuals of Italian origin were at lower risk than individuals from northern or central European countries.

CONCLUSIONS:

Alcohol drinking and tobacco smoking were responsible for the majority of oral cancer cases in this population of US Veterans.

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: Suggested articles for Sharepoint
Date: Monday, March 24, 2014 11:09:06 AM

Suggesting the following articles for inclusion on the CLCW Sharepoint:

1. Qureshi, A., Ramsey, D., Kramer, J. Whitehead, L., El-Serag, H. (2013). Occupational Exposure and the Risk of Barrett's Esophagus: A Case-Control Study. *Dig Dis Sci.* 2013 Jul;58(7): 1967-75. Doi: 10.1007/s10620-013-2572-6. Epub 2013 Feb 5.
2. Pohl, H., Wrobel, K., Bojarski, C., Voderholzer, W., Sonnenberg, A., Rosch, T. & Baumgart, D. (2013). Risk Factors in the Development of Esophageal Adenocarcinoma. *The American Journal of Gastroenterology*, 2013 Feb; 108(2): 200-7. Doi: 10.1038/ajg.2012.387. Epub 2012 Dec 18.

Tetrachloroethylene Exposure and Bladder Cancer Risk: A Meta-Analysis of Dry-Cleaning-Worker Studies.

[Vlaanderen J](#)¹, [Straif K](#)², [Ruder A](#)³, [Blair A](#)⁴, [Hansen J](#)⁵, [Lynge E](#)⁶, [Charbotel B](#)⁷, [Loomis D](#)², [Kauppinen T](#)⁸, [Kyyronen P](#)⁹, [Pukkala E](#)¹⁰, [Weiderpass E](#)¹¹, [Guha N](#)².

Abstract

BACKGROUND: In 2012, the International Agency for Research on Cancer classified tetrachloroethylene, used in the production of chemicals and the primary solvent used in dry cleaning, as *probably carcinogenic to humans* based on *limited* evidence of an increased risk of bladder cancer in dry cleaners.

OBJECTIVES:

We assessed the epidemiological evidence for the association between exposure to tetrachloroethylene and bladder cancer from published studies estimating occupational exposure to tetrachloroethylene or in workers in the 'dry cleaning' industry.

METHODS: Random-effects meta-analyses were carried out separately for occupational exposure to tetrachloroethylene and employment as a dry cleaner. We qualitatively summarized exposure-response data because of the limited number of studies available.

RESULTS:

The meta-relative risk (mRR) among tetrachloroethylene exposed workers was 1.08 (95% CI: 0.82, 1.42; 3 studies; 463 exposed cases). For employment as dry cleaner the overall mRR was 1.47 (95% CI: 1.16, 1.85; 7 studies; 139 exposed cases) and for smoking-adjusted studies 1.50 (95% CI: 0.80, 2.84; 4 case-control studies).

CONCLUSIONS:

Our meta-analysis demonstrates an increased risk of bladder cancer in dry cleaners, reported in both cohort and case-control studies, and some evidence for an exposure-response relationship. Although dry cleaners incur mixed exposures, tetrachloroethylene could be responsible for the excess risk of bladder cancer because it is the primary solvent used and it is the only chemical commonly used by dry cleaners that is currently identified as a potential bladder carcinogen. Relatively crude exposure assessment approaches in the studies of 'tetrachloroethylene exposed workers' may have attenuated the relative risks

Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis.

[Karami S](#), [Lan Q](#), [Rothman N](#), [Stewart PA](#), [Lee KM](#), [Vermeulen R](#), [Moore LE](#).

Source

National Cancer Institute, Division of Cancer Epidemiology and Genetics, Occupational and Environmental Epidemiology Branch, 6120 Executive Blvd, EPS 8102, Rockville, MD 20852, USA.

Abstract

OBJECTIVES:

Inconsistent epidemiological findings, debate over interpretation, and extrapolation of findings from animal studies to humans have produced uncertainty surrounding the carcinogenicity of trichloroethylene (TCE) exposure in occupational settings. We updated meta-analyses of published case-control and cohort studies exploring occupational TCE exposure and kidney cancer risk, incorporating new analytical results from three recently published cohort studies and a case-control study.

METHODS:

PubMed MEDLINE was searched for studies published from 1950 to 2011 assessing occupational exposure to chlorinated solvents, degreasers or TCE. All cohort (N=15) and case-control (N=13) studies included in analyses were stratified by assessment of occupational exposure to TCE specifically and to any chlorinated solvent.

RESULTS:

Significantly elevated summary estimates were observed for cohort studies (relative risk (RR) 1.26, 95% CI 1.02 to 1.56; p heterogeneity=0.65), case-control studies (OR 1.35, 95% CI 1.17 to 1.57; p heterogeneity=0.41), and cohort and case-control studies combined (RR 1.32, 95% CI 1.17 to 1.50, p heterogeneity=0.63) that specifically assessed TCE exposure after excluding outlier studies that contributed to heterogeneity. Non-significantly elevated summary estimates were generally observed for studies of workers exposed to chlorinated solvents but who were not assessed for TCE specifically.

CONCLUSIONS:

Regardless of study design, significant and stronger estimates were only observed in studies specifically assessing occupational exposure to TCE. Estimates were lower in studies assessing occupational exposure to chlorinated solvents. This updated meta-analysis supports an association between occupational TCE exposure and kidney cancer and provides evidence that exposure misclassification may weaken estimates assessing exposure to the broader class of chlorinated solvents.

PMID:

23000822

[PubMed - indexed for MEDLINE]

A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia.

[Alexander DD](#), [Mink PJ](#), [Mandel JH](#), [Kelsh MA](#).

Source

Exponent-Health Sciences, 185 Hansen Court, Suite 100, Wood Dale, IL 60191, USA.
dalexander@exponent.com

Abstract

BACKGROUND:

Trichloroethylene (TCE) has been widely used as an industrial solvent and degreasing agent.

AIMS:

We conducted a meta-analysis of epidemiologic studies of occupational TCE exposure and multiple myeloma (MM) or leukaemia.

METHODS:

We identified a total of eight cohort or case-control studies that enumerated a TCE-exposed study population and presented relative risk (RR) estimates for MM (n = 7) and/or leukaemia (n = 7). The individual studies included aerospace or aircraft workers (n = 3 studies), workers from a transformer manufacturing plant (n = 1 study) and workers from numerous occupations who, based on biomonitoring or extensive industrial hygiene exposure measurements, were likely exposed to TCE (n = 4). We used random effects models to calculate summary relative risk estimates (SRRE). In addition, we examined heterogeneity across studies and the relative influence of each individual study on the overall meta-analysis.

RESULTS:

No association was observed for MM (SRRE = 1.05, 95% CI: 0.80-1.38; P value for heterogeneity = 0.94) or leukaemia (SRRE = 1.11, 95% CI: 0.93-1.32; P value for heterogeneity = 0.50), based on TCE-exposed subgroup meta-analyses. Study-specific RR estimates for MM ranged between 0.57 and 1.62. RRs for leukaemia ranged between 1.05 and 1.15 in five studies, while one study reported a 2-fold increased RR and another study reported an inverse association of 0.60. All confidence intervals (CIs) for study-specific estimates included 1.0.

CONCLUSIONS:

The results of this meta-analysis do not support an etiologic association between occupational TCE exposure and risk of MM or leukaemia.

FULL TEXT

Skeletal Plasmacytoma: Progression of disease and impact of local treatment; an analysis of SEER database

Muhammad U Jawad and Sean P Scully*

Journal of Hematology & Oncology 2009, **2**:41 doi:10.1186/1756-8722-2-41

Abstract

Background

Previous reports suggest an as yet unidentifiable subset of patients with plasmacytoma will progress to myeloma. The current study sought to establish the risk of developing myeloma and determine the prognostic factors affecting the progression of disease.

Methods

Patients with plasmacytoma diagnosed between 1973 and 2005 were identified in the SEER database (1164 patients). Patient demographics and clinical characteristics, treatment(s), cause of death, and survival were extracted. Kaplan-Meier, log-rank, and Cox regression were used to analyze prognostic factors.

Results

The five year survival among patients initially diagnosed with plasmacytoma that later progressed to multiple myeloma and those initially diagnosed with multiple myeloma were almost identical (25% and 23%; respectively). Five year survival for patients with plasmacytoma that did not progress to multiple myeloma was significantly better (72%). Age > 60 years was the only factor that correlated with progression of disease ($p = 0.027$).

Discussion

Plasmacytoma consists of two cohorts of patients with different overall survival; those patients that do not progress to systemic disease and those that develop myeloma. Age > 60 years is associated with disease progression. Identifying patients with systemic disease early in the treatment will permit aggressive and novel treatment strategies to be implemented.

From: (b) (6),
To: (b) (6),
Subject: smoking and breast cancer risk: new article:
Date: Thursday, January 23, 2014 9:39:20 AM

Cancer Epidemiol Biomarkers Prev.
<<http://www.ncbi.nlm.nih.gov/pubmed/24420985>> 2014 Jan;23(1):37-46. doi:
10.1158/1055-9965.EPI-13-1081.

The surgeon general report on smoking and health 50 years later: breast cancer and the cost of increasing caution.

Glantz SA <http://www.ncbi.nlm.nih.gov/pubmed?term=Glantz%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=24420985>,
Johnson KC <http://www.ncbi.nlm.nih.gov/pubmed?term=Johnson%20KC%5BAuthor%5D&cauthor=true&cauthor_uid=24420985>.

(b) (6), could you put this on the share point?

Thanks

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FULL TEXT

[N Engl J Med](#). 2015 Feb 12;372(7):631-40. doi: 10.1056/NEJMsa1407211.

Smoking and mortality--beyond established causes.

[Carter BD](#)¹, [Abnet CC](#), [Feskanich D](#), [Freedman ND](#), [Hartge P](#), [Lewis CE](#), [Ockene JK](#), [Prentice RL](#), [Speizer FE](#), [Thun MJ](#), [Jacobs EJ](#).

Abstract

BACKGROUND:

Mortality among current smokers is 2 to 3 times as high as that among persons who never smoked. Most of this excess mortality is believed to be explained by 21 common diseases that have been formally established as caused by cigarette smoking and are included in official estimates of smoking-attributable mortality in the United States. However, if smoking causes additional diseases, these official estimates may significantly underestimate the number of deaths attributable to smoking.

METHODS:

We pooled data from five contemporary U.S. cohort studies including 421,378 men and 532,651 women 55 years of age or older. Participants were followed from 2000 through 2011, and relative risks and 95% confidence intervals were estimated with the use of Cox proportional-hazards models adjusted for age, race, educational level, daily alcohol consumption, and cohort.

RESULTS:

During the follow-up period, there were 181,377 deaths, including 16,475 among current smokers. Overall, approximately 17% of the excess mortality among current smokers was due to associations with causes that are not currently established as attributable to smoking. These included associations between current smoking and deaths from renal failure (relative risk, 2.0; 95% confidence interval [CI], 1.7 to 2.3), intestinal ischemia (relative risk, 6.0; 95% CI, 4.5 to 8.1), hypertensive heart disease (relative risk, 2.4; 95% CI, 1.9 to 3.0), infections (relative risk, 2.3; 95% CI, 2.0 to 2.7), various respiratory diseases (relative risk, 2.0; 95% CI, 1.6 to 2.4), breast cancer (relative risk, 1.3; 95% CI, 1.2 to 1.5), and prostate cancer (relative risk, 1.4; 95% CI, 1.2 to 1.7). Among former smokers, the relative risk for each of these outcomes declined as the number of years since quitting increased.

CONCLUSIONS: A substantial portion of the excess mortality among current smokers between 2000 and 2011 was due to associations with diseases that have not been formally established as caused by smoking. These associations should be investigated further and, when appropriate, taken into account when the mortality burden of smoking is investigated. (Funded by the American Cancer Society.).

Solvents and Parkinson disease: A systematic review of toxicological and epidemiological evidence.

[Lock EA](#), [Zhang J](#), [Checkoway H](#).

Source

Liverpool John Moores University, School of Pharmacy and Biomolecular Sciences, Byrom Street, Liverpool, UK. Electronic address: e.lock@ljamu.ac.uk.

Abstract

Parkinson disease (PD) is a debilitating neurodegenerative motor disorder, with its motor symptoms largely attributable to loss of dopaminergic neurons in the substantia nigra. The causes of PD remain poorly understood, although environmental toxicants may play etiologic roles. Solvents are widespread neurotoxicants present in the workplace and ambient environment. Case reports of parkinsonism, including PD, have been associated with exposures to various solvents, most notably trichloroethylene (TCE). Animal toxicology studies have been conducted on various organic solvents, with some, including TCE, demonstrating potential for inducing nigral system damage. However, a confirmed animal model of solvent-induced PD has not been developed. Numerous epidemiologic studies have investigated potential links between solvents and PD, yielding mostly null or weak associations. An exception is a recent study of twins indicating possible etiologic relations with TCE and other chlorinated solvents, although findings were based on small numbers, and dose-response gradients were not observed. At present, there is no consistent evidence from either the toxicological or epidemiologic perspective that any specific solvent or class of solvents is a cause of PD. Future toxicological research that addresses mechanisms of nigral damage from TCE and its metabolites, with exposure routes and doses relevant to human exposures, is recommended. Improvements in epidemiologic research, especially with regard to quantitative characterization of long-term exposures to specific solvents, are needed to advance scientific knowledge on this topic.

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PMID:

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Subject: some articles
Date: Wednesday, January 22, 2014 3:00:33 PM
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Attachments:

Moore renal cell ca risk factors.pdf (516838 Bytes)
Karami TCE kidney cancer OEM 2012.full.pdf (560836 Bytes)
Theis renal ca and smoking BMCCancer 2008.pdf (809240 Bytes)
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smoking and esophageal ca.pdf (339210 Bytes)
veterans oral cancer.pdf (703694 Bytes)
Occupational and Env Exposures with Testic Germ Cell Tumours.pdf (639414 Bytes)

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#)¹, [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Author information

Abstract

OBJECTIVE:

To evaluate the association between exposure to chlorinated solvents and cancer.

METHODS:

We conducted a case-control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer.

RESULTS:

The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS:

There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

PubMed

Abstract

Full text links



See 1 citation found by title matching your search:

Lancet. 2014 Aug 30;384(9945):755-65. doi: 10.1016/S0140-6736(14)60892-8. Epub 2014 Aug 13.

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults.

Bhaskaran K¹, Douglas I², Forbes H², dos-Santos-Silva I², Leon DA², Smeeth L³.

Author information

Abstract

BACKGROUND: High **body-mass index** (BMI) predisposes to several **site-specific cancers**, but a large-scale systematic and detailed characterisation of patterns of **risk** across all common **cancers** adjusted for potential confounders has not previously been undertaken. We aimed to investigate the links between BMI and the most common **site-specific cancers**.

METHODS: With primary care data from individuals in the Clinical Practice Research Datalink with BMI data, we fitted Cox models to investigate associations between BMI and **22** of the most common **cancers**, adjusting for potential confounders. We fitted linear then non-linear (spline) models; investigated effect modification by sex, menopausal status, smoking, and age; and calculated population effects.

FINDINGS: 5·24 million individuals were included; 166,955 developed **cancers** of interest. BMI was associated with 17 of **22 cancers**, but effects varied substantially by site. Each 5 kg/m² increase in BMI was roughly linearly associated with **cancers** of the uterus (hazard ratio [HR] 1·62, 99% CI 1·56-1·69; p<0·0001), gallbladder (1·31, 1·12-1·52; p<0·0001), kidney (1·25, 1·17-1·33; p<0·0001), cervix (1·10, 1·03-1·17; p=0·00035), thyroid (1·09, 1·00-1·19; p=0·0088), and leukaemia (1·09, 1·05-1·13; p≤0·0001). BMI was positively associated with liver (1·19, 1·12-1·27), colon (1·10, 1·07-1·13), ovarian (1·09, 1·04-1·14), and postmenopausal breast **cancers** (1·05, 1·03-1·07) overall (all p<0·0001), but these effects varied by underlying BMI or individual-level characteristics. We estimated inverse associations with prostate and premenopausal breast cancer **risk**, both overall (prostate 0·98, 0·95-1·00; premenopausal breast cancer 0·89, 0·86-0·92) and in never-smokers (prostate 0·96, 0·93-0·99; premenopausal breast cancer 0·89, 0·85-0·94). By contrast, for lung and oral cavity cancer, we observed no association in never smokers (lung 0·99, 0·93-1·05; oral cavity 1·07, 0·91-1·26): inverse associations overall were driven by current smokers and ex-smokers, probably because of residual confounding by smoking amount. Assuming causality, 41% of uterine and 10% or more of gallbladder, kidney, liver, and colon **cancers** could be attributable to excess weight. We estimated that a 1 kg/m² population-wide increase in BMI would result in 3790 additional annual UK patients developing one of the ten **cancers** positively associated with BMI.

INTERPRETATION: BMI is associated with cancer **risk**, with substantial population-level effects. The heterogeneity in the effects suggests that different mechanisms are associated with different cancer sites and different patient subgroups.

FUNDING: National Institute for Health Research, Wellcome Trust, and Medical Research Council.

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Comment in

The obesity and cancer link. [Ann Oncol. 2015]

Overweight and obesity are linked to 10 common **cancers** and more than 12,000 **UK** cases. [BMJ. 2014]

[Fat people have common **cancers**]. [MMW Fortschr Med. 2014]

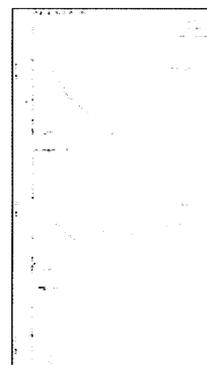
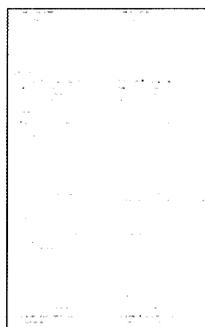
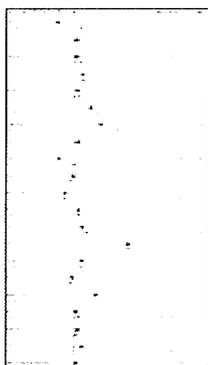
Obesity: a certain and avoidable cause of cancer. [Lancet. 2014]

[Obesity and cancer]. [Soins. 2014]

PMID: 25129328 [PubMed - indexed for MEDLINE] PMCID: PMC4151483 **Free PMC Article**



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Ann Oncol. 2013 Mar;24(3):807-16. doi: 10.1093/annonc/mds508. Epub 2012 Oct 26.

Alcohol drinking and all cancer mortality: a meta-analysis.

Jin M¹, Cai S, Guo J, Zhu Y, Li M, Yu Y, Zhang S, Chen K.

Author information

Abstract

BACKGROUND: Epidemiological studies have suggested an inconsistent relationship between **alcohol drinking** and risk of all **cancer mortality**. As far as we know, no **meta-analysis** has been conducted to explore this issue.

PATIENTS AND METHODS: We carried out a PubMed search to find relevant articles published before April 2012 in English. Categorical and dose-response meta-analyses were conducted to identify the impact of **alcohol drinking** on all **cancer mortality**. Potential sources of heterogeneity were detected by meta-regression and stratification analyses. Sensitivity and cumulative meta-analyses were also carried out.

RESULTS: Eighteen independent cohort studies met the inclusion criteria. Compared with non/occasional drinkers, the pooled relative risks (RRs) were 0.91 [95% confidence interval (CI) 0.89-0.94] for light, 1.02 (95% CI 0.99-1.06) for moderate, and 1.31 (95% CI 1.23-1.39) for heavy drinkers. Former drinkers presented a higher risk (RR = 1.32, 95% CI 1.15-1.50) than current drinkers (RR = 1.06, 95% CI 0.98-1.16). There was a J-shaped relationship between all **cancer mortality** and **alcohol** consumption in males but not in females.

CONCLUSIONS: This **meta-analysis** confirms the health hazards of heavy **drinking** (≥ 50 g/day) and benefits of light **drinking** (≤ 12.5 g/day). Large-sample, well-designed, prospective epidemiological studies, especially on heavy **drinking** among women, should be developed in future.

Comment in

Re: light **drinking** has positive public health consequences. [*Ann Oncol.* 2013]

Heavy consumption of **alcohol**: a risk factor for **cancer** deaths? [*Natl Med J India.* 2013]

Light **drinking** has positive public health consequences. [*Ann Oncol.* 2013]

PMID: 23104725 [PubMed - indexed for MEDLINE] [Free full text](#)



Publication Types, MeSH Terms

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Cancer Res. 2014 Jun 1;74(11):3076-83. doi: 10.1158/0008-5472.CAN-13-2430.

Breast cancer risk after occupational solvent exposure: the influence of timing and setting.

Ekenqa CC¹, Parks CG², D'Aloisio AA², DeRoo LA³, Sandler DP².

Author information

Abstract

Organic solvents are ubiquitous in **occupational** settings where they may contribute to risks for carcinogenesis. However, there is limited information on organic solvents as human **breast** carcinogens. We examined the relationship between **occupational exposure** to solvents and **breast cancer** in a prospective study of 47,661 women with an **occupational** history in the Sister Study cohort. **Occupational solvent exposure** was categorized using self-reported job-specific **solvent** use collected at baseline. Multivariable Cox regression analyses were used to assess **breast cancer risk**, adjusting for established **breast cancer risk** factors. A total of 1,798 women were diagnosed with **breast cancer** during follow-up, including 1,255 invasive cases. Overall the **risk** of invasive **breast cancer** was not associated with lifetime **exposure** to solvents [HR, 1.04; 95% confidence interval (CI), 0.88-1.24]. Parous women who worked with solvents before their first full-term birth had an increased **risk** of estrogen receptor-positive invasive **breast cancer** compared with women who never worked with solvents (HR, 1.39; 95% CI, 1.03-1.86). A significantly elevated **risk** for estrogen receptor-positive invasive **breast cancer** was associated with **solvent exposure** among clinical laboratory technologists and technicians (HR, 2.00; 95% CI, 1.07-3.73). **Occupational exposure** to solvents before first birth, a critical period of **breast** tissue differentiation, may result in increased vulnerability for **breast cancer**. Our findings suggest a need for future studies in this area to focus on **exposure** time windows and **solvent** types in different **occupational** settings.

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PMID: 24879566 [PubMed - indexed for MEDLINE] PMCID: PMC4059370 [Available on 2015-06-01]



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JAMA Internal Med

JAMA Intern Med. 2014 Dec;174(12):1922-8. doi: 10.1001/jamainternmed.2014.5219.

Estimation of cigarette smoking-attributable morbidity in the United States.

Rostron BL¹, Chang CM¹, Pechacek TF².

Author information

Abstract

IMPORTANCE: Cigarette smoking has been found to harm nearly every bodily organ and is a leading cause of preventable disease, but current estimates of **smoking-attributable morbidity** by condition for the **United States** are generally unavailable.

OBJECTIVE: To estimate the burden of major medical conditions attributable to **cigarette** smoking in the **United States**.

DESIGN, SETTING, AND PARTICIPANTS: The disease burden of smoking was estimated using population-attributable risk calculations, taking into account the uncertainty of estimates. Population estimates came from 2009 US Census Bureau data and smoking prevalence, disease prevalence, and disease relative risk estimates came from National Health Interview Survey data for surveyed adults from 2006 through 2012. National Health and Nutrition Examination Survey spirometry data obtained from medical examination of surveyed adults from 2007 through 2010 was used to adjust for underreporting of chronic obstructive pulmonary disease.

EXPOSURES: Smoking status was assessed from self-reported National Health Interview Survey data.

MAIN OUTCOMES AND MEASURES: The number of adults 35 years and older who had had a major **smoking-attributable** disease by sex and condition and the total number of these conditions were estimated for the **United States** in 2009.

RESULTS: Using National Health Interview Survey data, we estimated that 6.9 million (95% CI, 6.5-7.4 million) US adults had had a combined 10.9 million (95% CI, 10.3-11.5 million) self-reported **smoking-attributable** medical conditions. Using chronic obstructive pulmonary disease prevalence estimates obtained from National Health and Nutrition Examination Survey self-reported and spirometry data, we estimated that US adults had had a combined 14.0 million (95% CI, 12.9-15.1 million) **smoking-attributable** conditions in 2009.

CONCLUSIONS AND RELEVANCE: We estimate that US adults have had approximately 14 million major medical conditions that were attributable to smoking. This figure is generally conservative owing to the existence of other diseases and medical events that were not included in these estimates. **Cigarette** smoking remains a leading cause of preventable disease in the **United States**, underscoring the need for continuing and vigorous smoking-prevention efforts.

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Environ Health. 2014 Feb 19;13(1):10. doi: 10.1186/1476-069X-13-10.



Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

Bove FJ¹, Ruckart PZ, Maslia M, Larson TC.

Author information

Abstract

BACKGROUND: Two drinking water systems at U.S. Marine Corps Base **Camp Lejeune**, North Carolina were contaminated with solvents during 1950s-1985.

METHODS: We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at **Camp Lejeune** or **Camp Pendleton**, California during this period. **Camp Pendleton's** drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between **Camp Lejeune** (N = 154,932) and **Camp Pendleton** (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the **Camp Lejeune** cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS: There were 8,964 and 9,365 deaths respectively, in the **Camp Lejeune** and **Camp Pendleton** cohorts. Compared to **Camp Pendleton**, **Camp Lejeune** had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the **Camp Lejeune** cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

CONCLUSION: The study found elevated HRs at **Camp Lejeune** for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposures at the base.

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See 1 citation found by title matching your search:

Environ Health Perspect. 2014 Apr;122(4):325-34. doi: 10.1289/ehp.1307359. Epub 2014 Feb 14.

Human health effects of tetrachloroethylene: key findings and scientific issues.

Guyton KZ¹, Hogan KA, Scott CS, Cooper GS, Bale AS, Kopylev L, Barone S, Makris SL, Glenn B, Subramaniam RP, Gwinn MR, Dzubow RC, Chiu WA.

Author information

Abstract

BACKGROUND: The U.S. Environmental Protection Agency (EPA) completed a toxicological review of **tetrachloroethylene** (perchloroethylene, PCE) in February 2012 in support of the Integrated Risk Information System (IRIS).

OBJECTIVES: We reviewed **key findings** and **scientific issues** regarding the **human health effects** of PCE described in the U.S. EPA's Toxicological Review of **Tetrachloroethylene** (Perchloroethylene).

METHODS: The updated assessment of PCE synthesized and characterized a substantial database of epidemiological, experimental animal, and mechanistic studies. **Key scientific issues** were addressed through modeling of PCE toxicokinetics, synthesis of evidence from neurological studies, and analyses of toxicokinetic, mechanistic, and other factors (tumor latency, severity, and background rate) in interpreting experimental animal cancer **findings**. Considerations in evaluating epidemiological studies included the quality (e.g., specificity) of the exposure assessment methods and other essential design features, and the potential for alternative explanations for observed associations (e.g., bias or confounding).

DISCUSSION: Toxicokinetic modeling aided in characterizing the complex metabolism and multiple metabolites that contribute to PCE toxicity. The exposure assessment approach—a **key** evaluation factor for epidemiological studies of bladder cancer, non-Hodgkin lymphoma, and multiple myeloma—provided suggestive evidence of carcinogenicity. Bioassay data provided conclusive evidence of carcinogenicity in experimental animals. Neurotoxicity was identified as a sensitive noncancer **health** effect, occurring at low exposures: a conclusion supported by multiple studies. Evidence was integrated from **human**, experimental animal, and mechanistic data sets in assessing adverse **health effects** of PCE.

CONCLUSIONS: PCE is likely to be carcinogenic to humans. Neurotoxicity is a sensitive adverse **health** effect of PCE.

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Environ Health. 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.



Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

Bove FJ¹, Ruckart PZ, Maslia M, Larson TC.

Author information

Abstract

BACKGROUND: Two drinking water systems at U.S. Marine Corps Base **Camp Lejeune**, North Carolina were contaminated with solvents during 1950s-1985.

METHODS: We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at **Camp Lejeune** during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 **Camp Pendleton** workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between **Camp Lejeune** and **Camp Pendleton** workers and assess the effects of estimated cumulative contaminant exposures within the **Camp Lejeune** cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at **Camp Lejeune**. The confidence interval (CI) indicated precision of effect estimates.

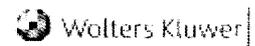
RESULTS: Compared to **Camp Pendleton**, **Camp Lejeune** workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the **Camp Lejeune** cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION: The study found elevated HRs in the **Camp Lejeune** cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the **Camp Lejeune** cohort died by end of follow-up, producing small numbers of cause-specific deaths and wide CIs. Additional follow-up would be necessary to comprehensively assess drinking water exposure effects at the base.

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[J Occup Environ Med.](#) 2013 Feb;55(2):198-208. doi: 10.1097/JOM.0b013e3182728eab.

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#)¹, [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Author information

Abstract

OBJECTIVE: To evaluate the association between **exposure to chlorinated solvents** and cancer.

METHODS: We conducted a **case-control study** of **occupational exposures** and cancer in **Montreal, Quebec, Canada**, including 3730 cancer cases and 533 population controls.

Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six **chlorinated solvents** with 11 sites of cancer.

RESULTS: The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS: There was little evidence of associations between **chlorinated solvents** and cancer. Limited power precludes strong inferences about absence of **risk**. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

PMID: 23147555 [PubMed - indexed for MEDLINE]



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QJM. 2015 Mar;108(3):205-12. doi: 10.1093/qjmed/hcu195. Epub 2014 Sep 9.

The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis.

Cheungpasitporn W¹, Thongprayoon C², O'Corragain OA², Edmonds PJ², Ungprasert P², Kittanamongkolchai W², Erickson SB².

Author information

Abstract

BACKGROUND: The objective of this **meta-analysis** was to evaluate the association between a history of **kidney stones** and **kidney cancer**.

METHODS: A literature search was performed from inception until June 2014. Studies that reported odds ratios or hazard ratios comparing the **risk** of renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of the upper urinary tract in **patients** with the history of **kidney stones** versus those without the history of **kidney stones** were included. Pooled **risk** ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

RESULT: Seven studies were included in our analysis to assess the association between a history of **kidney stones** and RCC. The pooled RR of RCC in **patients** with **kidney stones** was 1.76 (95% CI, 1.24-2.49). The subgroup analysis found that the history of **kidney stones** was associated with increased RCC **risk** only in males (RR, 1.41 [95% CI, 1.11-1.80]), but not in females (RR, 1.13 [95% CI, 0.86-1.49]). Five studies were selected to assess the association between a history of **kidney stones** and TCC. The pooled RR of TCC in **patients** with **kidney stones** was 2.14 (95% CI, 1.35-3.40).

CONCLUSION: Our study demonstrates a significant increased **risk** of RCC and TCC in **patients** with prior **kidney stones**. However, the increased **risk** of RCC was noted only in male **patients**. This finding suggests that a history of **kidney stones** is associated with **kidney cancer** and may impact clinical management and **cancer** surveillance.

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PMID: 25208892 [PubMed - in process]



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((Trichloroethylene[Title] AND cancer: epidemiologic evidence[Title]

Abstract

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Environ Health Perspect. 2000 May;108 Suppl 2:161-76.

Trichloroethylene and cancer: epidemiologic evidence.

Wartenberg D¹, Reyner D, Scott CS.

Author information

Abstract

Trichloroethylene is an organic chemical that has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins. It has been shown to cause liver and kidney **cancer** in experimental animals. This article reviews over 80 published papers and letters on the **cancer** epidemiology of people exposed to **trichloroethylene**. Evidence of excess **cancer** incidence among occupational cohorts with the most rigorous exposure assessment is found for kidney **cancer** (relative risk [RR] = 1.7, 95% confidence interval [CI] 1.1-2.7), liver **cancer** (RR = 1.9, 95% CI(1.0-3.4), and non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9-2.3) as well as for cervical **cancer**, Hodgkin's disease, and multiple myeloma. However, since few studies isolate **trichloroethylene** exposure, results are likely confounded by exposure to other solvents and other risk factors. Although we believe that solvent exposure causes **cancer** in humans and that **trichloroethylene** likely is one of the active agents, we recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk.

Comment in

Errors in TCE analysis. [Environ Health Perspect. 2001]

The a posteriori probability of a kidney **cancer** cluster attributed to **trichloroethylene** exposure. [Environ Health Perspect. 2002]

Carcinogenicity of **trichloroethylene**. [Environ Health Perspect. 2002]

Meta-analyses of TCE carcinogenicity. [Environ Health Perspect. 2000]

PMID: 10807550 [PubMed - indexed for MEDLINE] PMCID: PMC1637753 **Free PMC Article**



Publication Types, MeSH Terms, Substances, Grant Support

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Secondary malignancies following radiotherapy for prostate cancer.

[Sountoulides P¹](#), [Koletsas N](#), [Kikidakis D](#), [Paschalidis K](#), [Sofikitis N](#).

[Author information](#)

Abstract

Human exposure to sources of radiation as well as the use of radiation-derived therapeutic and diagnostic modalities for medical reasons has been ongoing for the last 60 years or so. The carcinogenetic effect of radiation either due to accidental exposure or use of radiation for the treatment of cancer has been undoubtedly proven during the last decades. The role of radiation therapy in the treatment of patients with prostate cancer is constantly increasing as less-invasive treatment modalities are sought for the management of this widely, prevalent disease. Moreover the wide adoption of screening for prostate cancer has led to a decrease in the average age that patients are diagnosed with prostate cancer. Screening has also resulted in the diagnosis of low-grade, less-aggressive prostate cancers which would probably never lead to complications or death from the disease. Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer. Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal. Care should be given to the long-term follow up of patients under radiation therapy for prostate cancer, while the indications for its use in certain cases should be reconsidered.

KEYWORDS:

brachytherapy; prostate cancer; radiation therapy; secondary bladder cancer

Secondary malignancies following radiotherapy for prostate cancer.

[Sountoulides P¹](#), [Koletsas N](#), [Kikidakis D](#), [Paschalidis K](#), [Sofikitis N](#).

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Abstract

Human exposure to sources of radiation as well as the use of radiation-derived therapeutic and diagnostic modalities for medical reasons has been ongoing for the last 60 years or so. The carcinogenetic effect of radiation either due to accidental exposure or use of radiation for the treatment of cancer has been undoubtedly proven during the last decades. The role of radiation therapy in the treatment of patients with prostate cancer is constantly increasing as less-invasive treatment modalities are sought for the management of this widely, prevalent disease. Moreover the wide adoption of screening for prostate cancer has led to a decrease in the average age that patients are diagnosed with prostate cancer. Screening has also resulted in the diagnosis of low-grade, less-aggressive prostate cancers which would probably never lead to complications or death from the disease. Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer. Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal. Care should be given to the long-term follow up of patients under radiation therapy for prostate cancer, while the indications for its use in certain cases should be reconsidered.

KEYWORDS:

brachytherapy; prostate cancer; radiation therapy; secondary bladder cancer

FULL TEXT

[Int Arch Occup Environ Health](#). 2006 Mar;79(3):251-8. Epub 2005 Oct 12.

Reproductive history, occupational exposures, and thyroid cancer risk among women textile workers in Shanghai, China.

[Wong EY¹](#), [Ray R](#), [Gao DL](#), [Wernli KJ](#), [Li W](#), [Fitzgibbons ED](#), [Feng Z](#), [Thomas DB](#), [Checkoway H](#).

Author information

Abstract

OBJECTIVES:

Thyroid cancer risk has been previously associated with increased age at first pregnancy and history of miscarriage. Occupational risk factors for thyroid cancer, with the exception of radioactive iodine, have not been well investigated. We conducted a case-cohort study nested in a cohort of 267,400 female textile workers in Shanghai, China, who had been followed for cancer incidence during 1989-1998.

METHODS:

The analysis included 130 incident thyroid cases and 3,187 subcohort non-cases. Reproductive history was determined by questionnaire at baseline. Historical exposures were reconstructed from work history and information on factory processes and exposures. Cox proportional hazards analysis was performed to estimate hazard ratios (HR) for reproductive factors and occupational exposures.

RESULTS:

Associations were observed between thyroid cancer and employment in jobs with 10 or more years of benzene exposure (HR 6.43, 95% CI: 1.08, 38) and formaldehyde exposure (HR 8.33, 95% CI: 1.16, 60). Administration workers also had an increased risk (HR 1.56, 95% CI: 1.08, 2.25). No associations between examined reproductive factors and thyroid cancer were observed in this study.

CONCLUSIONS:

Despite statistically imprecise risk estimates, the findings suggest potential associations with some occupational chemical exposures in this cohort of textile workers.

Brownson R, Reif J, Keefe T, Ferguson S, Pritzl J. Risk Factors for Adenocarcinoma of the Lung. Am J Epi 125(1): 25-34.

RISK FACTORS FOR ADENOCARCINOMA OF THE LUNG

1. [ROSS C. BROWNSON^{1,3}](#),
2. [JOHN S. REIF¹](#),
3. [THOMAS J. KEEFE¹](#),
4. [STANLEY W. FERGUSON²](#) and
5. [JANE A. PRITZL²](#)

[±](#) Author Affiliations

1. ¹*Department of Microbiology and Environmental Health Colorado State University, Fort Collins, CO.*
 2. ²*Colorado Department of Health Denver, CO.*
 1. ³Reprint requests to Dr. Ross C. Brownson at current address: Cancer Epidemiology and Control Program, Division of Environmental Health and Epidemiology Services, Missouri Department of Health, P. O. Box 1268, Columbia, MO 65205.
- Received March 28, 1986.

Brownson R, Reif J, Keefe T, Ferguson S, Pritzl J. Risk Factors for Adenocarcinoma of the Lung. Am J Epi 125(1): 25-34.

[Oxford Journals](#)

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[American Journal of Epidemiology](#)

[Volume 125, Issue 1](#)

Pp. 25-34.

Abstract

The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979–1982 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio (OR) = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age-and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval (CI) = 0.39–2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% CI = 0.97–5.12). The results suggest the need to develop cell type-specific etiologic hypotheses.

Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490374/>

[Clin Epidemiol.](#) 2012;4:1-11. doi: 10.2147/CLEP.S16747. Epub 2012 Jan 5.

Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates.

[Leitzmann MF](#), [Rohrmann S](#).

Source

Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany.

Abstract

At present, only three risk factors for prostate cancer have been firmly established; these are all nonmodifiable: age, race, and a positive family history of prostate cancer. However, numerous modifiable factors have also been implicated in the development of prostate cancer. In the current review, we summarize the epidemiologic data for age, location, and selected behavioral factors in relation to the onset of prostate cancer. Although the available data are not entirely consistent, possible preventative behavioral factors include increased physical activity, intakes of tomatoes, cruciferous vegetables, and soy. Factors that may enhance prostate cancer risk include frequent consumption of dairy products and, possibly, meat. By comparison, alcohol probably exerts no important influence on prostate cancer development. Similarly, dietary supplements are unlikely to protect against the onset of prostate cancer in healthy men. Several factors, such as smoking and obesity, show a weak association with prostate cancer incidence but a positive relation with prostate cancer mortality. Other factors, such as fish intake, also appear to be unassociated with incident prostate cancer but show an inverse relation with fatal prostate cancer. Such heterogeneity in the relationship between behavioral factors and nonadvanced, advanced, or fatal prostate cancers helps shed light on the carcinogenetic process because it discerns the impact of exposure on early and late stages of prostate cancer development. Inconsistent associations between behavioral factors and prostate cancer risk seen in previous studies may in part be due to uncontrolled detection bias because of current widespread use of prostate-specific antigen testing for prostate cancer, and the possibility that certain behavioral factors are systematically related to the likelihood of undergoing screening examinations. In addition, several genes may modify the study results, but data concerning specific gene-environment interactions are currently sparse. Despite large improvements in our understanding of prostate cancer risk factors in the past two decades, present knowledge does not allow definitive recommendations for specific preventative behavioral interventions.



NIH Public Access

Author Manuscript

Expert Opin Med Diagn. Author manuscript; available in PMC 2013 July 01.

Published in final edited form as:

Expert Opin Med Diagn. 2012 July 1; 6(4): 323–333. doi:10.1517/17530059.2012.686996.

Risk Factors of Follicular Lymphoma

Shuangge Ma, Ph.D [Associate Professor]

School of Public Health, Yale University

Abstract

Introduction—Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of malignancies with over thirty different subtypes. Follicular lymphoma (FL) is the most common form of indolent NHL and the second most common form of NHL overall. It has morphologic, immunophenotypic and clinical features significantly different from other subtypes. Considerable effort has been devoted to the identification of risk factors for etiology and prognosis of FL. These risk factors may advance our understanding of the biology of FL and have an impact on clinical practice.

Areas covered—The epidemiology of NHL and FL is briefly reviewed. For FL etiology and prognosis separately, we review clinical, environmental and molecular (including genetic, genomic, epigenetic and others) risk factors suggested in the literature.

Expert opinion—A large number of potential risk factors have been suggested in recent studies. However, there is a lack of consensus, and many of the suggested risk factors have not been rigorously validated in independent studies. There is a need for large-scale, prospective studies to consolidate existing findings and discover new risk factors. Some of the identified risk factors are successful at the population level. More effective individual-level risk factors and models remain to be identified.

Keywords

Follicular lymphoma; Etiology; Non-Hodgkin lymphoma; Prognosis; Risk factor

1. Introduction

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of malignancies of lymphocyte origin. It usually arises or is present in lymphoid tissues, such as lymph nodes, spleen and

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#)¹, [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Author information

Abstract

OBJECTIVE:

To evaluate the association between exposure to chlorinated solvents and cancer.

METHODS:

We conducted a case-control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer.

RESULTS:

The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS:

There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: RE: RF for follicular lymphoma
Date: Monday, December 22, 2014 2:38:13 PM

Let's add to the library if not already entered.

thanks

From: (b) (6), [REDACTED]
Sent: Monday, December 22, 2014 10:40 AM
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: RF for follicular lymphoma

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384553/pdf/nihms374241.pdf>

From: (b) (6),
To: (b) (6),
Cc: (b) (6),
Subject: RE: Suggested articles for Sharepoint
Date: Monday, March 24, 2014 11:13:19 AM

Additional article also suggested for uploading.

Spechler, S. (2013). Barrett Esophagus and Risk of Esophageal Cancer A Clinical Review. *JAMA* 2013 Aug 14. 310 (6): 627-36. Doi: 10.1001/jama.2013.226450.

From: (b) (6),
Sent: Monday, March 24, 2014 11:09 AM
To: (b) (6),
Cc: (b) (6),
Subject: Suggested articles for Sharepoint

Suggesting the following articles for inclusion on the CLCW Sharepoint:

1. Qureshi, A., Ramsey, D., Kramer, J. Whitehead, L., El-Serag, H. (2013). Occupational Exposure and the Risk of Barrett's Esophagus: A Case-Control Study. *Dig Dis Sci.* 2013 Jul;58(7): 1967-75. Doi: 10.1007/s10620-013-2572-6. Epub 2013 Feb 5.
2. Pohl, H., Wrobel, K., Bojarski, C., Voderholzer, W., Sonnenberg, A., Rosch, T. & Baumgart, D. (2013). Risk Factors in the Development of Esophageal Adenocarcinoma. *The American Journal of Gastroenterology*, 2013 Feb; 108(2): 200-7. Doi: 10.1038/ajg.2012.387. Epub 2012 Dec 18.

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: renal and bladder ca and impaired kidney function
Date: Monday, June 02, 2014 8:20:20 AM

Medscape

Impaired Kidney Function Linked to Higher Renal Cancer Risk

Diedtra Henderson

May 30, 2014

-

Impaired kidney function, as measured by depressed glomerular filtration rates (GFR), is associated with a significantly higher risk of being diagnosed with renal and urothelial cancers, according to a retrospective cohort study.

William T. Lowrance, MD, MPH, from the Huntsman Cancer Institute, University of Utah, Division of Urology, Salt Lake City, and colleagues report the findings of their study, powered by Kaiser Permanente Northern California records for 1.19 million adult patients with no history of cancer and known kidney function, in an article published online May 29 in the Journal of the American Society of Nephrology.

The number of patients diagnosed with chronic kidney disease (CKD) is rising, Dr. Lowrance and coauthors note, with an estimated 11.5% of US residents registering diminished estimated GFR (eGFR) levels. To determine whether the level of kidney function was associated with a higher risk for subsequent cancer, the research team analyzed data from the regional cancer registry, looking for heightened risk for a wide variety of cancers. The patients were more likely to be older, people of color, poorer, and current or former smokers.

The researchers identified 76,809 incident cancers during the 5-plus years of follow-up, with the strongest correlations found between reduced kidney function and increased risk for renal and urothelial cancers.

The researchers adjusted for confounders including age, gender, race, socioeconomic status, comorbidities, proteinuria, hematuria, and body mass index. When eGFR rates ranged between 45 and 59 mL/minute/1.73 m², incident diagnosed renal cancer rate increased by 1.39 (95% confidence interval [CI], 1.22 - 1.58). That hazard ratio inched up to 1.81 (95% CI, 1.51 - 2.17) for eGFR ranging from 30 to 44 mL/minute/1.73 m². And when eGFR dropped to less than 30 mL/minute/1.73 m², risk for renal cancer rate soared to 2.28 (95% CI, 1.78 - 2.92), and there also was a 48% increased rate of urothelial cancer.

The authors found no similarly heightened risk for breast, colorectal, lung, or prostate cancer.

"Our findings reveal the association of CKD and cancer risk is site-specific for renal and urothelial cancers, and does not appear to be associated with an individual's overall cancer risk," the authors

write. Although the study team asserts that their findings could more effectively target cancer screening recommendations for patients with CKD, an accompanying editorial says the cancer associations are "smaller than that generally considered acceptable for screening purposes."

J Am Soc Nephrol. Published online May 29, 2014. Abstract

Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review.

[Moore LE](#), [Wilson RT](#), [Campleman SL](#).

Author information

Abstract

Malignant kidney tumors account for approximately 2% of all new primary cancer cases diagnosed in the United States, with an estimated 30,000 cases occurring annually. Although a variety of agents, chemical and biological, have been implicated as causal agents in the development of renal cell carcinoma (RCC), the etiology remains enigmatic. The strongest association has been developed between cigarette smoking and renal cancer however consistent, positive associations between RCC and obesity, diabetes, and hypertension have also been reported. In addition, more recent investigations of familial kidney cancer syndromes indicate that a strong genetic component contributes to RCC development. Several genes have been identified through investigation of familial kidney cancer syndromes. This review article describes recent trends in RCC incidence and the currently identifiable etiological causes that account for approximately half of the RCC cases diagnoses. The remainder of this review then focuses on additional risk factors that have thus far not been well examined but may be helpful in explaining the increasing incidence trends and the geographic or racial variation observed nationally and worldwide.

Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study.

[Theis RP](#), [Dolwick Grieb SM](#), [Burr D](#), [Siddiqui T](#), [Asal NR](#).

[Author information](#)

Abstract

BACKGROUND:

Kidney and renal pelvis cancers account for 4% of all new cancer cases in the United States, among which 85% are renal cell carcinomas (RCC). While cigarette smoking is an established risk factor for RCC, little is known about the contribution of environmental tobacco smoke (ETS) to RCC incidence. This study assesses the role of smoking and ETS on RCC incidence using a population-based case-control design in Florida and Georgia.

METHODS:

Incident cases (n = 335) were identified from hospital records and the Florida cancer registry, and population controls (n = 337) frequency-matched by age (+/- 5 years), gender, and race were identified through random-digit dialing. In-person interviews assessed smoking history and lifetime exposure to ETS at home, work, and public spaces. Home ETS was measured in both years and hours of exposure. Odds ratios and 95% confidence intervals were calculated using logistic regression, controlled for age, gender, race, and BMI.

RESULTS:

Cases were more likely to have smoked 20 or more pack-years, compared with never-smokers (OR: 1.35, 95% CI: 0.93 - 1.95). A protective effect was found for smoking cessation, beginning with 11-20 years of cessation (OR: 0.39, 95% CI: 0.18-0.85) and ending with 51 or more years of cessation (OR: 0.11, 95% CI: 0.03-0.39) in comparison with those having quit for 1-10 years. Among never-smokers, cases were more likely to report home ETS exposure of greater than 20 years, compared with those never exposed to home ETS (OR: 2.18; 95% CI: 1.14-4.18). Home ETS associations were comparable when measured in lifetime hours of exposure, with cases more likely to report 30,000 or more hours of home ETS exposure (OR: 2.37; 95% CI: 1.20-4.69). Highest quartiles of combined home/work ETS exposure among never-smokers, especially with public ETS exposure, increased RCC risk by 2 to 4 times.

CONCLUSION:

These findings confirm known associations between smoking and RCC and establish a potential etiologic role for ETS, particularly in the home. Differences in methods of retrospective measurement of lifetime smoking and ETS exposure may contribute to discrepancies in measures of associations across studies, and should be addressed in future research.

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: RE: CLCW: Library
Date: Sunday, February 22, 2015 9:46:42 PM

Thanks, (b) (6), .
(b) (6), chat?
(6)

As I'm struggling with these I've created myself a directory at home with disease, subdisease, the most recent case anonymized, and specific references. So, for example, I have subfolders for squamous and for adeno ca of the esophagus. Lets chat.

From: (b) (6), [REDACTED]
Sent: Tuesday, February 17, 2015 12:36 PM
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: CLCW: Library

(b) (6), [REDACTED]: Thank you for your comments and suggestions concerning improving the organization of the SharePoint Library. I look forward to receiving input from you and (b) (6), [REDACTED] for improvements.

(b) (6), [REDACTED]
Office of Disability & Medical Assessment
Department of Veterans Affairs
810 Vermont Ave NW
Washington, DC 20420
202.461.1703 office
(b) (6), [REDACTED] blackberry



Please consider your environmental responsibility before printing this e-mail & any documents

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: RE: cml 6.1.2014
Date: Tuesday, June 17, 2014 11:56:52 AM

Hi guys, there is evidence that CML is related to obesity (2—3 fold increase in rates);

FYI

(b) (6), [REDACTED]

Cancer Epidemiol Biomarkers Prev. 2009 May ; 18(5): 1501–1506. doi:10.1158/1055-9965.EPI-09-0028.

Obesity, Weight Gain, and Risk of Chronic Myeloid Leukemia

Sara S. Strom, Yuko Yamamura, Hagop M. Kantarjian, and Jorge E. Cortes-Franco

Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas (SSS, YY); Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas (HK, JC)

From: (b) (6), [REDACTED]
Sent: Monday, June 16, 2014 7:17 PM
To: VHA CO CLCW SME
Subject: cml 6.1.2014

Fyi CML

From: (b) (6),
To: (b) (6),
Cc: (b) (6), (b) (6),
Subject: RE: FYI October 2014 draft ATSDR TOXICOLOGIC PROFILES are available online fo PCE and TCE::
Date: Wednesday, May 06, 2015 11:50:47 AM

I will look into this further:

The Mattei article seems to be an abstract or a publication of an oral presentation: It is not likely peer reviewed and is therefore suspect;

(b) (6)

0139 OCCUPATIONAL EXPOSURE TO CHLORINATED
SOLVENTS AND LUNG CANCER: RESULTS FROM THE
ICARE STUDY

1Francesca Mattei, 1Florence Guida, 1Marie Sanchez, 1Sylvie C n e, 2Jo lle F votte,

3Daniele Luce, 1Isabelle St cker. 1Inserm, CESP Centre for Research in
Epidemiology and

Population Health, U1018, Environmental Epidemiology of Cancer Team, Villejuif,

France; 2Inserm, CESP Centre for Research in Epidemiology and Population Health,

U1018, Epidemiology of Occupational and Social Determinants of Health Team,
Villejuif,

France; 3UMRESTTE (Unit  Mixte de Recherche  pid miologique Et de Surveillance en

Transport, Travail Et Environnement), University Claude Bernard, Lyon, France

10.1136/oemed-2014-102362.52

Objectives We aimed to investigate the role of occupational
exposure to chlorinated solvents in the aetiology of lung cancer.

Method ICARE is a multicenter population-based case-control
study conducted in France between 2001 and 2006. Information
on subjects lifelong work history was collected by face to face
interviews using standardised questionnaires. Occupational exposures

were assessed using job-exposure matrices (JEM) relative to five chlorinated solvents including trichloroethylene (TCE), methylene chloride, perchloroethylene (PER), chloroform and carbon tetrachloride. Solvents were studied separately and since overlapping among exposures analyses for combined solvents exposure were performed. In the questionnaire, subjects also had to report if they were exposed to TCE or other substances (PER was among them). Odds ratios (ORs) were computed using unconditional logistic regression models adjusted for classical risk factors.

Results A total of 2926 cases (2276 men and 650 women) and 3555 controls (2780 men and 775 women) were included. A statistically significant positive association for lung cancer risk was observed in both men (OR 1.47, 95% CI: 1.00–2.17) and in women (OR 3.86, 95% CI: 1.36 -11.01) exposed to PER combined with TCE and/or methylene chloride. In contrast, no statistically significant associations were found for TCE or other solvent combinations. Finally for subjects, who reported the exposure to PER, the ORs were 3.25 (95% CI: 1.23, 8.59) and 3.12 (95% CI: 0.50, 19.28) among men and women respectively.

Conclusions The results of this study suggest that PER alone or in combination with TCE and/or methylene chloride may increase the risk of lung cancer.

From: (b) (6), [REDACTED]
Sent: Wednesday, May 06, 2015 6:25 AM
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

What do you guys think about these studies? Do we know anything about the degree of exposure? I would think we'd want to include that.

(b) (6),

Compensation & Pension

Environmental Health Clinician

DMA Subject Matter Expert Panel

VISN 11 Primary MRO

Ann Arbor VAMC

734-769-7100 x (b) (6), (office)

(b) (6), (cell)

(b) (6),

From: (b) (6),

Sent: Tuesday, May 05, 2015 4:02 PM

To: (b) (6),

Cc:

Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

Do you want to study or use the below?

A multicenter case-control study in France in 2014 sampling occupational exposure to PCE and TCE found a positive association for lung cancer risk in men (OR 1.47, 95% CI: 1.00-2.17) (26), and after adjustment for exposure to asbestos, they observed a positive, significant association with lung cancer for men and women exposed to a combination of perchloroethylene (PCE), and trichloroethylene (27). Two case-control studies in Quebec found indications of an increased risk of lung cancer associated with occupational exposure to perchloroethylene (OR(any exposure) 2.5, 95% CI 1.2 to 5.6; OR(substantial exposure) 2.4, 95% CI 0.8 to 7.7) (28)

26; Occup Environ Med. 2014 Jun;71 Suppl 1:A17. doi: 10.1136/oemed-2014-102362.52.

0139 Occupational exposure to chlorinated solvents and lung cancer: results from the ICARE study.

Mattei F1, Guida F1, Sanchez M1, C  n  e S1, F  votte J2, Luce D3, St  cker I1.

27; Occup Environ Med. 2014 Oct;71(10):681-9. doi: 10.1136/oemed-2014-102182. Epub 2014 Jul 11.

Exposure to chlorinated solvents and lung cancer: results of the ICARE study.

Mattei F1, Guida F1, Matrat M2, Cenée S1, Cyr D3, Sanchez M1, Radoi L4, Menvielle G5, Jellouli F6, Carton M3, Bara S7, Marrer E8, Luce D9, Stücker I1.

28: Occup Environ Med. 2013 Feb;70(2):81-5. doi: 10.1136/oemed-2012-101155. Epub 2012 Oct 26.

Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montreal, Canada. Vizcaya D1, Christensen KY, Lavoué J, Siemiatycki J.

From: (b) (6), [REDACTED]
Sent: Tuesday, May 05, 2015 12:42 PM
To: (b) (6), [REDACTED].
Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

You don't need to look at the lung cancer template. I fixed all the references and some other things. Unless you want to but know that I did make some changes.

From: (b) (6), [REDACTED].
Sent: Tuesday, May 05, 2015 3:37 PM
To: (b) (6), [REDACTED]
Subject: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

These are still in draft form, and not officially sanctioned, but check them out:

<http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

<http://www.atsdr.cdc.gov/toxprofiles/tp18.pdf>

From: (b) (6),
To: (b) (6),
Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::
Date: Tuesday, May 05, 2015 4:13:35 PM

This is the someone I sent you a month ago..

From: (b) (6), .

Sent: Tuesday, April 14, 2015 12:33 PM

To: (b) (6),

Subject: RE: <http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

I think this document is useful for reading but cannot be used as a reference as 1) it is "Draft" form and 2) there are now many more recent documents which have a different perspective on this, such as USDHHS RoC.

(b)
(6)

From: (b) (6),

Sent: Tuesday, May 05, 2015 2:37 PM

To: (b) (6),

Subject: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

These are still in draft form, and not officially sanctioned, but check them out:

<http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

<http://www.atsdr.cdc.gov/toxprofiles/tp18.pdf>

From: (b) (6),
To: (b) (6),
Subject: RE: good article for the sharepoint: breast ca and environmental exposures
Date: Monday, May 12, 2014 12:45:23 PM

<http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2014/5/ehp.1307455.pdf>

From: (b) (6),
Sent: Monday, May 12, 2014 5:39 AM
To: (b) (6),
Subject: RE: CLCW: vacation

Thanks (b) (6),

I will make note of it. I hope you are planning to do something fun.

(b) (6)

From: (b) (6),
Sent: Friday, May 09, 2014 11:24 AM
To: (b) (6),
Subject: RE: CLCW: vacation

Hi (b) (6),

I will be on vacation May 26-June 2.

Thanks

(b) (6)

From: (b) (6),
Sent: Thursday, May 08, 2014 11:50 AM
To: (b) (6),
Cc: (b) (6),
Subject: CLCW: data extraction.

(b) (6),

I want to have (b) (6) start working a few of the cases in your queue. I am giving him : S6110 prostate cancer, B0664 (b) (6) bladder cancer. He will provide the data extraction file via email upon completion.
Thanks,

(b) (6),
Office of Disability & Medical Assessment
Department of Veterans Affairs
810 Vermont Ave. NW

Washington, DC 20420
202.461.1703 office
(b) (6), blackberry



Please consider your environmental responsibility before printing this e-mail & any documents

PARKINSON'S DISEASE AND ORGANIC SOLVENTS

Human studies: epidemiology

Trichloroethylene (TCE) has been widely used in the workplace, in drycleaning and degreasing, and in environmental exposures, including in typewriter fluids, adhesives, paints, carpet cleaners, spot removers. In 1977 FDA banned its use as an anesthetic and decaffeinating agent.

Since 1981, a robust body of literature has explored the relationship between exposure to organic solvents and Parkinson's disease (PD). At least nine case control studies explored the relationship of solvents, pesticides and PD. Six showed a clear relationship between exposure to organic solvents and the development of disease. The "better" the exposure assessment techniques the more likely associations are to be evident. Two studies failed to distinguish pesticide from solvent exposure and found only elevated risks associated with pesticides. One study failed to find an increased risk of PD after exposure to solvents. Two studies identified interactions between specific genetic markers and the risk for Parkinson's disease

Several formal cohort studies failed to show an increased rate of disease, but PD is only rarely the actual cause of death so that these are not ideal approaches to identifying such relationships. The one cross-sectional study conducted in the workplace identified a strong relationship between the degree of exposure to trichloroethylene and PD or, at lower levels of exposure, early signs of basal ganglion involvement

Mechanistic studies of solvents in general and TCE in particular identified ways that general damage in dopaminergic neurons in the brainstem.

Few studies provide approximate exposure data, much less information allowing precise dose estimates. The most pertinent and useful study was conducted by Goldman et al: the World War II Veterans Twins study. An exposure to TCE of at least one hour a day or 2% of the work day for at least six months was associated with a six-fold risk of disease; PERC in that same exposure definition was associated with a 10-fold risk.

Toxicology, Exposures, and Dose Extrapolation

The Environmental Protection Agency (EPA) considers the amounts that can be "safely" consumed each day for a lifetime without concerns for adverse health effects, i.e., the reference dose (RfD) for each of the agents as listed below. The source is EPA's Integrated Risk Information System (IRIS). That dose incorporates a safety factor listed in column 2. Similarly, the Agency for Toxic Substances and Disease Registry provides No Adverse Observed Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for each of the four contaminants of concern. The table below summarizes the EPA IRIS doses and the associated safety factors. In general, these safety factors take into consideration extrapolation of dose effects from animals to humans and inter-subject variability.

| | RFD (+) in mg/kg/day | Safety factor |
|--------------------------|----------------------|---------------|
| Trichloroethylene (TCE) | 0.0005 | 1,000 |
| Perchloroethylene (PERC) | 0.006 | 1,000 |
| Benzene | 0.004 | 300 |
| Vinyl Chloride | 0.003 | 1,000 |

*: animal data, as no human data are available

For Trichloroethylene, acute levels of interest for neurological outcomes as NOAEL and LOAELs are, respectively, 100 vs 200 mg/kg/day. For intermediate duration, a LOAEL of 200 mg/kg/day exists for “less serious effects, but no NOAEL exists. No data are available for chronic ingestion exposures.

For Perchloroethylene, acute levels of interest for neurological outcomes exist for humans only as LOAEL at 100 mg/kg/day. No animal data and no data on intermediate or chronic doses associated with adverse neurological exist.

For Benzene, 10 mg/kg/day and 30 mg/kg/day represent respectively NOAEL and LOAELs for intermediate duration (15 – 365 days) of doses associated with adverse neurological exist. Chronic exposure to 100 mg/kg/day was not associated with adverse neurological health effects.

For Vinyl chloride,

Use of the calculation spreadsheet provides an estimate of the likely doses and sets them into a relation with RfD and Toxprofile specific data

Competing exposures

Additional pertinent considerations include other known risk factors for Parkinson’s disease. Smoking is known to be protective, with consistent relative risks of 0.5 – 0.6; similarly, coffee drinking reduces the risk. No explanation exists for these two factors.

Several other exposures are known to increase the risk of Parkinson’s disease, most prominently, managanese, carbon monoxide, and pesticides. Carbon monoxide represents a known risk factor, but that onset of disease is relatively prompt after over-exposure. Common events leading to onset include suicidal gestures with combustion products, “accidental” overexposures from use of internal combustion (indoor chain saws, gas-powered buffers, and entrainment of grill exhaust). Manganese in mining and manufacturing and in welding is clearly associated with disease.

Examiners should make efforts to identify an acute onset of disease (CO) or exposures to pesticides (farming, pesticide application) or welding. Smoking may reduce the risk for Parkinson's disease for an unknown reason

PARKSON REFERENCES

CASE-CONTROL STUDIES

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- Ohlson CG, Hogstedt C. Parkinson's disease and occupational exposure to organic solvents, agricultural chemicals and mercury--a case-referent study. *Scand J Work Environ Health*. 1981 Dec;7(4):252-6.
- Goldman SM, Quinlan PJ, Ross GW, Marras C, Meng C, Bhudhikanok GS, Comyns K, Korell M, Chade AR, Kasten M, Priestley B, Chou KL, Fernandez HH, Cambi F, Langston JW, Tanner CM. Solvent exposures and Parkinson disease risk in twins. *Ann Neurol*. 2012 Jun;71(6):776-84. doi: 10.1002/ana.22629
- Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, Mariani CB, Tenconi F, Tesesi S, Zecchinelli A, Leenders KL. Hydrocarbon exposure and Parkinson's disease. *Neurology*. 2000 Sep 12;55(5):667-73. (earlier onset, more severe symptoms)
- McDonnell L, Maginnis C, Lewis S, Pickering N, Antoniak M, Hubbard R, Lawson I, Britton J. Occupational exposure to solvents and metals and Parkinson's disease. *Neurology*. 2003 Sep 9;61(5):716-7.
- Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. *Arch Neurol*. 2009 Sep;66(9):1106-13. (pesticides, no solvents)
- Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, Semple S, Dick S, Counsell C, Mozzoni P, Haites N, Wettinger SB, Mutti A, Otelea M, Seaton A, Söderkvist P, Felice A; Geoparkinson study group. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup Environ Med*. 2007 Oct;64(10):666-72. Epub 2007 Mar 1. (pesticides, no solvents)
- Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT Jr, Checkoway H. Occupational factors and risk of Parkinson's disease: A population-based case-control study. *Am J Ind Med*. 2010 Mar;53(3):217-23. (no effect of solvents)
- Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology*. 1996 May;46(5):1275-84. (solvents by self-report but not by JEM)

COHORT AND CROSS-SECTIONAL STUDIES

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- P Gash DM, Rutland K, Hudson NL, Sullivan PG, Bing G, Cass WA, Pandya JD, Liu M, Choi DY, Hunter RL, Gerhardt GA, Smith CD, Slevin JT, Prince TS. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. *Ann Neurol*. 2008 Feb;63(2):184-92.
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Dick FD, De Palma G, Ahmadi A, Osborne A, Scott NW, Prescott GJ, Bennett J, Semple S, Dick S, Mozzoni P, Haites N, Wettinger SB, Mutti A, Otelea M, Seaton A, Soderkvist P, Felice A; Geoparkinson Study Group. Gene-environment interactions in parkinsonism and Parkinson's disease: the Geoparkinson study. *Occup Environ Med*. 2007 Oct;64(10):673-80. Epub 2007 Apr 20.

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Community Cancer Assessment in Response to Long-Time Exposure to Perchlorate and Trichloroethylene in Drinking Water

Abstract

In response to concerns about cancer stemming from drinking water contaminated with ammonium perchlorate and trichloroethylene, we assessed observed and expected numbers of new cancer cases for all sites combined and 16 cancer types in a California community (1988 to 1998). The numbers of observed cancer cases divided by expected numbers defined standardized incidence ratios (SIRs) and 99% confidence intervals (CI). No significant differences between observed and expected numbers were found for all cancers (SIR, 0.97; 99% CI, 0.93 to 1.02), thyroid cancer (SIR, 1.00; 99% CI, 0.63 to 1.47), or 11 other cancer types. Significantly fewer cases were observed than expected for cancer of the lung and bronchus (SIR, 0.71; 99% CI, 0.61 to 0.81) and the colon and rectum (SIR, 0.86; 0.74 to 0.99), whereas more cases were observed for uterine cancer (SIR, 1.35; 99% CI, 1.06 to 1.70) and skin melanoma (SIR, 1.42; 99% CI, 1.13 to 1.77). These findings did not identify a generalized cancer excess or thyroid cancer excess in this community.

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Subject: Please circulate to SME's
Date: Wednesday, April 02, 2014 11:42:21 AM
Attachments: [EAS](#)

Thanks

From: (b) (6), [redacted]
To: (b) (6), [redacted]
Cc: (b) (6), [redacted]
Subject: RE: Camp Lejeune studies and updates
Date: Monday, December 09, 2013 8:24:52 PM
Attachments: [EAS](#)

The occ med list serv interpretation you mentioned below seems to relate to an earlier survey of parents that took place in 1999-2002.

There are updates on the ATSDR website of a more recent survey of parents that started in 2005:

“Page last updated: December 5, 2013”

[“Birth Defects and Childhood Cancers Study
<<http://www.atsdr.cdc.gov/sites/lejeune/update.html>>](#)

The current study is entitled *Exposure to Volatile Organic Compounds in Drinking Water and Specific Birth Defects and Childhood Cancers, United States Marine Corps Base Camp Lejeune, North Carolina*. Interviews of parents started in April 2005.”

“In 2005 ATSDR began a full study of specific birth defects and childhood cancers in children born to mothers who lived on base any time during their pregnancies from 1968-1985.”

(b) (6), [redacted]

From: (b) (6), [redacted]
Sent: Monday, December 09, 2013 8:56 AM
To: (b) (6), [redacted]
Cc: (b) (6), [redacted]
Subject: RE: Camp Lejeune studies and updates

Here is the occ med listserv interpretation of the study, which is a bit different from that noted in the AP. I'd be curious to hear (b) (6), [redacted] interpretation of the study.

Birth Defects and Childhood Cancers Study

Exposure to Contaminated Drinking Water and Specific Birth Defects and Childhood Cancers at Marine Corps Base Camp Lejeune, North Carolina

Study Purpose

The purpose of this study was to determine if maternal exposures to the drinking water contaminants at Camp Lejeune increased the risk of neural tube defects (NTDs), oral clefts, and childhood hematopoietic cancers. This study also examined whether children exposed to contaminated drinking water during the first year of life had an increased risk of childhood cancers. Drinking water at Camp Lejeune was

contaminated with volatile organic compounds (VOCs) including trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, 1,2-dichloroethylene (DCE) and vinyl chloride from the 1950s through 1985.

What Was Studied

The Agency for Toxic Substances and Disease Registry (ATSDR) surveyed the parents of 12,598 children during 1999-2002 to identify potential cases of birth defects and childhood cancers. ATSDR asked parents if their child had a birth defect or developed a childhood cancer. To be eligible for the survey, the mother had to reside on base some time during her pregnancy and children had to be born between 1968-1985.

The survey's participation rate was approximately 76% (ATSDR 2003). Survey participants reported 106 cases: 35 NTDs, 42 oral clefts, and 29 childhood hematopoietic cancers. ATSDR made extensive efforts to obtain medical information from health providers to confirm reported cases. ATSDR was able to confirm 15 NTDs, 24 oral clefts, and 13 cancers. Only confirmed cases from the survey were eligible for the study.

Based on the survey results, the study focused on NTDs (spina bifida and anencephaly), oral clefts (cleft lip and cleft palate), and childhood hematopoietic cancers (leukemia and non-Hodgkin's lymphoma [NHL]) diagnosed before 20 years of age.

Features of this Study

Due to the lack of exposure information, ATSDR used extensive water modeling to reconstruct exposures before 1987. This study is unique because it used this water modeling to thoroughly examine associations between monthly exposures to VOCs in drinking water at the residence and the risk of developing specific birth defects and childhood cancers. Most previous studies that have evaluated these associations have done so at the broad water system level versus drinking water at the residence.

Conclusion and Key Results

ATSDR's study results suggested associations between TCE and benzene in Camp Lejeune drinking water and NTDs.

- In this study, these effects were seen in children born from 1968-1985 whose mothers were exposed to contaminated drinking water in their residences at Camp Lejeune.
- During the first trimester of pregnancy, the risk of a NTD increased with increasing levels of exposure to TCE.
 - o This finding is consistent with a previous study conducted in New Jersey, which found similar risk of NTDs when exposed to TCE during the first trimester.

- Investigators observed an association between NTDs and first trimester exposure to benzene. ATSDR was unable to evaluate whether increasing levels of exposure to benzene were associated with increased risk of NTDs because of small numbers of exposed cases.

ATSDR's study results suggested weaker associations between 1st trimester exposure to PCE, vinyl chloride, and 1,2- DCE and childhood hematopoietic cancers such as leukemia.

- These associations are weaker than those found for NTDs.
- Researchers did not observe an increased risk for these cancers with increasing levels of exposure to the chemicals.

The study found no evidence suggesting any other associations between outcomes and exposures.

- For childhood cancers, ATSDR also looked at exposures during the second and third trimesters, the entire pregnancy as a whole, and exposures in the first year of life. The investigators did not see any associations between these chemicals with these time periods.
- Exposure to contaminants in Camp Lejeune drinking water did not increase the risk of oral clefts.

Additional Resources

- Journal Article (provisional)
<<http://www.ehjournal.net/content/12/1/104/abstract>>

From: (b) (6), [REDACTED]
Sent: Saturday, December 07, 2013 12:18 PM
To: (b) (6), [REDACTED]
(b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: Camp Lejeune studies and updates

Hi, All

updates about Camp Lejeune Studies were posted on Dec 5, 2013 re: adverse pregnancy outcomes (birth defects and childhood cancers) and male breast cancer

<<http://www.atsdr.cdc.gov/sites/lejeune/activities.html>>

Also from the Associated Press is the following:

“RALEIGH, N.C. (AP) — A long-awaited study by the U.S. Centers for Disease Control and Prevention confirms a link between tainted tap water at a U.S. Marine Corps base in North Carolina and increased risk of serious birth defects and childhood cancers.

The study released late Thursday by the CDC's Agency for Toxic Substances & Disease Registry surveyed the parents of 12,598 children born at Camp Lejeune between 1968 and 1985, the year drinking-water wells contaminated with chemicals from a leaky fuel depot and a dry cleaner were closed.

The study concludes that babies born to mothers who drank the tap water while pregnant were four times more likely than normal to have such serious birth defects as spinal bifida. Babies whose mothers were exposed also had an elevated risk of such childhood cancers as leukemia”

Keep in contact and Best to all during the Holiday season!

(b)
(6)

(b) (6), [REDACTED], Syracuse VAMC)

Attachments:

image001.png (298 Bytes)

Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis.

[Karami S](#), [Bassig B](#), [Stewart PA](#), [Lee KM](#), [Rothman N](#), [Moore LE](#), [Lan Q](#).

Author information

- Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20852, USA.

Abstract

The carcinogenic potential of trichloroethylene (TCE) continues to generate much controversy, even after the US Environmental Protection Agency raised its classification to 'carcinogenic to humans'. We conducted a meta-analysis of published cohort and case-control studies exploring occupational TCE exposure in relation to five different lymphatic and haematopoietic cancers: non-Hodgkin's lymphoma (NHL, N=24), Hodgkin's lymphoma (HL, N=13), multiple myeloma (MM, N=11), leukaemia (N=12) and chronic/small lymphocytic leukaemia (CLL/SLL, N=7). Studies published between 1950 and 2011 were identified through a PubMed Medline search. All studies included in analyses were classified as those that assessed either occupational TCE exposure specifically ('TCE-exposure' studies) or a broader classification of all chlorinated solvents ('chlorinated solvent-exposure' studies). A significantly raised summary estimate for NHL was seen for all cohort and case-control 'TCE-exposure' studies combined (N=19; relative risk (RR)=1.32, 95% CI 1.14 to 1.54; I(2)=25.20; p-heterogeneity=0.12) and for cohort 'TCE-exposure' studies (N=10; RR=1.52, 95% CI 1.29 to 1.79; I(2)=7.09; p-heterogeneity=0.63). A non-significant but raised summary estimate was seen for NHL case-control 'TCE-exposure' studies. No significant association with NHL risk was detected overall for any 'chlorinated solvent-exposure' studies. Summary estimates for occupational TCE exposure were not associated with risk of HL, MM, leukaemia or CLL/SLL. Our updated meta-analysis of NHL, which incorporates new analytical results from three cohort and four case-control studies, supports an association between occupational TCE exposure and NHL.

Topic: ASTDR Mortality Study of Marines at Camp Lejeune and Camp Pendleton

Review of: Bove FJ, Ruckart PZ, Maslia M, et.al. Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC base camp LeJeune: a retrospective cohort study. *Environmental Health* 2014, 13:10.

Issue:

- Contaminated drinking water was discovered in the 1980s at Camp Lejeune; there are concerns about long term health effects
- The Department of Veterans Affairs (VA) is responsible for the provision of care for Veterans who lived at Camp Lejeune. Additionally, VA is responsible for payment of care for 15 specific conditions for family members of Veterans who lived at Camp Lejeune.
- On February 19, 2014 the Agency for Toxic Substances and Disease Registry (ASTDR), a branch of the CDC, published a mortality study of Marines and sailors who lived at Camp Lejeune during the time of the water contamination.

Analysis:

- Since 1991, ATSDR has been performing health surveillance of former residents of Camp Lejeune. These studies have been funded by the Navy, totaling more than \$40 million.
- The research question of the mortality study was to determine if exposure of Marine and Navy personnel to contaminated drinking water at Camp Lejeune increased the risk of mortality from cancers and other chronic diseases”.
- The mortality rate of 154,932 Marines at Camp Lejeune was compared to mortality rates of 154,969 Marines at Camp Pendleton. Mortality rates were also compared to the general US population.
- By the end of the study period about 6% (n=9,000) of the Marines in **both** groups died.
- Multiple comparisons were performed on the data, with only three statistically significant findings:
 - Both groups of Marines were significantly healthier than the general population. Both group of Marines had decreased mortality for all causes and for all cancers. It is expected that Marines would be healthier than the general population (healthy soldier effect)
 - The Camp Lejeune Marines had a significant increase in prostate cancer death (18 deaths) compared to the US population, but **NOT** compared to the Camp Pendleton group
 - The Camp Lejeune Marines had a 10% increase in mortality from all cancers, compared to the Camp Pendleton group.

Methodological Flaws

- ATSDR concludes that there were “elevated risks” for several types of cancer and amyotrophic lateral sclerosis. This is misleading, and not supported by data. These results were **NOT** statistically significant.
 - Although risk estimates between two populations may differ from each other in magnitude (i.e., one risk estimated being “elevated” over another), it **does not** mean that they are statistically and meaningfully different from each from an epidemiological perspective. You must use statistical testing to interpret if the difference in magnitude is meaningful. The authors did not use statistical significance testing (p-values testing the null hypothesis of no difference) to interpret these differences, and therefore, there is limited confidence in the conclusions.
 - Another method that is commonly used to test for significance in population statistics is to examine the 95% confidence intervals for the two risk estimates. If the 95% confidence intervals for each of the two risk estimates overlap, it can be deduced that those two risk estimates do not differ significantly (although one may be larger in magnitude). Table 4 demonstrates this.
- The authors state “We did not use statistical significance testing to interpret findings”. It is methodologically suspect that in a study sample this large (N=20,000), statistical testing was not performed, since statistical significance (p-values) is largely a function of sample size.
 - Multiple comparisons were performed (which lead to chance associations) without any corrections for p-values (Bonferroni corrections should have been performed).
 - The 95% confidence intervals for almost all comparisons were unstable and not significant, due to the small number of deaths from each condition.
 - Table 5, which compares the risk of specific cause mortality between Camp Pendleton and Camp Lejeune (which is the best table to assess if cause specific mortality is different between the “exposed” and “unexposed” cohort) reports **all non-significant results**. All p-values are not significant, and all 95% confidence intervals include 1 (which means no association).
 - Data on major confounders was not collected.
 - Data on confounders was limited to administrative data from DMDC, which is known to have errors, namely for race.
 - For example, alcohol consumption and hepatitis C status are greatest predictors of liver cancer, and should have been controlled for in any analysis of liver cancer mortality.
 - Exposure data is based on a theoretical model, which makes several assumptions, years after the exposure occurred. No scientific body, outside of ATSDR, has validated this exposure model. This can result in major bias.
 - Results from one study cannot be considered scientific proof. Replication or concordance with other studies of the same exposure in a different population is needed to make a statement on certainty of results.
 - *Environmental Health* is not a high profile journal--its impact factor is 2.71. It is an open access, online journal. Authors pay to have their studies published in it. It is possible that other journals would have questioned these methodological issues and not selected this paper for publication.

- ATSDR published a similar study of birth defects in the same journal in December of 2013. The same flaws were present in that report and the data did not support the conclusions.

Implications:

- ATSDR will release four more studies in the upcoming year.
- ATSDR has refused to share study results prior to publication with DoD or VA; however, they do share their results with the new media early.
- This study may have direct impact on disability compensation. Congress and Veterans groups are likely to pressure VA for make a presumption of service connection for the diseases in the mortality study and birth defect study, even though the epidemiological/statistical methodology is flawed, producing **potentially** misleading results.

Review by the Office of Public Health, VHA

Reviewer: (b) (6),

March 3, 2014

Article link: <http://www.jstor.org/stable/3552700>

[Lynge E](#), [Anttila A](#), [Hemminki K](#).. Organic solvents and cancer. [Cancer Causes Control](#). 1997 May;8(3):406-19.

Organic Solvents and Cancer

Abstract

Epidemiologic evidence on the relationship between organic solvents and cancer is reviewed. In the 1980s, more than a million persons were potentially exposed to some specific solvents in the United States; in Canada, 40 percent of male cancer patients in Montreal had experienced exposure to solvents; in the Finnish population, one percent was regularly exposed. There is evidence for increased risks of cancer following exposure to: trichloroethylene (for the liver and biliary tract and for non-Hodgkin's lymphomas); tetrachloroethylene (for the esophagus and cervix -- although confounding by smoking, alcohol, and sexual habits cannot be excluded -- and non-Hodgkin's lymphoma); and carbon tetrachloride (lymphohematopoietic malignancies). An excess risk of liver and biliary tract cancers was suggested in the cohort with the high exposure to methylene chloride, but not found in the other cohorts where an excess risk of pancreatic cancer was suggested. 1,1,1-trichloroethane has been used widely, but only a few studies have been done suggesting a risk of multiple myeloma. A causal association between exposure to benzene and an increased risk of leukemia is well-established, as well as a suggested risk of lung and nasopharynx cancer in a Chinese cohort. Increased risks of various gastrointestinal cancers have been suggested following exposure to toluene. Two informative studies indicated an increased risk of lung cancer, not supported by other studies. Increased risks of lymphohematopoietic malignancies have been reported in some studies of persons exposed to toluene or xylene, but not in the two most informative studies on toluene. Occupation as a painter has consistently been associated with a 40 percent increased risk of lung cancer. (With the mixed exposures, however, it is not possible to identify the specific causative agent[s].) A large number of studies of workers exposed to styrene have evidenced no consistent excess risk of all lymphohematopoietic malignancies, although the most sensitive study suggested an excess risk of leukemia among workers with a high exposure.

Organic Solvents as Risk Factor for Autoimmune Diseases: A Systematic Review and Meta-Analysis

Carolina Barragán-Martínez, Cesar A. Speck-Hernández, Gladis Montoya-Ortiz, Rubén D. Mantilla, Juan-Manuel Anaya, Adriana Rojas-Villarraga*

Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

[FULL TEXT](#)

Abstract

Background: Genetic and epigenetic factors interacting with the environment over time are the main causes of complex diseases such as autoimmune diseases (ADs). Among the environmental factors are organic solvents (OSs), which are chemical compounds used routinely in commercial industries. Since controversy exists over whether ADs are caused by OSs, a systematic review and meta-analysis were performed to assess the association between OSs and ADs.

Methods and Findings: The systematic search was done in the PubMed, SCOPUS, SciELO and LILACS databases up to February 2012. Any type of study that used accepted classification criteria for ADs and had information about exposure to OSs was selected. Out of a total of 103 articles retrieved, 33 were finally included in the meta-analysis. The final odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by the random effect model. A sensitivity analysis confirmed results were not sensitive to restrictions on the data included. Publication bias was trivial. Exposure to OSs was associated to systemic sclerosis, primary systemic vasculitis and multiple sclerosis individually and also to all the ADs evaluated and taken together as a single trait (OR: 1.54; 95% CI: 1.25–1.92; p-value, 0.001).

Conclusion: Exposure to OSs is a risk factor for developing ADs. As a corollary, individuals with non-modifiable risk factors (i.e., familial autoimmunity or carrying genetic factors) should avoid any exposure to OSs in order to avoid increasing their risk of ADs.

Citation: Barragán-Martínez C, Speck-Hernández CA, Montoya-Ortiz G, Mantilla RD, Anaya J-M, et al. (2012) Organic Solvents as Risk Factor for Autoimmune

Diseases: A Systematic Review and Meta-Analysis. PLoS ONE 7(12): e51506. doi:10.1371/journal.pone.0051506

Editor: Sudha Chaturvedi, Wadsworth Center, United States of America

Received July 12, 2012; Accepted November 1, 2012; Published December 19, 2012

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permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This project did not have any specific funding, but the work was supported by the School of Medicine and Health Sciences, Universidad del Rosario.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: adrirojas@gmail.com

Parkinson's References, Case Control Studies

3.14.2013

Gallegos-Arreola MP, Figuera LE, Ortiz GG, Jiménez-Gil FJ, Ramírez-Vega J, Ruíz-Sandoval JL, Puebla-Pérez AM, Troyo-Sanroman R, García-Ortiz JE, Sanchez-Corona J, Zúñiga-González GM. Apolipoprotein E genotypes in Mexican patients with Parkinson's disease. *Dis Markers*. 2009;27(5):225-30.

Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT Jr, Checkoway H. Occupational factors and risk of Parkinson's disease: A population-based case-control study. *Am J Ind Med*. 2010 Mar;53(3):217-23.

Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. *Arch Neurol*. 2009 Sep;66(9):1106-13.

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Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, Semple S, Dick S, Counsell C, Mozzoni P, Haites N, Wettinger SB, Mutti A, Otelea M, Seaton A, Söderkvist P, Felice A; Geoparkinson study group. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup Environ Med*. 2007 Oct;64(10):666-72. Epub 2007 Mar 1.

Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, Mariani CB, Tenconi F, Tesei S, Zecchinelli A, Leenders KL. Hydrocarbon exposure and Parkinson's disease. *Neurology*. 2000 Sep 12;55(5):667-73.

De Palma G, Mozzoni P, Mutti A, Calzetti S, Negrotti A. Case-control study of interactions between genetic and environmental factors in Parkinson's disease. *Lancet*. 1998 Dec 19-26;352(9145):1986-7.

Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. *Neurotoxicology*. 1998 Aug-Oct;19(4-5):709-12.

Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology*. 1996 May;46(5):1275-84.

Occupational cancer in Britain ([full text](#))

Urinary tract cancers: bladder and kidney

[Terry Brown](#),³ [Rebecca Slack](#),⁵ [Lesley Rushton](#),^{1,*} and with the British Occupational Cancer Burden Study Group

³Institute of Environment and Health, Cranfield Health, Cranfield University, Cranfield MK43 0AL, UK

⁵School of Geography, University of Leeds, Leeds LS2 9JT, UK

¹Department of Epidemiology and Biostatistics, School of Public Health and MRC-HPA Centre for Environment and Health, Imperial College London, St Mary's Campus, Norfolk Place, London W2 3PG, UK

*E-mail: l.rushton@imperial.ac.uk

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Occupational exposure to organic solvents and breast cancer in women

Beata Peplonska,¹ Patricia Stewart,² Neonila Szeszenia-Dabrowska,¹ Jolanta Lissowska,³ Louise A Brinton,⁴ Jan Piotr Gromiec,⁵ Slawomir Brzezinski,⁵ Xiaohong R Yang,⁴ Mark Sherman,⁴ Montserrat Garcia 'a-Closas,⁴ Aaron Blair²

Occup Environ Med 2010;67:722e729.

ABSTRACT

Background Although studies in rodents suggest possible associations between exposure to organic solvents and breast cancer, the evidence in humans is limited.

Methods We evaluated job histories of 2383 incident breast cancer cases diagnosed during 2000e2003, and 2502 controls who participated in a large populationbased case-control study in Poland. Industrial hygienists reviewed occupational histories and developed exposure metrics for total organic solvents and benzene.

Unconditional logistic regression analyses estimated ORs and 95% CIs as the measure of association with breast cancer, controlling for breast cancer risk factors.

Stratified analyses examined the potential modification by known breast cancer risk factors. Associations were also evaluated by oestrogen and progesterone receptor status and by other clinical characteristics of the tumours using polytomous regression analyses.

Results Women who ever worked at jobs with organic solvents exposure had a small, non-significant increase in breast cancer risk (OR 1.16; 95% CI 0.99 to 1.4). A significant association was present for oestrogen receptor- and progesterone receptor-negative tumours (OR 1.40; 95% CI 1.1 to 1.8), but there was no association with tumours with both positive receptors (OR 0.97; 95% CI 0.8 to 1.2 (p heterogeneity: 0.008)).

We did not observe trends with increasing level of exposure. Known breast cancer risk factors did not modify the association between organic solvents and breast cancer risk. No association with breast cancer was found for benzene exposure (OR 1.00; 95% CI 0.8 to 1.3).

Conclusion Our study provides weak evidence for a possible association between occupational exposure to organic solvents as a class and breast cancer risk. The association might be limited to hormone receptornegative tumours.

Occupational exposure to organic solvents and lymphoid neoplasms in men: results of a French case-control study.

[Orsi L](#), [Monnereau A](#), [Dananche B](#), [Berthou C](#), [Fenaux P](#), [Marit G](#), [Soubeyran P](#), [Huguet F](#), [Milpied N](#), [Leporrier M](#), [Hemon D](#), [Troussard X](#), [Clavel J](#).

Source

Inserm U1018, Centre for Research in Epidemiology and Population Health, 16 av. Paul Vaillant-Couturier, F-94807 Villejuif Cedex, France. laurent.orsi@inserm.fr

Abstract

OBJECTIVES:

Investigating the role of occupational exposure to solvents in the occurrence of lymphoid neoplasms (LNs) in men.

METHODS:

The data were generated by a French hospital-based case-control study, conducted in six centres in 2000-2004. The cases were incident cases aged 18-75 years with a diagnosis of LN. During the same period, controls of the same age and gender as the cases were recruited in the same hospitals, mainly in the orthopaedic and rheumatological departments. Exposure to solvents was assessed using standardised occupational questionnaires and case-by-case expert assessment. Specific quantification of benzene exposure was attempted. The analyses included 491 male patients (244 cases of non-Hodgkin's lymphoma (NHL), 87 of Hodgkin's lymphoma, 104 of lymphoproliferative syndrome and 56 of multiple myeloma) and 456 male controls. Unconditional logistic regressions were used to estimate OR and 95% CI.

RESULTS:

Solvent exposure, all solvents considered together, was marginally associated with NHL (OR=1.4 (1.0 to 2.0) p=0.06), but not with other LNs. No association with the main chemical series of solvents was observed. There was no trend with the average intensity or frequency of exposure. Exposure to pure benzene was not significantly related to NHL (OR=3.4 (0.8 to 15.0)). The highest maximum intensities of benzene exposure were associated with diffuse large cell lymphoma (OR=2.1 (1.0 to 4.6)).

CONCLUSION:

The results of the present study provide estimates compatible with the hypothesis that exposures to pure benzene and high benzene intensities may play a role in some NHL. There was no evidence for a role of other organic solvents in the occurrence of LN.

PMID: 20837648 [PubMed - indexed for MEDLINE]

Occupational exposures in rare cancers: A critical review of the literature.

[Charbotel B](#)¹, [Fervers B](#)², [Droz JP](#)².

Author information

Abstract

The contribution of occupational exposures to rare cancers, which represent 22% of all cancers diagnosed annually in Europe, remains insufficiently considered. We conducted a comprehensive review of occupational risk factors in 67 rare cancers (annual incidence <6/100,000). An examination of relevant articles in PubMed (1960-2012) and the International Agency for Research on Cancer (IARC) monographs revealed that 26 cancer sites, such as mesothelioma, nasal, larynx, liver, ovarian cancer, bone sarcoma, and hematopoietic malignancies were consistently linked to occupational factors. Main exposures included asbestos, wood dust, metals/metalloids, formaldehyde, benzene, vinyl chloride, and radiation. There was inconsistent evidence regarding 22 rare malignancies. We did not identify relevant data for 19 rare cancers. Despite limitations of published evidence, our review provides useful information that can facilitate the identification of work-related factors that contribute to rare cancers. International collaborations, development of improved exposure assessment methods, and molecular approaches can improve future studies.

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KEYWORDS:

Classification; Epidemiology; Exposure; IARC; Occupational; Rare cancer

Free Article

[Occup Environ Med](#). 2012 Dec;69(12):858-67. doi: 10.1136/oemed-2012-100932. Epub 2012 Sep 21.

Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis.

[Karami S](#), [Lan Q](#), [Rothman N](#), [Stewart PA](#), [Lee KM](#), [Vermeulen R](#), [Moore LE](#).

Author information

Abstract

OBJECTIVES:

Inconsistent epidemiological findings, debate over interpretation, and extrapolation of findings from animal studies to humans have produced uncertainty surrounding the carcinogenicity of trichloroethylene (TCE) exposure in occupational settings. We updated meta-analyses of published case-control and cohort studies exploring occupational TCE exposure and kidney cancer risk, incorporating new analytical results from three recently published cohort studies and a case-control study.

METHODS:

PubMed MEDLINE was searched for studies published from 1950 to 2011 assessing occupational exposure to chlorinated solvents, degreasers or TCE. All cohort (N=15) and case-control (N=13) studies included in analyses were stratified by assessment of occupational exposure to TCE specifically and to any chlorinated solvent.

RESULTS:

Significantly elevated summary estimates were observed for cohort studies (relative risk (RR) 1.26, 95% CI 1.02 to 1.56; p heterogeneity=0.65), case-control studies (OR 1.35, 95% CI 1.17 to 1.57; p heterogeneity=0.41), and cohort and case-control studies combined (RR 1.32, 95% CI 1.17 to 1.50, p heterogeneity=0.63) that specifically assessed TCE exposure after excluding outlier studies that contributed to heterogeneity. Non-significantly elevated summary estimates were generally observed for studies of workers exposed to chlorinated solvents but who were not assessed for TCE specifically.

CONCLUSIONS:

Regardless of study design, significant and stronger estimates were only observed in studies specifically assessing occupational exposure to TCE. Estimates were lower in studies assessing occupational exposure to chlorinated solvents. This updated meta-analysis supports an

association between occupational TCE exposure and kidney cancer and provides evidence that exposure misclassification may weaken estimates assessing exposure to the broader class of chlorinated solvents.

[Full Text](#)

[Arch Clin Neuropsychol.](#) 1990;5(1):31-47.

Neuropsychological sequelae of exposure to the chlorinated hydrocarbon solvents trichloroethylene and trichloroethane.

[Tröster AI](#), [Ruff RM](#).

Source

University of California School of Medicine, SDSU Clinical Psychology Program, San Diego 92182-0551, USA.

Abstract

Reports in the literature concerning the acute neurobehavioral effects of trichloroethylene (TCE) and trichloroethane (TCA) conflict as to whether or not cognitive deficits ensue. Our study of two patients acutely exposed to low concentrations of TCE suggests that (a) acute, low-dose exposures are sufficient to produce the mild to moderate impairments in psychomotor speed, attention and memory also reported after chronic exposures; (b) these memory impairments may be characterized by storage and/or retrieval difficulties; (c) the neural damage produced by TCE exposure is likely to be diffuse, but temporal lobe structures supporting memory may be more sensitive to TCE exposure than other brain structures; and (d) even brief exposures can lead to prolonged, but not necessarily chronic mild to moderate cognitive impairment. In a third case, exposed to trichloroethane (TCA), the neuropsychological profile suggests that this substance has few, if any, neurobehavioral effects at low concentrations.

PMID:

14589542

[PubMed]

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[Mayo Clin Proc.](#) 2008 May; 83(5):584-94. doi: 10.4065/83.5.584.

Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship.

[Molina JR](#), [Yang P](#), [Cassivi SD](#), [Schild SE](#), [Adjei AA](#).

Source

Department of Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA.
molina.julian@mayo.edu

Abstract

Lung cancer is the leading cause of cancer-related mortality not only in the United States but also around the world. In North America, lung cancer has become more predominant among former than current smokers. Yet in some countries, such as China, which has experienced a dramatic increase in the cigarette smoking rate during the past 2 decades, a peak in lung cancer incidence is still expected. Approximately two-thirds of adult Chinese men are smokers, representing one-third of all smokers worldwide. Non-small cell lung cancer accounts for 85% of all lung cancer cases in the United States. After the initial diagnosis, accurate staging of non-small cell lung cancer using computed tomography or positron emission tomography is crucial for determining appropriate therapy. When feasible, surgical resection remains the single most consistent and successful option for cure. However, close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. Chemotherapy is beneficial for patients with metastatic disease, and the administration of concurrent chemotherapy and radiation is indicated for stage III lung cancer. The introduction of angiogenesis, epidermal growth factor receptor inhibitors, and other new anti-cancer agents is changing the present and future of this disease and will certainly increase the number of lung cancer survivors. We identified studies for this review by searching the MEDLINE and PubMed databases for English-language articles published from January 1, 1980, through January 31, 2008. Key terms used for this search included non-small cell lung cancer, adenocarcinoma, squamous cell carcinoma, bronchioalveolar cell carcinoma, large cell carcinoma, lung cancer epidemiology, genetics, survivorship, surgery, radiation therapy, chemotherapy, targeted therapy, bevacizumab, erlotinib, and epidermal growth factor receptor.

PMID:

18452692

[PubMed - indexed for MEDLINE]

PMCID:

PMC2718421

[Free PMC Article](#)

Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis.

[Larsson SC](#), [Wolk A](#).

Source

Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden. susanna.larsson@ki.se

Abstract

Obesity is associated with altered immune and inflammatory responses and it may therefore influence the risk of non-Hodgkin's lymphoma. However, epidemiologic findings on obesity in relation to non-Hodgkin's lymphoma have been inconsistent. We conducted a meta-analysis to summarize the epidemiologic evidence on the association between excess body weight and risk of non-Hodgkin's lymphoma. Relevant studies were identified by searching MEDLINE (1966 to February 2007) and the reference lists of retrieved publications. We included cohort and case-control studies that reported relative risk (RR) estimates with 95% confidence intervals (CIs) for the association of body mass index (BMI) with non-Hodgkin's lymphoma incidence or mortality. A random-effects model was used to combine results from individual studies. Sixteen studies (10 cohorts and 6 case-control studies), with 21,720 cases, met the inclusion criteria. Compared to individuals of normal weight (BMI < 25.0 kg/m²), the summary RRs of non-Hodgkin's lymphoma were 1.07 (95% CI, 1.01-1.14) for overweight individuals (BMI between 25 and 30 kg/m²) and 1.20 (95% CI, 1.07-1.34) for those who were obese (BMI ≥ 30.0 kg/m²). Meta-analysis stratified by histologic subtypes showed that obesity was associated with a statistically significant increased risk of diffuse large B-cell lymphoma (RR, 1.40; 95% CI, 1.18-1.66; n = 6 studies) but not of follicular lymphoma (RR, 1.10; 95% CI, 0.82-1.47; n = 6 studies) or small lymphocytic lymphoma/chronic lymphocytic leukemia (RR, 0.95; 95% CI, 0.76-1.20; n = 3 studies). These findings indicate that excess body weight is associated with an increased risk of non-Hodgkin's lymphoma, especially of diffuse large B-cell lymphoma.

PMID:

17443495

[PubMed - indexed for MEDLINE]

Obesity, Lifestyle Factors, and Risk of Myelodysplastic Syndromes in a Large US Cohort

Xiaomei Ma, Unhee Lim, Yikyung Park, Susan T. Mayne, Rong Wang, Patricia Hartge, Albert R. Hollenbeck, and Arthur Schatzkin

Initially submitted December 8, 2008; accepted for publication March 10, 2009.

The etiology of myelodysplastic syndromes (MDS) is not well understood. The authors examined the relations of obesity and lifestyle factors to MDS in a cohort of 471,799 persons aged 50–71 years who were recruited into the National Institutes of Health-AARP Diet and Health Study, a large US prospective study, in 1995–1996. Incident MDS was diagnosed in 193 persons during 2001–2003. A significant positive association was observed between body mass index (BMI; weight (kg)/height (m)²) at baseline and MDS. Compared with persons with a BMI less than 25.0, the hazard ratios for persons with BMIs of 25.0–<30.0 and ≥30.0 were 1.15 (95% confidence interval (CI): 0.81, 1.64) and 2.18 (95% CI: 1.51, 3.17; P for trend < 0.001), respectively. The association was not affected by physical activity, cigarette smoking, or alcohol intake. As reported in previous studies, the risk of MDS was elevated among former smokers (hazard ratio ¼ 1.68, 95% CI: 1.17, 2.41) and current smokers (hazard ratio ¼ 3.17, 95% CI: 2.02, 4.98) as compared with never smokers. Physical activity, alcohol consumption, meat intake, and fruit and vegetable intake did not appear to significantly influence the risk of MDS in this analysis. This prospective investigation of MDS implicates both obesity and smoking as modifiable risk factors.

life style; myelodysplastic syndromes; obesity; smoking

[FULL TEXT](#)

[Cancer Epidemiol Biomarkers Prev.](#) 2009 May;18(5):1501-6. doi: 10.1158/1055-9965.EPI-09-0028.

Obesity, weight gain, and risk of chronic myeloid leukemia.

[Strom SS](#)¹, [Yamamura Y](#), [Kantarijian HM](#), [Cortes-Franco JE](#).

[Author information](#)

Abstract

To date, little is known about the risk factors for the development of chronic myeloid leukemia (CML). Obesity, measured as body mass index, has been identified as a possible risk factor for several solid tumors as well as some adult hematopoietic malignancies. This case-control study (N = 253 cases and 270 controls), conducted at the University of Texas M. D. Anderson Cancer Center, investigated the role of obesity and adulthood weight gain in CML risk. Cases and controls were similar with respect to smoking, alcohol consumption, and occupational solvent and ionizing radiation exposure. Cases were significantly more likely to have a history of occupational exposure to agricultural chemicals (11% cases versus 3% controls, P = 0.001). Cases were more likely to be obese during adulthood compared with controls at age 25 [odds ratios (OR) = 4.29; 95% confidence intervals (95% CI), 1.63-11.3], at age 40 (OR = 5.12; 95% CI, 1.92-13.6), and at diagnosis (OR = 3.09; 95% CI, 1.56-6.13). Obesity at all ages was found to be an independent risk factor, with a significant dose-response effect. Among participants > or =45 years, cases gained significantly more weight each year between ages 25 and 40 compared with controls (0.78 versus 0.44 kg/y, P < 0.001) with the association strongest among those who gained >1 kg/y between 25 and 40 years of age (OR, 3.63; 95% CI, 1.46-9.04). Our results suggest that obesity and adulthood weight gain play important roles in CML risk. Several plausible biological mechanisms have been proposed and warrant further investigation. In the future, cancer prevention interventions aimed at reducing the incidence of CML could be developed.

[Environ Health](#). 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.

Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

[Bove FJ¹](#), [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

Author information

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at Camp Lejeune during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 Camp Pendleton workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune and Camp Pendleton workers and assess the effects of estimated cumulative contaminant exposures within the Camp Lejeune cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at Camp Lejeune. The confidence interval (CI) indicated precision of effect estimates.

RESULTS:

Compared to Camp Pendleton, Camp Lejeune workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the Camp Lejeune cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION:

The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the Camp Lejeune cohort died by end of follow-up, producing small numbers of ca

Multiple Sclerosis

IOM 2003 Conclusions

At the time of the IOM (2003) report, four case-control studies of solvent exposure (in general) and multiple sclerosis (MS) had been conducted in Scandinavia. Two had negative results, and the other two, conducted in Sweden and based on overlapping populations, reported some positive associations between self-reported occupational and leisure-time solvent exposure and MS in men. The positive findings are tempered by the limited quality of exposure assessment, the lack of adjustment for potential confounders, and small sample and were thus short of "limited/suggestive" evidence of an association. No studies focused specifically on TCE or PCE were found. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and MS.

2008 Evaluation

No additional studies of solvent exposure and MS were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and MS.

Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3502195/>

[J Natl Cancer Inst.](#) 2012 Nov 21;104(22):1724-37. doi: 10.1093/jnci/djs411. Epub 2012 Oct 30.

Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis.

[Schnatter AR](#), [Glass DC](#), [Tang G](#), [Irons RD](#), [Rushton L](#).

Source: Occupational and Public Health Division, ExxonMobil Biomedical Sciences, Inc, 1545 US Highway 22 East, Annandale, NJ 08801-3059, USA. a.r.schnatter@exxonmobil.com

BACKGROUND:

Benzene at high concentrations is known to cause acute myeloid leukemia (AML), but its relationship with other lymphohematopoietic (LH) cancers remains uncertain, particularly at low concentrations. In this pooled analysis, we examined the risk of five LH cancers relative to lower levels of benzene exposure in petroleum workers.

METHODS:

We updated three nested case-control studies from Australia, Canada, and the United Kingdom with new incident LH cancers among petroleum distribution workers through December 31, 2006, and pooled 370 potential case subjects and 1587 matched LH cancer-free control subjects. Quantitative benzene exposure in parts per million (ppm) was blindly reconstructed using historical monitoring data, and exposure certainty was scored as high, medium, or low. Two hematopathologists assigned diagnoses and scored the certainty of diagnosis as high, medium, or low. Dose-response relationships were examined for five LH cancers, including the three most common leukemia cell-types (AML, chronic myeloid leukemia [CML], and chronic lymphoid leukemia [CLL]) and two myeloid tumors (myelodysplastic syndrome [MDS] and myeloproliferative disease [MPD]). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression, controlling for age, sex, and time period.

RESULTS:

Cumulative benzene exposure showed a monotonic dose-response relationship with MDS (highest vs lowest tertile, >2.93 vs ≤ 0.348 ppm-years, OR = 4.33, 95% CI = 1.31 to 14.3). For peak benzene exposures (>3 ppm), the risk of MDS was increased in high and medium certainty diagnoses (peak exposure vs no peak exposure, OR = 6.32, 95% CI = 1.32 to 30.2) and in workers having the highest exposure certainty (peak exposure vs no peak exposure, OR = 5.74, 95% CI = 1.05 to 31.2). There was little evidence of dose-response relationships for AML, CLL, CML, or MPD.

CONCLUSIONS:

Relatively low-level exposure to benzene experienced by petroleum distribution workers was associated with an increased risk of MDS, but not AML, suggesting that MDS may be the more relevant health risk for lower exposures.

[Full text](#)

Neurotoxicity of chronic low-dose exposure to organic solvents: A skeptical review

1. Paul R. Lees-Haley*
2. Christopher W. Williams

Article first published online: 6 DEC 1998

DOI: 10.1002/(SICI)1097-4679(199711)53:7<699::AID-JCLP7>3.0.CO;2-D

The health effects of long-term, low-level exposure to organic solvents have been studied for many years. While the volume of literature is great, definitive conclusions regarding chronic neurobehavioral effects of environmental exposure are premature. Methodological shortcomings in research preclude confidence in studies allegedly supporting a causal link between chronic low-dose solvent exposure and lasting neurobehavioral deficits. In this article, the shortcomings reviewed include selection bias in recruitment of research subjects, overreliance on subjective recall in determining levels and duration of exposure, between-study variability in kinds of solvents examined, variability in tests selected to assess neurobehavioral functioning, and diversity in reported findings. The implications of these for characterizing the state of organic solvent research are discussed. © 1997 John Wiley & Sons, Inc. *J Clin Psychol* **53**: 699–712, 1997.

NEUROBEHAVIORAL EFFECTS

Summary

Organic solvents have been associated with various forms of central nervous system toxicity since at least the mid 1960s, where literature (Munchinger 1963) describes disease, and compensation, among solvent-exposed workers. Early systematic work (Axelson 1975) identified an almost twofold risk of psychiatric disturbances among solvent-exposed painters. There is a widespread agreement that chronic effects are seen primarily after long-term, high-level exposure, with objective testing showing decrements in concentrating ability, visuospatial skills, and fine motor abnormalities, generally 10 years of occupational exposure (Flodin 1984). Such long-term exposures are also associated with the development of personality changes (Chen 2001). Earlier, mild disease may be seen after as little as three years. Some patients also demonstrate peripheral neuropathy (Flodin 1984). Mild disease, with acute symptoms, generally resolves after cessation of exposure but is certainly not progressive (van Walen 2009). Low-level exposures are not associated with adverse long-term cognitive outcomes (Dick 2010). Overlaps between mood and personality changes and other syndromes, such as anxiety, posttraumatic stress disorders, and other chronic conditions, often make that diagnosis difficult. Nevertheless, disease is never progressive and there are no known cases of onset after cessation of exposure.

Two classification systems have been in use over the last 30 years. The more recent was developed at a Consensus Development Conference [Anonymous 1986], provided in the table below, replaced in the original World Health Organization approach.

Type 1: Acute symptoms only, including impairment of memory, poor concentration, fatigue, and decreased motivation. In general these resolve rapidly after cessation of exposure. Although not commonly included in a listing of symptoms, because some nonspecific, headaches are widely considered a common phenomenon .

Type 2A: A sustained change in mood and / or personality, with reduced motivation, poor impulse control, often anxiety, and irritability is seen after longer term exposures. This form is generally not assessed with performance decrements

Type 2B: Impairment in intellectual function is associated with cognitive deficits, including attention concentrating, visuospatial skills, and verbal memory. In addition, fine motor performance is impaired.

Type 3: Intellectual impairment, not resolving with resolution of exposure; commonly considered Chronic Toxic Encephalopathy

Type I was called the Organic Affective Syndrome in the WHO classification; Types 2 A and B were called Mild Chronic Toxic Encephalopathy, and Type 3 Severe Chronic Toxic Encephalopathy (NIOSH 1987).

Three reports, over 10 years, raise the question of ground-water contamination (Feldman 1988, Kilburn 1993, Reif 2003) associated with abnormal CNS effects. The first measured trigeminal responsiveness (“Blink reflex”), a sensitive indicator of toxicity, and documented delays in subjects exposed to trichlorethylene-contaminated well water. The second involved daily exposure from between one to twenty-five years during active exposure (Kilburn 1993) and examined the presence of disease using a range of appropriate tools, including color vision testing and questionnaires. A third examined symptom levels, neuropsychological test results, and visual contrast sensitivity documented relationships with level of exposure over five years later. All three found objective evidence of disease on formal testing. One demonstrated a major effect of interaction with alcohol. In general, the levels of exposure associated with effects in these three studies are well below those associated with effects in animal studies.

Epidemiology

Multiple reviews (Baker 1988,1994; Dick 2006; Meyer-Baron 2008) provide useful overviews of the disorder and its characteristics. In general, occupational exposures are required to cause CNS disorders.

Clinical Diagnosis

Screening for disease with an initial questionnaire (Hogstedt) was deemed invalid (Lundberg, Smargiassi); a modification performed somewhat better (Carter 2002). Still, symptoms consistent with any form of solvent neurotoxicity are very common in primary care; they alone are generally not considered evidence of disease. Formal neuropsychological testing is critical to the diagnosis. Two widely used batteries include a tool developed at the Harvard School of Public Health (Baker 1983) the Pittsburgh Occupational Exposures Test (POET), used beginning in the mid 1980s for clinical and field work (Ryan 1988; Morrow 1989). In the absence of tests, no diagnosis of neurobehavioral effects can be made. Importantly, in many patients, and subjects, inadequate effort contributes to poor performance, so that signs of illness behavior must be sought (van Hout 2010). Additional clinical tools include color vision testing (Attarchi 2010, Costa 2012) and vestibular evaluation (Zamyslowska-Szmytko 2011, Hodgkinson 2006), although auditory evoked potentials do not appear as useful discriminant diagnostic tools despite ongoing work (Keski 2007, 2012)

Recent animal studies

Benignus provided a recent update on animal toxicology.

Toxicology, Exposures, and Dose Extrapolation

The Environmental Protection Agency (EPA) considers the amounts that can be “safely” consumed each day for a lifetime without concerns for adverse health effects, i.e., the reference dose (RfD) for each of the agents as listed below. The source is EPA’s Integrated Risk Information System (IRIS). That dose incorporates a safety factor listed in column 2. Similarly, the Agency for Toxic Substances and Disease Registry provides No Adverse Observed Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for each of the four contaminants of concern. The table below summarizes the EPA IRIS doses and the associated safety factors. In general, these safety factors take into consideration extrapolation of dose effects from animals to humans and inter-subject variability.

| | RFD (+) in mg/kg/day | Safety factor |
|--------------------------|----------------------|---------------|
| Trichloroethylene (TCE) | 0.0005 | 1,000 |
| Perchloroethylene (PERC) | 0.006 | 1,000 |
| Benzene | 0.004 | 300 |
| Vinyl Chloride | 0.003 | 1,000 |

*: animal data, as no human data are available

For Trichloroethylene, acute levels of interest for neurological outcomes as NOAEL and LOAELs are, respectively, 100 vs 200 mg/kg/day. For intermediate duration, a LOAEL of 200 mg/kg/day exists for “less serious effects, but no NOAEL exists. No data are available for chronic ingestion exposures.

For Perchloroethylene, acute levels of interest for neurological outcomes exist for humans only as LOAEL at 100 mg/kg/day. No animal data and no data on intermediate or chronic doses associated with adverse neurological exist.

For Benzene, 10 mg/kg/day and 30 mg/kg/day represent respectively NOAEL and LOAELs for intermediate duration (15 – 365 days) of doses associated with adverse neurological exist. Chronic exposure to 100 mg/kg/day was not associated with adverse neurological health effects.

For Vinyl chloride, no data exist

Use of the calculation spreadsheet provides an estimate of the likely doses and sets them into a relation with RfD and Toxprofile specific data

Competing exposures

Additional pertinent considerations include other known risk factors for neurobehavioral effects, of cognitive processing delays, difficulty concentrating, memory loss, and fine-motor performance. Alcohol has similar effects.

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Q16 / Initial

- 1 Do you have a short memory?
- 2 Have your relatives told you that you have a short memory?
- 3 Do you often have to make notes about what you must remember?
- 4 Do you generally find it hard to get the meaning from reading newspapers and books?
- 5 Do you often have problems with concentrating?
- 6 Do you often feel irritated without any particular reason?
- 7 Do you often feel depressed without any particular reason?
- 8 Are you abnormally tired?
- 9 Do you have palpitations of the heart even when you don't exert yourself?
- 10 Do you sometimes feel an oppression in your chest?
- 11 Do you often perspire without any particular reason?
- 12 Do you have an headache at least once a week?
- 13 Are you less interested in sex than what you think is normal?
- 14 Do you have problems with buttoning and unbuttoning?
- 15 Do you often have painful tingling in some part of your body?
- 16 Do you often have to go back and check things you have done such as turned off the stove, locked the door?

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Subject: literature
Date: Tuesday, November 19, 2013 8:53:25 AM
Attachments: [EAS](#)

Hi ,

I just unsuccessfully tried to add this.

thanks

(b) (6), [REDACTED]

Compensation and Pension Service

Charles George VAMC

Asheville, North Carolina 28805

(828) 298-7911 ext (b) (6)
(6)

Attachments:
scleroderma.docx (16092 Bytes)

From: (b) (6),
To: (b) (6),
Subject: male and female breast cancer are the same condition-reference
Date: Thursday, January 23, 2014 11:44:06 AM

Appl Clin Genet. 2011; 4: 145–158.

Published online 2011 November 14. doi: 10.2147/TACG.S13226
<<http://dx.doi.org/10.2147%2FTACG.S13226>>

PMCID: PMC3681186

Inherited and acquired alterations in development of breast cancer

Piera Rizzolo <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Rizzolo%20P%5Bauth%5D>>, Valentina Silvestri <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Silvestri%20V%5Bauth%5D>>, Mario Falchetti <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Falchetti%20M%5Bauth%5D>>, and Laura Ottini <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Ottini%20L%5Bauth%5D>>

“Overall, current epidemiologic and pathologic data, such as age-frequency distribution, age-specific incidence rate patterns, and prognostic factor profiles, suggest that male breast cancer is similar to postmenopausal female breast cancer. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3681186/#b2-tacg-4-145>> It is generally accepted that breast cancer may represent the same disease entity in both genders, and common hormonal, genetic, and environmental risk factors are involved in the pathogenesis of breast cancer in women and men.”

(b) (6), could you put this on the share point?

1. Epidemiology and risk factors for breast cancer [UpToDate]

Authors

Mary E Costanza, MD

Wendy Y Chen, MD, MPH

Section Editor

Daniel F Hayes, MD

Deputy Editor

Don S Dizon, MD, FACP

Disclosures

All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

Literature review current through: Dec 2012. |**This topic last updated:** Jan 29, 2012.

ENVIRONMENTAL EXPOSURES — Organochlorines include polychlorinated biphenyls (PCB's), dioxins, and organochlorine pesticides such as DDT. These compounds are weak estrogens, highly lipophilic, and capable of persisting in body tissues for years. However, most large studies have failed to find an association [[207,208](#)].

[207] Calle EE, Frumkin H, Henley SJ, et al. Organochlorines and breast cancer risk. *CA Cancer J Clin* 2002; 52:301.

[208] Willett WC, Rockhill B, Hankinson SE, et al. factors in the causation of breast cancer. In: *Diseases of the Breast*, Harris JR, Lippman ME, Morrow M, Osborne CK (Eds), Lippincott, Williams and Wilkins, Philadelphia 2004. p.255.

RISK FACTORS FOR MALE BREAST CANCER — Men are more than one hundred times less likely to get breast cancer than women. Risk factors for male breast cancer include Klinefelter's syndrome, testicular and liver pathology, a family history of breast cancer, and BRCA2 mutations. (See "[Male breast cancer](#)".)

Male breast cancer [UpToDate]

Author

William J Gradishar, MD

Section Editors

Daniel F Hayes, MD

Anees B Chagpar, MD, MSc, MA, MPH, FACS, FRCS(C)

Deputy Editors

Don S Dizon, MD, FACP

Rosemary B Duda, MD, MPH, FACS

Disclosures

All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

Literature review current through: Dec 2012. |**This topic last updated:** Nov 15, 2012.

INTRODUCTION — Male breast cancer (MBC) is rare in contrast to female breast cancer, which is the most common cancer and second leading cause of cancer deaths in women [1]. Although MBC shares many similarities with cancer of the female breast, there are also important differences [2].

EPIDEMIOLOGY AND RISK FACTORS — In the United States, approximately 2140 new cases of MBC are diagnosed annually, and 450 deaths occur; this represents less than 0.5 percent of all cancer deaths in men annually [1]. By contrast, in Tanzania and areas of central Africa, breast cancer accounts for up to 6 percent of cancers in men [3].

In the United States, the ratio of female to male breast cancer is approximately 100:1 in whites, but lower (70:1) in blacks [2,3]. Blacks also have a poorer prognosis, even after adjustment for clinical, demographic, and treatment factors. (See '[Racial disparities](#)' below.)

The median age of onset of MBC is 65 to 67, approximately 5 to 10 years older than in women [2,4-9]. Like female breast cancer, the incidence of MBC has been increasing; one report suggests that incidence has increased 26 percent over the past 25 years [10].

Risk factors — Although the majority of men with breast cancer have no identifiable risk factors, several have been identified, many related to hormone levels. Many of these risk factors are the same as in women, including family history, Jewish ancestry, obesity, low levels of physical activity, prior chest wall irradiation, and benign breast disease [3,11]. (See "[Epidemiology and risk factors for breast cancer](#)".)

[3] Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. *Int J Cancer* 1993; 53:538.

[11] Brinton LA, Richesson DA, Gierach GL, et al. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* 2008; 100:1477.

Other risk factors that are modestly unique to men include never being married, gynecomastia, and a history of testicular or liver pathology [3], a history of a bone fracture after age 45 [11], and Klinefelter's syndrome:

- Gynecomastia, which is most often drug-related ([table 1](#)), may be associated with the development of male breast cancer because of shared hormonal risk factors. (See

"Epidemiology and pathogenesis of gynecomastia" and "Causes and evaluation of gynecomastia".)

- Testicular conditions associated with an increased risk of MBC include orchitis, undescended testes (cryptorchidism) and testicular injury [4,8,12]. Among the chronic liver diseases that are associated with MBC are cirrhosis, alcoholic liver disease, and schistosomiasis [13-17].
- Klinefelter syndrome is a rare condition resulting from the inheritance of an additional X chromosome [4,18-20]. The Klinefelter syndrome consists of atrophic testes, gynecomastia, high serum concentrations of gonadotropins (follicle-stimulating hormone, luteinizing hormone), and low serum testosterone levels; the net effect is a high ratio of estrogen-to-testosterone. (See "Causes of primary hypogonadism in males".)

Few carefully conducted epidemiologic studies have been undertaken given the rarity of both Klinefelter syndrome and male breast cancer. The largest cohort study of 3518 men who were cytogenetically diagnosed with Klinefelter syndrome found 19- and 58-fold increases in incidence and mortality, respectively, compared to the general population, with particularly high risks among 47,XXY mosaics [21].

Additional studies are needed to clarify which patients with Klinefelter syndrome are at a high risk of developing MBC and to define the contribution of possible predisposing factors, including altered endogenous hormones. The role of breast cancer screening in men with Klinefelter syndrome is unclear. Although the relative risk of breast cancer is increased, the absolute risk is still much lower than it is in women. Although routine mammography is not advocated for all affected men, the importance of patient education, self examination, and regular physician examinations are stressed [21].

Several of the risk factors for MBC involve imbalance in estrogenic versus androgenic influences (ie, relative estrogen excess or lack of androgen) [3,4]. As an example, men with liver disease have increased production of androstenedione from the adrenal glands, enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol [22]. On the other hand, androgens may convey a protective effect on breast tissue by inhibiting cell proliferation. The association of MBC with prolactinoma, a condition often associated with low plasma testosterone levels, is consistent with this hypothesis [23,24].

It is hypothesized that relative changes in endogenous hormones may play a causative role in MBC. However, abnormalities in peripherally detectable hormone levels have not been detected in affected men [25]. Furthermore, other conditions associated with an increased estrogen-to-testosterone ratio such as obesity, thyroid disease, use of marijuana, and exogenous estrogen use (eg, transsexuals, treatment of prostate cancer) have a less certain relationship to MBC [4,12].

2. Abstract:

The etiology of male breast cancer is largely unknown, reflecting its relative rarity. Although a number of previous studies have suggested relationships with a variety of medical conditions, the results have largely derived from case-control studies and may reflect recall biases. Within the large U.S. Veterans Affairs computerized medical care system database, we had the opportunity to access 26 million hospital discharge records over the period 1969-1996 and to relate various documented medical conditions to the risk of subsequent male breast cancer. This allowed us to calculate relative risks (RR) and 95% confidence intervals (CI) for male breast cancer associated with conditions occurring one or more years after initial hospitalization, adjusted for age, race, calendar year, duration of follow-up, and number of hospital visits. Among 4,501,578 men aged 18-100 years, a total of 642 cases of primary male breast cancer were identified (523 among whites, 119 among blacks). Medical conditions that were significantly related to risk were diabetes (RR 1.30, 95% CI 1.05-1.60), obesity (1.98, 1.55-2.54), orchitis/epididymitis (1.84, 1.10-3.08), Klinefelter syndrome (29.64, 12.26-71.68), and gynecomastia (5.86, 3.74-9.17). Additionally, among black patients, cholelithiasis emerged as a significant risk predictor (3.45, 1.59-7.47). Diseases that have previously been related to male breast cancer risk that were not supported by our study results included thyroid diseases, smoking-related conditions, liver cirrhosis, prostatic hyperplasia, and fractures. After adjustment for obesity, the association with diabetes disappeared, but that with gynecomastia persisted. In multivariate models that simultaneously considered all important medical predictors of risk, significant risks were seen for Klinefelter syndrome (16.83, 6.81-41.62), gynecomastia (5.08, 3.21-8.03), obesity (1.91, 1.50-2.44), and orchitis/epididymitis (1.80, 1.08-3.01). These results support previous speculations that male breast cancer is influenced not only by tissue at risk, but also by hormonal and inflammatory factors.

Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database.

Brinton LA - *Breast Cancer Res Treat* - 01-JAN-2010; 119(1): 185-92

3. Abstract:

BACKGROUND: The overall incidence of male breast cancer is around 1% of all breast cancers and is on the rise. In this review we aim to present various aspects of

male breast cancer with particular emphasis on incidence, risk factors, pathophysiology, treatment, prognostic factors, and outcome. **METHODS:** Information on all aspects of male breast cancer was gathered from available relevant literature on male breast cancer from the MEDLINE database over the past 32 years from 1975 to 2007. Various reported studies were scrutinized for emerging evidence. Incidence data were also obtained from the IARC, Cancer Mondial database. **CONCLUSION:** There is a scenario of rising incidence, particularly in urban US, Canada and UK. Even though more data on risk factors is emerging about this disease, more multi-institutional efforts to pool data with large randomized trials to show treatment and survival benefits are needed to support the existing vast emerging knowledge about the disease.

Citation:

Male breast cancer: is the scenario changing.

Contractor KB - *World J Surg Oncol* - 01-JAN-2008; 6: 58

Etiology and risk factors

The definite etiology of MBC is unknown. Factors such as alteration in hormonal milieu, family history and genetic alterations are known to influence its occurrence. Various studies have shown that conditions that alter the estrogen-testosterone ratio in males predispose to breast cancer [14,15]. Among these conditions the strongest association is with Klinefelter's syndrome. Males with this condition have a fifty times increased risk and accounts for 3% of all MBC [16]. Conditions, which are associated with increased estrogen levels, like cirrhosis [17,18] and exogenous administration of estrogen (either in transsexuals or as therapy for prostate cancer) have been implicated as causative factors [19-22]. Also, androgen deficiency due to testicular disease like mumps, undescended testes, or testicular injury, has been linked to the occurrence of breast cancer in men [23,24]. Occupational exposure to heat and electromagnetic radiation, causing testicular damage and further leading to the development of MBC is also postulated [25,26]. An inherited predisposition for breast cancer is noticed in males-analogous to that in females [27-31]. A positive family history of a first-degree female relative having breast cancer is seen in up to 15–20% patients [32]. This increased risk is conferred by mutations in the breast cancer susceptibility genes (BRCA1 and BRCA2). Mutations in both the BRCA1 and BRCA2 genes are linked to female breast cancer. Genetic studies in males however, have shown that germline mutations in BRCA2 alone account for the majority of hereditary breast cancer [33-36].

No link between BRCA1 and familial breast cancer has been noticed in one study [37], whereas other studies have suggested a possible link [38,39]. The Cambridge study showed that 8% of patients had BRCA2 mutations and all the carriers had a family history of breast, ovarian, prostate or pancreatic cancer [40]. The highest prevalence of BRCA2 mutation in MBC has been noted in Iceland where 40% have the mutation [41]. Several case reports have linked MBC with other genetic disorders like Cowden syndrome [42] and Hereditary Non-Polyposis Colonic Cancer (HNPCC) [43]. It has been recently reported that male breast cancer may also predispose to increased risk of developing a second cancer of the stomach, skin and breast [44].

A strong racial predilection is noted in MBC, with studies establishing a high-risk for Jews. Among them, the Sephardic Jews present at a younger age with advanced stage disease whereas the Ashkenazi Jews have an increased lifetime risk of suffering from the disease [45,46]. Gynecomastia, present in 6–38% of MBC patients has also been implicated as a risk factor [47,48] and some studies have shown positive correlation between the two [49]. An interesting study in the US comparing incidence, pathology and outcomes in male and female breast cancer in a defined population showed more black males than white males to be affected. Also black men with breast cancer had more involved axillary lymph nodes and higher stage than whites at presentation [50]. This is in stark contrast to the high incidence of male breast cancer preponderance in whites as shown in another recently reported study in the US which showed higher incidence in white males, although black males were more not likely to see an oncologist for consideration of chemotherapy and had higher mortality associated with the disease (hazard ratio = 3.29; 95% CI, 1.10 to 9.86) [51]. Reports have shown that an association of MBC and gynecomastia could also represent a chance occurrence as 35–40% of healthy men have clinical or histological gynecomastia [52].

Alcohol has been variably linked as a causative factor in the genesis of MBC. A large Swedish study has not shown any such correlation [53], although it has been implicated as a causal agent in other studies [54]. A case control study conducted in Europe has shown that for alcohol intakes of less than 60 grams per day, the relative risk of MBC is comparable to that in females,

and it continues to increase at high consumption levels [55]. Other risk factors mentioned in various studies are low socioeconomic status, obesity, pacemakers, tuberculosis and hyperthyroidism [56,57]. A meta analysis of 7 case-control studies revealed that the risk of MBC to be significantly increased in males with the following characteristics; never married, benign breast disease, gynecomastia, Jewish or history of breast cancer in a first-degree relative [58-61].

4. Abstract:

OBJECTIVES: Male breast cancer is a rare disease of largely unknown aetiology. In addition to genetic and hormone-related risk factors, a large number of environmental chemicals are suspected of playing a role in breast cancer. The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men may help to identify mammary carcinogens in the environment.

METHODS: Occupational risk factors for male breast cancer were investigated in a multi-centre case-control study conducted in eight European countries which included 104 cases and 1901 controls. Lifetime work history was obtained during in-person interviews. Occupational exposures to endocrine disrupting chemicals (alkylphenolic compounds, phthalates, polychlorinated biphenyls (PCBs) and dioxins) were assessed on a case-by-case basis using expert judgement.

RESULTS: Male breast cancer incidence was particularly increased in motor vehicle mechanics (OR 2.1, 95% CI 1.0 to 4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers, and furniture manufacture workers. The OR for exposure to alkylphenolic compounds above the median was 3.8 (95% CI 1.5 to 9.5). This association persisted after adjustment for occupational exposures to other environmental oestrogens.

CONCLUSION: These findings suggest that some environmental chemicals are possible mammary carcinogens. Petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer.

Citation:

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.

Villeneuve S - *Occup Environ Med* - 01-DEC-2010; 67(12): 837-44

5. Abstract:

Most risk factors for male breast cancer have been derived from retrospective studies that may reflect selective recall. In the prospective National Institutes of Health-AARP Diet and Health Study, we studied 324 920 men, among whom 121 developed breast cancer. Men who reported a first-degree relative with breast cancer had an increased risk of breast cancer (relative risk [RR] = 1.92, 95% confidence interval [CI] = 1.19 to 3.09). Among the medical conditions examined, a new finding emerged regarding increased male breast cancer risk associated with a history of a bone fracture (RR = 2.20, 95% CI = 1.24 to 3.91). Obesity was positively related to risk (RR = 1.79, 95% CI = 1.10 to 2.91, for body mass indices of ≥ 30 vs < 25 kg/m²) and physical activity inversely related, even after adjustment for body mass index. Smokers were at somewhat elevated risk, although trends with smoking characteristics were inconsistent. Alcohol consumption was not related to risk. The identified risk factors show some commonalities with female breast cancer and indicate the importance of hormonal mechanisms. Differences in risk factors may reflect unique mechanisms associated with androgens and their ratio to bioavailable estrogens.

Citation:

Prospective evaluation of risk factors for male breast cancer.
Brinton LA - *J Natl Cancer Inst* - 15-OCT-2008; 100(20): 1477-81

Johansen Taber, Katherine A (11/2010). "Male breast cancer: risk factors, diagnosis, and management (Review)". *Oncology reports*(1021-335X), 24(5), p.1115.

Table I. Risk factors for MBC (3,4,7,13-41).

Known presence of *BRCA* mutation
History of *BRCA*-suggestive cancer, either in self or family
Estrogen exposure/androgen insufficiency
Klinefelter syndrome
Testicular abnormality
Obesity
Liver cirrhosis
Exogenous estrogen therapy
Radiation exposure
Occupational exposure
High ambient temperature

Occupational risks. Men who work in high-temperature environments, such as blast furnaces, steel works, and rolling mills have a higher risk for breast cancer, probably due to testicular failure resulting from long-term exposure to high ambient temperatures (4,29). In a 1988 Swedish study, those who worked in the soap and perfume industry showed an almost eight-fold increase in risk for MBC, likely because during the 1950s and 1960s this industry made estrogen containing cosmetic creams, increasing workers' exposure to exogenous estrogens (35). Occupational carcinogen exposure, such as that found in gasoline and exhaust fumes, has also been implicated in increasing risk for breast cancer (4,36).

6. Abstract:

Male breast cancer (MaleBC) is a rare disease, accounting for <1% of all male tumors. During the last few years, there has been an increase in the incidence of this disease, along with the increase in female breast cancer (FBC). Little is known about the etiology of MaleBC: hormonal, environmental and genetic factors have been reported to be involved in its pathogenesis. Major risk factors include clinical disorders carrying hormonal imbalances, radiation exposure and, in particular, a positive family history (FH) for BC, the latter suggestive of genetic susceptibility. Rare mutations in high-penetrance genes (BRCA1 and BRCA2) confer a high risk of BC development; low-penetrance gene mutations (i.e. CHEK-2) are more common but involve a lower risk increase. About 90% of all male breast tumors have proved to be invasive ductal carcinomas, expressing high levels of hormone receptors with evident therapeutic returns. The most common clinical sign of BC onset in men is a painless palpable retroareolar lump, which should be evaluated by means of mammography, ultrasonography and core biopsy or fine needle aspiration (FNA). To date, there are no published data from prospective randomized trials supporting a specific therapeutic approach in MaleBC. Tumor size together with the number of axillary nodes involved are the main prognostic factors and should guide the treatment choice. Locoregional approaches include surgery and radiotherapy (RT), depending upon the initial clinical presentation. When systemic treatment (adjuvant, neoadjuvant and metastatic) is delivered, the choice between hormonal and or chemotherapy (CT) should depend upon the clinical and biological features, according to the FBC management guidelines. However great caution is required because of high rates of age-related comorbidities. 2009 Elsevier Ireland Ltd. All rights reserved.

Citation:

Male breast cancer.

Ottini L - *Crit Rev Oncol Hematol* - 01-FEB-2010; 73(2): 141-55

7. Madeira, Marcelo (2011). "A case report of male breast cancer in a very young patient: what is changing?". *World journal of surgical oncology*(1477-7819), 9(1), p.16.
-

Background

Breast cancer in men is rare, and it accounts for about 1% of all malignant breast neoplasm cases [1,2]. The estimated incidence is 1 case for each 100,000 men. In the United States, about 1,910 new cases were diagnosed in 2009, and 440 of these cases resulted in death [3]. Among the histologic types, invasive ductal carcinoma is the most prevalent breast cancer in males, with an incidence varying from 65 to 95% [2,4].

Male breast cancer has unimodal age-frequency distribution with a peak incidence at 71 years old. Conversely, female breast cancer has a bimodal age-frequency distribution with early-onset and late-onset peak incidences at 52 and 72 years old, respectively [5].

This study examined a 25-year-old man without important risk factors who was diagnosed with invasive ductal carcinoma. Although it is rare, there have been instances of breast cancer in younger males [6]. We evaluated the main aspects of the epidemiology of breast neoplasm in men and the best approach for treatment.

Discussion

There is a close relation between the BRCA2 gene mutation and male breast cancer. It has also been observed, however, that some cases involve BRCA1 participation [14-16]. Other conditions that have been associated with the occurrence of breast neoplasms in men are cirrhosis [17], testicular trauma, obesity, radiation therapy exposure, and the use of exogenous estrogen [18]. In addition to the very young age of the patient in the present report, this patient did not have a family, hormonal, or genetic history that could justify the high risk for breast cancer. Although gynecomastia has been suggested to be present in 6-38% of breast cancer cases in men [19], it was not evident in our patient.

It is fundamental to consider the history of breast tumors in first-degree relatives because that can be an indicator for increased breast cancer risk. Indeed, genetic diseases such as Klinefelter's syndrome and Cowden's disease have been shown to be related to breast cancer in men [1].

Conclusions

Invasive ductal carcinoma in young men is extremely rare; the peak incidence is around the seventh decade of life. Risk factors for male breast cancer include genetic factors and hormonal abnormalities. Despite an absence of a familial history of breast cancer, hormonal abnormalities, or a genetic disease, the male patient in the present study developed breast cancer at a very young age. The causative factors in this patient were unable to be definitively identified. The pathophysiology of breast cancer in males is not adequately understood. As more cases of breast cancer in young male patients are investigated, we may be able to gain a better understanding of the mechanism.

8. Review

Male breast cancer

Sandhu NP - *Journal of Men's Health* - September, 2012; 9(3); 146-153

Nicole P. Sandhu, MD, PhD^{a,□}

Marie Brid Mac Bride, MB, BCh^b

Christina A. Dilaveri, MD^b

Lonzetta Neal, MD^b

David R. Farley, MD^c

Charles L. Loprinzi, MD^d

Dietlind L. Wahner-Roedler, MD^b

Karthik Ghosh, MD, MS^b

^a Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA

^b Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA

^c Division of Gastroenterologic and General Surgery, Mayo Clinic, Rochester, MN, USA

^d Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA

* Corresponding author.

E-mail address: sandhu.nicole@mayo.edu

Manuscript received January 13, 2012 , accepted March 15, 2012

PII S1875-6867(12)00055-3

Abstract

Male breast cancer is rare, and many patients and health care providers are not familiar with this entity. Although the underlying causes are not well understood, certain populations are at higher risk, including certain gene mutation carriers, men with Klinefelter syndrome, and

certain ethnic groups. Male breast cancer typically presents at a later stage than female breast cancer. A palpable mass is the most common presentation, but nipple discharge or other nipple changes may be seen. Because the number of affected individuals is small, prospective trials have not been conducted; thus, treatment recommendations are typically taken from large trials involving female breast cancer populations. Although outcomes in male breast cancer were previously thought to be worse than female breast cancer outcomes, it appears that they are similar. Questions regarding the most effective surgical and adjuvant therapies remain. Mastectomy with axillary lymph node evaluation, adjuvant hormonal therapy, and chemotherapy are commonly used. Providers of health care to male patients must be aware of the possibility of breast cancer and appropriately evaluate any suspicious changes.

Introduction

Breast cancer is rare in men, accounting for less than 1% of all breast cancers diagnosed annually in the United States [1]. The American Cancer Society estimates that, in 2012, 2,190 new cases of breast cancer will be diagnosed in men, with 410 deaths attributable to male breast cancer (MBC) [2]. Many are at an advanced stage (stage III or greater) at the time of diagnosis [3]. Therefore, health care providers must be aware of the potential for men to develop breast cancer.

This article reviews risk factors, clinical features, diagnostic strategies, management, and follow-up recommendations after treatment for MBC.

Epidemiology

The incidence of MBC has increased since 1975, but the reasons are not known. It is unlikely to be due to improved detection; male patients, even in higher-risk groups, typically do not undergo breast cancer screening. Surveillance, Epidemiology, and End Results data from 1973 to 2006 showed the incidence of MBC to be about 1 case per 100,000 men in 1973 compared with 1.25 per 100,000 in 2006 [2]. According to the American Cancer Society, the annual incidence rate of MBC is 1.09 per 100,000 men compared with 68.73 per 100,000 women in the United States [4]. This is somewhat higher than the National Cancer Institute statistic, but still quite uncommon. The lifetime risk of MBC is 1 in 1,000 compared with 1 in 8 for women [2]. As in women, breast cancer is most often identified in older men.

Hormonal imbalance

A relative increase in endogenous estrogens relative to testosterone may be a risk factor for MBC. Klinefelter syndrome (XXY), in which affected men have a 50-fold increased risk of MBC, is associated with testicular dysgenesis, elevated gonadotropins, and low testosterone levels [24, 25]. Undescended testes, orchitis, and orchiectomy also increase the risk of MBC [26, 27]. Conditions associated with relative estrogen excess (e.g., hepatic cirrhosis) have also been associated with increased incidence of MBC [28, 29].

Obesity causes imbalanced estrogen-to-testosterone ratios. Men with body mass index (BMI) higher than 30 kg/m² have a higher risk of MBC (RR = 1.79; 95% CI = 1.10–2.91) than those with a BMI of <25 kg/m². The risk of MBC is also elevated in men with a history of bone fracture occurring after the age of 45 years (RR = 2.2; 95% CI = 1.24–3.91) [7]. The authors concluded that the association between bone fractures and MBC may be attributable to declining testosterone levels, a risk factor for osteoporosis in men, associated with increasing age. Physical activity may be protective against MBC because a current physical activity routine was associated with a statistically significant lower risk of developing MBC (RR = 0.49; 95% CI = 0.28–0.87) [7]. This relationship may have been associated with weight, as obese patients are less likely to exercise.

Environmental exposures

An increased incidence of MBC was found in male patients who worked in blast furnaces, steel mills, and rolling mills, suggesting that high environmental temperature could damage testicular health and predispose men to breast cancer [35]. A case–control study [36] demonstrated similar findings, but careful analysis failed to reveal a definite association with high ambient temperature based on a job-exposure matrix. Other environmental exposures, for example, chemical exposures from occupations like working in the soap and perfume industries, may also be associated with MBC [37]. Overall, the role of environmental and workplace exposures in MBC warrants further research.

9. Abstract:

BACKGROUND: We report our findings on a hospital-based retrospective pilot cohort with case-controls study, which we carried out to examine genetic, environmental, and occupational risk factors in men with breast cancer.

METHODS: 86 men with breast cancer were diagnosed in eight VA medical centers that agreed to collaborate on this project. A case-control analysis was conducted on a subset of the male breast cancer cases (n = 44) and age- and ethnicity-matched controls (n = 77). We compared host characteristics, comorbidities, and medications intake between cases and controls by using Chi-square analysis and Fisher's exact test.

RESULTS: The descriptive analysis showed that the majority of veterans with male breast cancer were non-Hispanic white (60%), older than 65 years at diagnosis (56%), and more likely estrogen receptor positive (45%). World War II veterans represented the largest group (22%), followed by the Vietnam era veterans (10%). Thirty-three percent reported a positive family history of cancer, while 18% had another primary cancer diagnosis. Prior alcohol (43%) and tobacco use (56%) was substantial among these patients. Twenty percent of patients were overweight or obese and 55% had comorbid diseases with heart disease being the most prevalent, followed by diabetes mellitus. The case-control analysis yielded a significantly greater proportion of cases with gynecomastia (p < 0.0001), a positive family history of cancer (p =

0.0028), history of antibiotic use ($p = 0.0112$), and history of tobacco use ($p = 0.0143$) compared to controls.

CONCLUSION: The findings of this hospital-based pilot study indicate case-control differences in gynecomastia and family history of cancer. The pilot study lacked sufficient power to determine a true association between the variables of interest and warrants a large-scale collaborative study between the VA medical centers.

Citation:

A pilot study of male breast cancer in the Veterans Affairs healthcare system.

Satram-Hoang S - *J Environ Pathol Toxicol Oncol* - 01-JAN-2010; 29(3): 235-44

Despite the increasing incidence of male breast cancer, it remains an uncommon cancer, accounting for less than 1% of all cancers in men. Because of the rarity of this cancer, randomized and prospective data are lacking. All studies are based on a small series of patients.

Only prospective national clinical trials through cooperative groups would further enhance our understanding of the biology and treatment of this uncommon disease.

10. Lynn, Karen (12/2010). "Rare male breast cancer has similarities to female disease". *MLO. Medical laboratory observer(0580-7247)*, 42(12), p.34.

Like female breast cancer, male breast cancer often is related to estrogen hormonal levels. In men, the risk increases when estrogen levels are abnormally high. Testicular abnormalities in development (e.g., undescended testes, congenital inguinal hernia, or testicular injury) may change the estrogen-level balance. Infertility and Klinefelter's syndrome (the XXY condition) also seem to increase a man's risk of getting breast cancer. Like women, if a man has a history of breast cancer in his family, or if he was treated with radiation for lymphoma to the chest area, his chances of developing this disease increase.^-^^

Another factor that increases a man's chances of getting breast cancer includes advanced age. The median age for diagnosis is age 67 for men and age 62 for women." Alcohol abuse and liver disease are also associated with increased risk for male breast cancer. Various causes of liver damage affect the liver's ability to metabolize steroid hormones, which is why obesity is also a known risk factor. "Just because a man has an increased risk does not mean he will get cancer," Zarka notes.

11. Male breast cancer: a multicentric study. - Culell P - *Breast J* - 01-MAR-2007; 13(2): 213-5

Male breast cancer (MBC) average is about 0.2% of all cancers and 1% of breast carcinomas. The etiology of MBC is obscure, although an excess risk has been associated with Klinefelter syndrome, testicular disorders, benign breast disease including gynecomastia, use of exogenous estrogens, radiation, and a family history of male or female breast cancer; obesity may increase the risk of MBC, possibly through hormonal mechanisms, while dietary factors, physical activity, and socioeconomic status deserve further investigation

12. White, Jonathan (2011). "Male breast carcinoma: increased awareness needed".
Breast cancer research : BCR(1465-5411), 13(5), p.219

13. Abstract:

Male breast cancer is a very rare disease with an incidence of about 0.5-1% comparing with the one of female breast cancer but relatively little is known about its cause. Treatment strategies for breast cancer in males are derived from studies performed among females. The probable reasons behind the frequent, late diagnoses presented at stages III or IV might be the lack of awareness. The rarity of the disease precludes large prospective randomized clinical trials. This study reviews male breast cancer and its risk factors, recommendations for diagnosis and the management of patients with male breast cancer.

Citation:

Male breast carcinoma: epidemiology, risk factors and current therapeutic approaches.
Zygianni AG - *Asian Pac J Cancer Prev* - 01-JAN-2012; 13(1): 15-9

14. Gynecomastia
Narula HS - *Endocrinol Metab Clin North Am* - 01-JUN-2007; 36(2): 497-519

Fortunately, breast cancer is rare in men; approximately 1400 men are diagnosed with invasive breast cancer in the United States each year—1 percent of the risk of developing breast cancer in

women. Men with a family history of breast cancer in female relatives have a 2.5 times increased risk of developing breast cancer, however, and those with an inherited germline BRCA2 mutation are at a 100-fold greater risk of developing a breast malignancy. With the exception of KS, gynecomastia does not increase the risk of future development of breast carcinoma [89]. Men with breast cancer seem to have a prognosis similar to women with the same stage of cancer at the time of diagnosis [89].

Introduction

Breast cancer is predominantly a female disease with 49,492 cases (invasive and non-invasive) diagnosed in the UK in 2006 [1]. According to data from the International Agency for Research on Cancer, this is broadly in line with figures from other western nations [2]. Tremendous strides in our understanding of breast cancer have been made over the past two decades and, when detected early, breast cancer is one of the most curable and treatable of all cancers. Male breast cancer is much less frequent with 334 cases diagnosed in the UK in 2006 [1], accounting for just under 1% of all breast cancers.

Risk factors for male breast cancer

Owing to the rarity of male breast cancer, establishing precise risk factors for the disease has proved challenging. Male and female breast cancers share many common risk factors; for example, advancing age and previous family history. In terms of male breast cancer, data from the Breast Cancer Linkage Consortium showed that men harbouring *BRCA2* mutations have a relative risk of 80 for developing breast cancer [3] - making *BRCA2* the strongest known gene associated with male breast cancer [4,5]. Androgen receptor mutations have also been reported [6]. Some suggested risk factors associated with male breast cancer are summarised in Table 1[4-8].

Table 1

Suggested risk factors for male breast cancer

Risk factor

Explanation

| | |
|-----------------------------|---|
| BRCA2 | <i>BRCA2</i> mutations are associated with most inherited MBC |
| Klinefelter syndrome | Hereditary condition characterised by the 47XXY karyotype, which is consistently associated with MBC |
| Androgen receptor mutation | Germline mutations in <i>AR</i> predispose to MBC |
| CYP17 | Encodes cytochrome P450c17 α , an enzyme involved in oestrogen and androgen biosynthesis |
| Cowden syndrome | Autosomal-dominant cancer susceptibility syndrome caused by germline mutation in the <i>PTEN</i> gene |
| CHEK2 | CHEK2*1100delC variants may increase risk of MBC by 10-fold |
| Endogenous oestrogen levels | Increased oestrogen levels as a result of obesity, male-female transsexuals and liver cirrhosis are all associated with MBC |
| Testicular disorders | Cryptorchidism, mumps orchitis, orchiectomy, congenital inguinal hernia and testicular injury are associated with MBC |
| Physical inactivity | Lack of exercise is associated with increased risk of MBC |

Data obtained from [3-7]. These references include comprehensive discussion on other considered risk factors for male breast cancer (MBC). CHEK, cell-cycle checkpoint kinase.

White *et al. Breast Cancer Research* 2011 **13**:219 doi:10.1186/bcr2930

This Reference is from a patient education handout:

The exact cause of breast cancer is not known. It is believed that breast cancer occurs due to many factors. Men are at a higher risk of developing breast cancer if they have:

- Other family members who have had breast cancer.
- Changes in certain genes (such as BRCA1 or BRCA2).
- A history of radiation exposure, such as treatment for another type of cancer.
- Higher than normal levels of the hormone estrogen in their bodies. This may be due to:
- Unknown origins.
- Treatment with estrogen-containing drugs.
- Cirrhosis of the liver.
- Being overweight (*obese*).

- Klinefelter's syndrome (*chromosome abnormality*).
- Large intake of alcohol.
- Abnormalities of the testicles:
 - Past history of mumps.
 - Undescended testicle.
 - Surgical removal of the testicles.
- Certain occupational exposures (not proven, but may be associated with male breast cancer). Such exposures may include:
 - High temperatures.
 - Gasoline fumes.

15. *Semper Fi: Always Faithful*; Burki TK - *Lancet Oncol* - April, 2012; 13(4); 344

“There is one thing of which there is no doubt: the water at the Camp Lejeune Marine base in North Carolina, USA, was contaminated. It was poisoned from 1957 to 1987; perhaps a million people were exposed to it. Firemen describe hydrants disgorging water that reeked of gasoline. The Marine Corps itself documented the improper disposal of cleaning solvents, while other documents outlined a fuel spill of 1·1 million gallons. The water contained more than 20 times the safe levels of tetrachloroethylene and a scarcely credible 280 times the safe level of trichloroethylene, both of which are carcinogenic. There were a host of other chemicals present too, including benzene.

How many people became sick is still unclear. We know of a cluster of cases of male breast cancer, the cemetery has high numbers of children, and efforts to contact those who lived on the base are turning up more and more people with serious health problems. A website dedicated to providing information on the contamination states that those exposed to the water—Marines, sailors, families, and civilian employees—have subsequently developed liver cancer, kidney cancer, breast cancer, bladder cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, leukaemia, and non-Hodgkin lymphoma.

Master Sergeant Jerry Ensminger trained some 2000 recruits during his time with the Marine Corps, which began in 1970. He lived on Camp Lejeune. It was there that his daughter Janey was born in 1975. Janey died from leukaemia before she reached her tenth birthday. Today the Janey Ensminger Act, which would force the military to provide health care for those affected by their exposure to the toxic water of Camp Lejeune, sits before Congress. It is testament to the tireless campaigning of her indefatigable father (and others). Their quest forms the subject of Rachel Libert and Tony Hardmon's slender documentary *Semper Fi: Always Faithful*.

Ensminger is a gruff man, greying at the temples. There is something of the American outdoorsman to him: diligent, well-mannered, and keen on hunting. His attempt to hold the military to account for Camp Lejeune has fully occupied his retirement. He has been joined in his efforts by the sensitive Mike Pantain, who was born on Camp Lejeune and diagnosed with male breast cancer in 2007, and the elderly and reclusive Major Tom Townsend. We accompany Ensminger et al on trips to Washington, DC, and interviews with environmental experts. It is an

endeavour that often appears hopeless, but Ensminger is unyielding, trawling through endless documents, traversing the country, and hearing testimony from those whose health has been wrecked.

In all this, the military appears obstructive, non-committal, and resistant to outside scrutiny. Most offensively, it seems to be dragging its feet in notifying former residents of Camp Lejeune. But *Semper Fi*'s impact is weakened by the fact that it does not contain any fresh interviews with military personnel or politicians. There is plenty of footage of select committee activity, but Libert and Hardmon remain firmly embedded in Ensminger's unit. It means the film lacks a little balance—we do not really get a feel for the context in which Ensminger is fighting his war. Moreover, it is not clear from what all this contamination resulted, nor exactly what these chemicals were, why they were in use, what kind of effect they might have, and how the situation is being addressed. “David versus Goliath” is a clean and affecting narrative but more attention to the wider issues—scientific, political, and ethical—would have been welcome.

Still, it is certainly a compelling tale and Ensminger is excellent and honourable company. The story meanders occasionally but builds to a satisfying conclusion with national news stations publicising the scandal and congressmen offering the campaign their backing. The Marine Corps destroyed the lives of many of those who lived on Camp Lejeune. *Semper Fi* further contends there are over 130 contaminated military sites in the USA, making the Department of Defence “the nation's largest polluter”. But there is a pleasing irony to the fact that the military also hardened their nemesis to the rigours that such a gruelling and long-running campaign would demand of him. Indeed, Ensminger seems to display a greater fealty to his former brothers-in-arms than their employer did. *Semper Fi* indeed.”

LITERATURE REVIEW OF THE ABOVE CITATIONS:

1. Epidemiology and risk factors for breast cancer. UpToDate, Dec 2012
2. Brinton LA. Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database. *Breast Cancer Res Treat* - 01-JAN-2010; 119(1): 185-92
3. Contractor KB. Male breast cancer: is the scenario changing. *World J Surg Oncol* - 01-JAN-2008; 6: 58
4. Villeneuve S. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. *Occup Environ Med* - 01-DEC-2010; 67(12): 837-44
5. Brinton LA. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* - 15-OCT-2008; 100(20): 1477-81
6. Ottini L. Male breast cancer. *Crit Rev Oncol Hematol* - 01-FEB-2010; 73(2): 141-55
7. Madeira M. *World J Surg Oncol* - 01-JAN-2011; 9: 16
8. Sandhu NP. Male breast cancer. *Journal of Men's Health* - September, 2012; 9(3); 146-153
9. Satram-Hoang S. A pilot study of male breast cancer in the Veterans Affairs healthcare system. *J Environ Pathol Toxicol Oncol* - 01-JAN-2010; 29(3): 235-44
10. Lynn K. Rare male breast cancer has similarities to female disease. *MLO Med Lab Obs* -

- 01-DEC-2010; 42(12): 34, 36
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 12. White, Jonathan (2011). Male breast carcinoma: increased awareness needed. *Breast cancer research : BCR(1465-5411)*, 13(5), p.219
 13. Zygogianni AG. Male breast carcinoma: epidemiology, risk factors and current therapeutic approaches. *Asian Pac J Cancer Prev* - 01-JAN-2012; 13(1): 15-9
 14. Narula HS. Gynecomastia. *Endocrinol Metab Clin North Am* - 01-JUN-2007; 36(2): 497-519
 15. Burki TK. Semper Fi: Always Faithful; *Lancet Oncol* - April, 2012; 13(4); 344

I didn't cite one of the references above in the body of this document by Johansen Taber, Katherine A, in my report so I didn't list it above in the literature review.

MY CONCLUSIONS IN MY REPORT:

I performed a review of the literature in regards to male breast cancer (MBC). The following is a summary of that review.

MBC is rare, accounting for approximately 1% of all breast cancers. Its incidence is increasing. One report suggests that incidence has increased 26% over the past 25 years. The median age of onset of MBC is 65 to 67, approximately 5 to 10 years older than in women. Because it is so rare, relatively little is known about its cause and establishing precise risk factors for the disease has been challenging [1-15]. Randomized and prospective data are lacking and all studies have been based on a small series of patients. The exact cause of breast cancer is not known and it is believed that it occurs due to many factors. Men are at a higher risk of developing breast cancer if they have:

- a) Other family members who have had breast cancer.
- b) Changes in certain genes (such as BRCA1 or BRCA2).
- c) A history of radiation exposure, such as treatment for another type of cancer.
- d) Higher than normal levels of the hormone estrogen in their bodies. This may be due to: Unknown origins, treatment with estrogen-containing drugs, cirrhosis of the liver, being overweight (obese).
- e) Klinefelter's syndrome (chromosome abnormality).
- f) Large intake of alcohol.
- g) Abnormalities of the testicles: past history of mumps, undescended testicle, surgical removal of the testicles.
- h) Certain occupational exposures (not proven, but may be associated with male breast cancer). Such exposures may include: high temperatures, gasoline fumes.

A literature review current through Dec 2012 by UpToDate has documented that “although the majority of men with breast cancer have no identifiable risk factors, several have been identified, many related to hormone levels. Many of these risk factors are the same as in women, including family history, Jewish ancestry, obesity, low levels of physical activity, prior chest wall irradiation, and benign breast disease. Other risk factors that are modestly unique to men include never being married, gynecomastia, a history of testicular or liver pathology, a history of a bone fracture after age 45, and Klinefelter’s syndrome.” Studies have been conflicting on whether gynecomastia is a true risk factor for the development of breast cancer. In terms of environmental exposures, “organochlorines including polychlorinated biphenyls (PCB's), dioxins, and organochlorine pesticides such as DDT are compounds that are weak estrogens, highly lipophilic, and capable of persisting in body tissues for years, however, most large studies have failed to find an association between exposure to these compounds and MBC.” [UpToDate, 1].

Another study which evaluated environmental chemicals suspected of playing a role in breast cancer concluded that their findings suggested that some environmental chemicals were possible mammary carcinogens, including petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons due to a consistent elevated risk of MBC observed in motor vehicle mechanics. This study included 104 cases and 1901 controls [Villeneuve, 4]. Overall, the role of environmental exposures in MBC warrants further research [Sandhu, 8].

In summary, after research of the current literature, there is no definitive medical evidence to suggest that the contaminated water at Camp Lejeune was a causative factor in the development of breast cancer in the veteran. Although the veteran’s oncologist states that the contaminated water more likely than not led to Mr. breast cancer, there is no definitive medical evidence found in the literature, based on multiple studies and observations, to support this statement. More research is required at this time since there is no medical evidence which shows that trichloroethylene, tetrachloroethylene, benzene or vinyl chloride are associated with an elevated risk of male breast cancer.

Metabolic risk score and cancer risk: pooled analysis of seven cohorts.

[Stocks T](#)¹, [Bjørge T](#)², [Ulmer H](#)³, [Manjer J](#)³, [Hägström C](#)³, [Nagel G](#)², [Engeland A](#)², [Johansen D](#)³, [Hallmans G](#)³, [Selmer R](#)³, [Concin H](#)³, [Tretli S](#)³, [Jonsson H](#)³, [Stattin P](#)³.

Abstract

BACKGROUND:

There are few data on the joint influence of metabolic factors on risk of separate cancers.

METHODS:

We analysed data on body mass index, blood pressure and plasma levels of glucose, total cholesterol and triglycerides from seven European cohorts comprising 564 596 men and women with a mean age of 44 years. We weighted those factors equally into a standardized metabolic risk score [MRS, mean = 0, standard deviation (SD) = 1], with an individual's level indicated as SDs from the sex- and cohort-specific means. Cancer hazard ratios were calculated by Cox regression with age as timescale and with relevant adjustments including smoking status. All statistical tests were two-sided.

RESULTS:

During a mean follow-up of 12 years, 21 593 men and 14 348 women were diagnosed with cancer. MRS was linearly and positively associated with incident cancer in total and at sites ($P < 0.05$). In men, risk per SD MRS was increased by 43% (95% confidence interval: 27-61) for renal cell cancer, 43% (16-76) for liver cancer, 29% (20-38) for colon cancer, 27% (5-54) for oesophageal cancer, 20% (9-31) for rectal cancer, 19% (4-37) for leukaemias, 15% (1-30) for oral cancer and 10% (2-19) for bladder cancer. In women, risk increases per SD MRS were 56% (42-70) for endometrial cancer, 53% (29-81) for pancreatic cancer, 40% (16-67) for renal cell cancer, 27% (9-47) for cervical cancer and 17% (3-32) for rectal cancer.

CONCLUSION:

This largest study to date on the joint influence of metabolic factors on risk of separate cancers showed increased risks for several cancers, in particular renal cell and liver cancer in men and endometrial and pancreatic cancer in women.

KEYWORDS:

cohort studies; metabolic syndrome x; neoplasms

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KIDNEY DISEASE

Summary

Organic solvents have been associated with various forms of kidney disease since the early 20th century. Initial forms of disease appeared related to active exposure, both inhalation and transdermal, with improvement after cessation. Beginning in the 1950s, interest in nephrotic syndrome and solvents arose, evolving into a recognition that Goodpasture's syndrome (anti-basement membrane glomerulonephritis and pulmonary disease) was consistently related (Bombassei – review 1992). Increasingly, reviews supported this view (Churchill 1983; Lauwerys 1985). A formal meta-analysis (Ravnskov 2000) summarizes the effects of solvent exposure on early and late forms of glomerular disease and elsewhere (Ravnskov 2000b) summarizes the epidemiology according to Hill criteria. Ravnskov (2000a) presents various studies in transparent tabular format. Solvent exposure clearly worsens existing renal disease. It may induce disease in susceptible individuals. Interruption of exposure ends progression of the disease. There appears to be no delayed onset attributable to solvent exposures. Some evidence supports sub-clinical acute tubular effects that precede glomerular damage.

Epidemiology

Case control studies, cohort and cross-sectional studies, case reports and series, and animal studies are summarized on the attached excel spreadsheet. They are nicely summarized in Ravnskov (2000a, 2000b). Formal tables present the data. Particular studies worth reviewing may include the following. A lifetime solvent exposure score (Hotz 1994) appears to be an important predictor of disease. Evidence in humans supports both tubular (Mutti 1981, Franchini 1983) and glomerular (summarized Ravnskov 2000a) disease. Cohort (Jacob 2007) and cross-sectional (Mutti 1981) studies suggest that increased doses are associated with worse disease and that ongoing exposure is also associated with progression of disease (Jacob 2007). Since the first reports, reports also suggest improvement on cessation of exposure (Ravnskov 1979; D'Apice 1978; Newman 1904, Anderson 1912).

Toxicology, Exposures, and Dose Extrapolation

The Environmental Protection Agency (EPA) considers the amounts that can be “safely” consumed each day for a lifetime without concerns for adverse health effects, i.e., the reference dose (RfD) for each of the agents as listed below. The source is EPA's Integrated Risk Information System (IRIS). That dose incorporates a safety factor listed in column 2. Similarly, the Agency for Toxic Substances and Disease Registry provides No Adverse Observed Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for each of the four contaminants of concern. The table below summarizes the EPA IRIS doses and the associated

safety factors. In general, these safety factors take into consideration extrapolations of dose effects from animals to humans and inter-subject variability.

| | RFD (+) in mg/kg/day | Safety factor |
|--------------------------|----------------------|---------------|
| Trichloroethylene (TCE) | 0.0005 | 1,000 |
| Perchloroethylene (PERC) | 0.006 | 1,000 |
| Benzene | 0.004 | 300 |
| Vinyl Chloride | 0.003 | 1,000 |

*: animal data, as no human data are available

For Trichloroethylene, six studies have an acute (<14 days of exposure) NOAEL of greater than 100 mg/kg/day, with one additional study showing excess kidney weight at that concentration. For intermediate exposures, three studies had an intermediate (14 – 365 days of exposure) NOAEL of greater than 100 mg/kg/day, with one study each showing tubular cell destruction and protein. Nine of ten studies showed a range of adverse effects between 250 and 1000 mg/kg/day, with one study below 100 showing no adverse events and one NOAEL of 50. No long-term (>365 days of exposure) are available.

For Perchloroethylene, few studies have examined renal effects. One study demonstrated increased kidney weight after acute (15 days) at a dose of 1,000 mg/kg/day, though one other study demonstrated a NOAEL above that level. Intermediate (15 – 365 days) duration of exposure at 150 mg/kg/day showed chronic effects as did chronic (>365) exposure at 120 – 150 mg/kg/day.

Benzene has not been shown to have any adverse renal effects, in short- intermediate or long-term exposures. Vinyl chloride was not studied for its renal effects

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Disparities in the prevalence, pathogenesis and progression of monoclonal gammopathy of undetermined significance and multiple myeloma between blacks and whites.

[Greenberg AJ](#), [Vachon CM](#), [Rajkumar SV](#).

Source

Division of Epidemiology, Department of Health Sciences Research, Rochester, MN, USA.

Abstract

There is marked racial disparity in the incidence of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma, with a two to threefold increased risk in blacks compared with whites. The increased risk has been seen both in Africans and African Americans. Similarly, an increased risk of monoclonal gammopathies in blacks compared with whites has been noted after adjusting for socioeconomic and other risk factors, suggesting a genetic predisposition. The higher risk of multiple myeloma in blacks is likely a result of the higher prevalence of the premalignant MGUS stage; there are no data to suggest that blacks have a higher progression rate of MGUS to myeloma. Studies are emerging that suggest the baseline cytogenetic characteristics, and progression may differ by race. In contrast, to the increased risk noted in blacks, studies suggest that the risk may be lower in certain racial and ethnic groups, notably persons from Japan and Mexico. We review the literature on racial disparity in the prevalence, pathogenesis and progression of MGUS and multiple myeloma between blacks and whites. We also discuss future directions for research that could inform management of these conditions and positively influence patient outcomes.

PMID:

22193966

[PubMed - indexed for MEDLINE]

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Light alcohol drinking and cancer: a meta-analysis.

[Bagnardi V](#), [Rota M](#), [Botteri E](#), [Tramacere I](#), [Islami F](#), [Fedirko V](#), [Scotti L](#), [Jenab M](#), [Turati F](#), [Pasquali E](#), [Pelucchi C](#), [Bellocco R](#), [Negri E](#), [Corrao G](#), [Rehm J](#), [Boffetta P](#), [La Vecchia C](#).

Source Department of Statistics, University of Milan-Bicocca, Milan, Italy.
vincenzo.bagnardi@unimib.it

Abstract

BACKGROUND:

There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day).

PATIENTS AND METHODS:

We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010.

RESULTS:

We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (CI) 1.06-1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09-1.56) and female breast cancer (RR = 1.05; 95% CI 1.02-1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

CONCLUSIONS:

Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast

<http://annonc.oxfordjournals.org/content/24/2/301.full>

Annals of Oncology

Volume 24, Issue 2

Pp. 301-308.

Light alcohol drinking and cancer: a meta-analysis

V. Bagnardi

University of Milan-Bicocca,

Abstract

Background There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day).

Patients and methods We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010.

Results We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (CI) 1.06–1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09–1.56) and female breast cancer (RR = 1.05; 95% CI 1.02–1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

Conclusions Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast.

Human health effects of tetrachloroethylene: key findings and scientific issues.

[Guyton KZ](#)¹, [Hogan KA](#), [Scott CS](#), [Cooper GS](#), [Bale AS](#), [Kopylev L](#), [Barone S](#), [Makris SL](#), [Glenn B](#), [Subramaniam RP](#), [Gwinn MR](#), [Dzubow RC](#), [Chiu WA](#).

Abstract

BACKGROUND:

The U.S. Environmental Protection Agency (EPA) completed a toxicological review of tetrachloroethylene (perchloroethylene, PCE) in February 2012 in support of the Integrated Risk Information System (IRIS).

OBJECTIVES: We reviewed key findings and scientific issues regarding the human health effects of PCE described in the U.S. EPA's Toxicological Review of Tetrachloroethylene (Perchloroethylene).

METHODS:

The updated assessment of PCE synthesized and characterized a substantial database of epidemiological, experimental animal, and mechanistic studies. Key scientific issues were addressed through modeling of PCE toxicokinetics, synthesis of evidence from neurological studies, and analyses of toxicokinetic, mechanistic, and other factors (tumor latency, severity, and background rate) in interpreting experimental animal cancer findings. Considerations in evaluating epidemiological studies included the quality (e.g., specificity) of the exposure assessment methods and other essential design features, and the potential for alternative explanations for observed associations (e.g., bias or confounding).

DISCUSSION:

Toxicokinetic modeling aided in characterizing the complex metabolism and multiple metabolites that contribute to PCE toxicity. The exposure assessment approach—a key evaluation factor for epidemiological studies of bladder cancer, non-Hodgkin lymphoma, and multiple myeloma—provided suggestive evidence of carcinogenicity. Bioassay data provided conclusive evidence of carcinogenicity in experimental animals. Neurotoxicity was identified as a sensitive noncancer health effect, occurring at low exposures: a conclusion supported by multiple studies. Evidence was integrated from human, experimental animal, and mechanistic data sets in assessing adverse health effects of PCE.

CONCLUSIONS: PCE is likely to be carcinogenic to humans. Neurotoxicity is a sensitive adverse health effect of PCE.

Impaired Kidney Function Linked to Higher Renal Cancer Risk

Diedtra Henderson

May 30, 2014

Impaired kidney function, as measured by depressed glomerular filtration rates (GFR), is associated with a significantly higher risk of being diagnosed with renal and urothelial cancers, according to a retrospective cohort study.

William T. Lowrance, MD, MPH, from the Huntsman Cancer Institute, University of Utah, Division of Urology, Salt Lake City, and colleagues report the findings of their study, powered by Kaiser Permanente Northern California records for 1.19 million adult patients with no history of cancer and known kidney function, in an article published online May 29 in the Journal of the American Society of Nephrology.

The number of patients diagnosed with chronic kidney disease (CKD) is rising, Dr. Lowrance and coauthors note, with an estimated 11.5% of US residents registering diminished estimated GFR (eGFR) levels. To determine whether the level of kidney function was associated with a higher risk for subsequent cancer, the research team analyzed data from the regional cancer registry, looking for heightened risk for a wide variety of cancers. The patients were more likely to be older, people of color, poorer, and current or former smokers.

The researchers identified 76,809 incident cancers during the 5-plus years of follow-up, with the strongest correlations found between reduced kidney function and increased risk for renal and urothelial cancers.

The researchers adjusted for confounders including age, gender, race, socioeconomic status, comorbidities, proteinuria, hematuria, and body mass index. When eGFR rates ranged between 45 and 59 mL/minute/1.73 m², incident diagnosed renal cancer rate increased by 1.39 (95% confidence interval [CI], 1.22 - 1.58). That hazard ratio inched up to 1.81 (95% CI, 1.51 - 2.17) for eGFR ranging from 30 to 44 mL/minute/1.73 m². And when eGFR dropped to less than 30 mL/minute/1.73 m², risk for renal cancer rate soared to 2.28 (95% CI, 1.78 - 2.92), and there also was a 48% increased rate of urothelial cancer.

The authors found no similarly heightened risk for breast, colorectal, lung, or prostate cancer.

"Our findings reveal the association of CKD and cancer risk is site-specific for renal and urothelial cancers, and does not appear to be associated with an individual's overall cancer risk," the authors write. Although the study team asserts that their findings could more effectively target cancer screening recommendations for patients with CKD, an accompanying editorial says the cancer associations are "smaller than that generally considered acceptable for screening purposes."

J Am Soc Nephrol. Published online May 29, 2014. Abstract

INFORMATION PAPER

ATSDR Mortality Study of Civilian Employees at Camp Lejeune and Camp Pendleton

Overview: The Department of Defense (DoD) and Department of Veterans Affairs (VA) coordinate on the provision of medical care for veterans who formerly lived at Marine Corps Base Camp Lejeune, NC. Contaminated drinking water was discovered in the 1980s at Camp Lejeune, which has caused concerns about potential long-term health effects. On 13 August 2014, the Agency for Toxic Substances and Disease Registry (ATSDR), which is part of the CDC, published a mortality study of civilian employees (reference below). ATSDR published a companion mortality study of Marines in February 2014. This Info Paper was written on behalf of the DoD/VA Deployment Health Work Group; and it summarizes the ATSDR study and the potential impact on DoD and VA. DoD and VA do not need to change their current policies related to the provision of medical care and disability benefits for veterans who previously lived at Camp Lejeune, as a result of this ATSDR study.

Background: Contamination of the drinking water supply was discovered at Camp Lejeune in the early 1980s. On-base water-supply systems were contaminated with low concentrations of trichloroethylene (TCE), a metal degreaser, and perchloroethylene (PCE), a dry cleaning agent. Low levels of benzene, vinyl chloride, and trans-1,2-dichloroethylene (DCE) were also found in the water. Groundwater contamination is estimated to have started as early as the mid-1950s. The contaminated wells supplying the water systems were identified and shut down in 1985. The Navy estimated that as many as 630,000 active-duty personnel may have been exposed, as well as family members and DoD civilians. Many questions remain unanswered regarding the extent of base water contamination, the type and duration of exposure experienced by individuals, and the likelihood that contaminant levels in the water supply were high enough to result in disease. ATSDR has been evaluating the health of previous residents of Camp Lejeune (CL) since 1991. The Navy has provided more than \$40 million to fund these ATSDR studies.

Summary of ATSDR study: The goal of this study was “to determine if potential exposures of employees to contaminated drinking water at Camp Lejeune increased the risk of mortality from cancers and other chronic diseases.” Civilian employees were identified who worked at either Camp Lejeune or Camp Pendleton, during the period of April 1973 to December 1985. Camp Pendleton did not have contaminated drinking water. 1973 was chosen as the starting year because that is when the relevant DoD personnel records became available at the Defense Manpower Data Center. 1985 was chosen as the ending year because the water contamination ended at Camp Lejeune during that year. The study included 4,647 civilians who worked at Camp Lejeune (CL) and 4,690 civilians who worked at Camp Pendleton (CP). Follow-up of vital status was performed from 1979 to 2008. In 2008, the median age was 58 years in the CL group and 60 years in the CP group. Deaths were identified through the records of the Social Security Administration and the National Death Index (NDI). The causes of death were determined from the NDI.

Potential exposure to contaminated drinking water was estimated by conducting a historical reconstruction. There is no way to validate this model, because there were no analyses of water samples for low-level contamination with the relevant chemicals, prior to the early 1980s. Estimated concentration levels were assigned to each individual employee. In addition to uncertainties related to the water model, there was no information on exposures of individual employees. Employees could only have had potential exposure during their work on the base, because they resided off-base. The median length of employment at CL or CP was 2.5 years. The authors stated: “Another serious limitation was exposure misclassification bias. There were several sources of exposure misclassification.” The authors stated “we did not have information on water usage by the workers at Camp Lejeune.” The authors also stated that some of the workers “may have been unexposed because they did not use the drinking water for any purpose during the workday.” In summary, the authors did not have any data to show that specific individual employees at CL were exposed to contaminated drinking water.

Two major types of comparisons of mortality rates were made. These comparisons assumed that the entire CL group was “exposed.” 1. Standardized Mortality Rates (SMR) were calculated using the rates of death in the CL and CP groups, which were compared to rates in the general US population, controlling for age, race, and sex. The control group in this analysis was the general US population. (Table 3) 2. The rates of death of the CL group were directly compared to the rates of death in the CP group. The control group in this analysis was the CP group. (Table 4)

Overall, the CL and CP populations were both significantly healthier than the general US population. There was a significant, 14% decrease in the overall death rate from all causes in the CL group, compared to the US population. 14.1% of the individuals in the CL group and 18.5% of the individuals in the CP group died by the end of the follow-up period in 2008. Therefore, there was a lower overall mortality rate in the CL group, compared to the CP group.

The CL population had a 12% increase in the death rate from all cancers, compared to the CP population. However, this apparent increase was not statistically significant. There were no significant differences between the CL group and the CP group in the death rates from any specific diseases. The authors state the CL group had increased mortality rates compared to the CP group for the following diseases: kidney cancer, leukemias, multiple myeloma, rectal cancer, oral cavity cancers, and Parkinson’s disease. However, none of these diseases showed a statistically significant increase in the CL group.

The authors stated “One serious limitation of the study was the small numbers of most causes of death which resulted in wide confidence intervals.” The term “wide confidence intervals” means the results were not statistically significant. The authors stated: “We did not use statistical significance testing to interpret findings.” However, they did not provide a justification for this unusual approach, which is completely contrary to acceptable epidemiological methodology. The analyses controlled for sex, race, education, and occupation (blue collar vs. white collar). There was no control for smoking, alcohol use, or other known, important risk factors for cancer and other chronic diseases. In particular, 27% of the individuals in both the CL and CP groups worked with solvents. In general, occupational exposure to solvents would greatly exceed potential exposure to solvents through ingestion of low concentrations in drinking water.

In summary, the CL and CP populations were both significantly healthier than the general US population. There were no significant increases in the mortality rates of any disease in the CL group, compared to the general US population. The overall mortality rate in the CL group was lower than the rate in the CP group. There were no significant increases in the mortality rates of any disease in the CL group, compared to the CP group.

Potential impact of ATSDR study on DoD and VA medical care and disability benefits: DoD and VA provide medical care and disability benefits to active-duty members and veterans, who previously lived at Camp Lejeune. This ATSDR study does not provide new scientific evidence that would change DoD and VA policies on medical care and disability benefits. There are currently no “presumptive” diseases attributed to service at Camp Lejeune by statute, regulation, or VA policy. DoD and VA do not need to change their current policies related to the provision of medical care and disability benefits for veterans who previously lived at Camp Lejeune, as a result of this ATSDR study.

ATSDR study: Bove, FJ, Ruckart, PZ, Maslia, M, Larson, TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environmental Health* 2014;13:68.

Dr. Kelley Brix, Defense Health Agency, Research and Development Directorate, 703-681-8211, 14 Aug 2014

INFORMATION PAPER

ATSDR Mortality Study of Marines and Sailors at Camp Lejeune and Camp Pendleton

Overview: The Department of Defense (DoD) and Department of Veterans Affairs (VA) coordinate on the provision of medical care for veterans who formerly lived at Marine Corps Base Camp Lejeune, NC. Contaminated drinking water was discovered in the 1980s at Camp Lejeune, which has caused concerns about potential long-term health effects. On 19 February 2014, the Agency for Toxic Substances and Disease Registry (ATSDR), which is part of the CDC, published a mortality study of Marines and sailors (reference below). Veterans and family members who formerly lived at Camp Lejeune show considerable interest in new ATSDR studies. In addition, VA uses the scientific literature to determine if presumptions of service connection are warranted for diseases, related to specific exposures. This Info Paper was written on behalf of the DoD/VA Deployment Health Work Group; and it summarizes the ATSDR study and the potential impact on DoD and VA. DoD and VA do not need to change their current policies related to the provision of medical care and disability benefits for veterans who previously lived at Camp Lejeune, as a result of this ATSDR study.

Background: Contamination of the drinking water supply was discovered at Camp Lejeune in the early 1980s. On-base water-supply systems were contaminated with low concentrations of trichloroethylene (TCE), a metal degreaser, and perchloroethylene (PCE), a dry cleaning agent. Low levels of benzene, vinyl chloride, and trans-1,2-dichloroethylene (DCE) were also found in the water. Groundwater contamination is estimated to have started as early as the mid-1950s. The contaminated wells supplying the water systems were identified and shut down in 1985. The Navy estimated that as many as 630,000 active-duty personnel may have been exposed, as well as family members and DoD civilians. Many unanswered questions remain regarding the extent of base water contamination, the type and duration of exposure experienced by individuals, and the likelihood that contaminant levels in the water supply were high enough to result in disease. ATSDR has been evaluating the health of previous residents of Camp Lejeune (CL) since 1991. The Navy has provided more than \$30 million to fund these ATSDR studies.

Summary of ATSDR study: The goal of this study was to determine if “exposures of Marine and Naval personnel to contaminated drinking water at Camp Lejeune increased the risk of mortality from cancers and other chronic diseases.” Marine and Naval personnel (“Marines”) were identified who were stationed at either Camp Lejeune or Camp Pendleton, during the period of April 1975 to December 1985. If a Marine was stationed at Camp Pendleton and later transferred to Camp Lejeune, he was assigned to the Camp Lejeune group. Camp Pendleton did not have contaminated drinking water; however, there are a number of Superfund sites on base. April 1975 was chosen as the starting date, because that is when the relevant DoD personnel records became available at the Defense Manpower Data Center. 1985 was chosen as the ending year, because the water contamination ended at Camp Lejeune during that year. The study included 154,932 Marines who were stationed at Camp Lejeune (CL) and 154,969 Marines who were stationed at Camp Pendleton (CP). Follow-up of vital status was performed from 1979 to 2008. Approximately 6% of the individuals in both the CL and CP groups had died by 2008; and approximately 1.5% of both groups were lost to follow-up. The relatively low number of deaths was related to the median age of 49 years at the end of follow-up in 2008. Deaths were identified through the records of the Social Security Administration and the National Death Index (NDI). The causes of death were determined from the NDI.

There were no analyses of water samples for low-level contamination with the relevant chemicals, prior to the early 1980s. Therefore, potential exposure to contaminated drinking water at each

individual's residence was estimated by conducting a historical reconstruction. The water contamination reconstruction used ground water fate and transport and distribution system models. There is no way to validate this model, because of a lack of water analyses before the early 1980s. Estimated monthly average concentration levels were assigned to each individual, based on the drinking water system that served that residence. Separate analyses were performed for 4 chemical contaminants, which were PCE, TCE, benzene, and vinyl chloride. In addition to uncertainties related to the water model, there was incomplete information on the residence of each individual. The authors stated: "A serious limitation was exposure misclassification."

Three types of comparisons of mortality rates were made. In the first and second analyses, the assumption was that the entire CL group was "exposed." 1. Standardized Mortality Rates (SMR) were calculated using the rates of death in the two Marine groups, which were standardized to rates in the general US population, controlling for age, race, and sex. (Table 4) The control group in this analysis was the general US population. 2. The rates of death of the CL group were directly compared to the rates of death in the CP group. (Table 5) The control group in this analysis was the CP group. 3. Cumulative exposures to the 4 chemicals were estimated for each individual who lived at CL. (Table 7) Each individual was classified into one of four exposure categories, based on the water model (high, medium, low, reference [control group]) (Table 6). The residents of CL, who had very low or no chemical exposure based on the water model, served as the control group. About 65,000 CL residents were in the control group. Mortality rates were calculated for 4 separate groups, who were exposed to each of the 4 chemicals. In addition, mortality rates were calculated for a fifth group, which used a combination of all the chemicals (the concentrations of all chemicals were added together to calculate "Total Volatile Organic Compounds," that is, TVOC).

Overall, the CL and CP populations were both significantly healthier than the general US population. For example, there was a significant, 17% decrease in the overall death rate from all causes in the CL group. There was also a significant, 15% decrease in the death rate from all cancers in the CL group. CL Marines had significantly lower rates of death from several specific diseases, compared to the general population, including non-Hodgkin lymphoma, female breast cancer, kidney diseases, and cardiovascular disease. It is noteworthy that only one death from male breast cancer was identified in the CL group. Prostate cancer was the only disease in which there was a significant, 73% increased rate in the CL group, compared to the general population. About half of the deaths in both the CL and CP groups were from suicides, homicides, transportation injuries, or other injuries.

The CL population had a 10% increase in the death rate from all cancers, compared to the CP population, which was marginally significant. There were no significant differences between the CL group and the CP group in the death rates from specific diseases. In particular, there was no difference in the death rates from prostate cancer between the two groups.

Many statistical analyses were performed in the comparisons of the 4 categories of chemical exposures in CL residents, as described on pages 7-8 (high, medium, low, and reference groups). The analyses evaluated whether exposures to increasing levels of a chemical were associated with a higher rate of disease. On page 7, the authors stated "because of the high correlations among the contaminants, it is not possible to separate the effects of each of the individual contaminants." Despite these methodological concerns, 4 separate groups of analyses were performed for the 4 chemicals. The results of all of these analyses related to specific chemicals were not significant. The authors highlighted four possible associations between specific chemicals and specific diseases, even though they were not significant. These were possible associations between: TVOC levels and kidney cancer; TCE levels and Hodgkin lymphoma; benzene levels and Hodgkin lymphoma; and vinyl chloride levels and amyotrophic lateral sclerosis.

In summary, the CL and CP populations were both significantly healthier than the general US population. Even though the CL and CP populations were very large, the numbers of deaths from specific diseases were small, in general. The only statistically significant increase in the CL group was an increase in deaths from prostate cancer, in comparison with the general US population (but not in comparison with the CP population). Many statistical comparisons were made, without adjustment for multiple comparisons. If a correction were made for multiple comparisons, it is likely that the one significant increase of prostate cancer deaths would disappear. The authors stated “the precision of many hazard ratio estimates was low as indicated by the wide confidence intervals.” This means that the results were not statistically significant. The authors stated: “We did not use statistical significance testing to interpret findings.” However, they did not provide a justification for this unusual decision. The analyses controlled for age, sex, race, rank, and education. There was no control for smoking or other known, important risk factors for cancer and other chronic diseases.

Potential impact of ATSDR study on DoD and VA medical care and disability benefits:

DoD and VA provide medical care and disability benefits to active-duty members and veterans, who previously lived at Camp Lejeune. This ATSDR study does not provide new scientific evidence that would change DoD and VA policies on medical care and disability benefits. There are currently no “presumptive” diseases attributed to service at Camp Lejeune by statute, regulation, or VA policy. President Obama signed a law in August 2012, entitled “Honoring America’s Veterans and Caring for Camp Lejeune Families Act of 2012.” This law requires VA to provide medical care to veterans and family members who lived at Camp Lejeune for 30 days or more from 1957 to 1987. The law includes a list of 15 diseases and disease categories, for which VA must provide care. Several of these 15 diseases were included in the ATSDR study. These diseases did not demonstrate a significant association with exposure at Camp Lejeune. DoD and VA do not need to change their current policies related to the provision of medical care and disability benefits for veterans who previously lived at Camp Lejeune, as a result of this ATSDR study.

Future ATSDR studies: Currently, the ATSDR is performing four other studies of the Camp Lejeune population: a mortality study of DoD civilians; an update of an earlier study of birth outcomes, including low birth weight; a health survey, which entails sending questionnaires to previous residents nationwide; and a study of male breast cancer. The mortality study has been completed, and will be submitted for publication soon. The other studies will not be completed until late 2014 or 2015.

ATSDR study: Bove, FJ, Ruckart, PZ, Maslia, M, Larson, TC. Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environmental Health* 2014 Feb;13:10.

Dr. Kelley Brix, Defense Health Agency, Research and Development Directorate, 703-681-8211, 19 Feb 2014

The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis.

[Cheungpasitporn W](#)¹, [Thongprayoon C](#)², [O'Corragain OA](#)², [Edmonds PJ](#)², [Ungprasert P](#)², [Kittanamongkolchai W](#)², [Erickson SB](#)².

Author information

Abstract

BACKGROUND:

The objective of this meta-analysis was to evaluate the association between a history of kidney stones and kidney cancer.

METHODS:

A literature search was performed from inception until June 2014. Studies that reported odds ratios or hazard ratios comparing the risk of renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of the upper urinary tract in patients with the history of kidney stones versus those without the history of kidney stones were included. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

RESULT:

Seven studies were included in our analysis to assess the association between a history of kidney stones and RCC. The pooled RR of RCC in patients with kidney stones was 1.76 (95% CI, 1.24-2.49). The subgroup analysis found that the history of kidney stones was associated with increased RCC risk only in males (RR, 1.41 [95% CI, 1.11-1.80]), but not in females (RR, 1.13 [95% CI, 0.86-1.49]). Five studies were selected to assess the association between a history of kidney stones and TCC. The pooled RR of TCC in patients with kidney stones was 2.14 (95% CI, 1.35-3.40).

CONCLUSION:

Our study demonstrates a significant increased risk of RCC and TCC in patients with prior kidney stones. However, the increased risk of RCC was noted only in male patients. This finding suggests that a history of kidney stones is associated with kidney cancer and may impact clinical management and cancer surveillance.

The Upper Midwest Health Study: gliomas and occupational exposure to chlorinated solvents.

[Ruder AM](#)¹, [Yiin JH](#), [Waters MA](#), [Carreón T](#), [Hein MJ](#), [Butler MA](#), [Calvert GM](#), [Davis-King KE](#), [Schulte PA](#), [Mandel JS](#), [Morton RF](#), [Reding DJ](#), [Rosenman KD](#), [Stewart PA](#); [Brain Cancer Collaborative Study Group](#).

Abstract

OBJECTIVES:

Occupational exposure to chlorinated aliphatic solvents has been associated with an increased cancer risk, including brain cancer. However, many of these solvents remain in active, large-volume use. We evaluated glioma risk from non-farm occupational exposure (ever/never and estimated cumulative exposure) to any of the six chlorinated solvents--carbon tetrachloride, chloroform, methylene chloride, trichloroethylene, tetrachloroethylene or 1,1,1--trichloroethane--among 798 cases and 1175 population-based controls, aged 18-80 years and non-metropolitan residents of Iowa, Michigan, Minnesota and Wisconsin. Methods Solvent use was estimated based on occupation, industry and era, using a bibliographic database of published exposure levels and exposure determinants. Unconditional logistic regression was used to calculate ORs adjusted for frequency matching variables age group and sex, and age and education. Additional analyses were limited to 904 participants who donated blood specimens (excluding controls reporting a previous diagnosis of cancer) genotyped for glutathione-S-transferases GSTP1, GSTM3 and GSTT1. Individuals with functional GST genes might convert chlorinated solvents crossing the blood-brain barrier into cytotoxic metabolites.

RESULTS:

Both estimated cumulative exposure (ppm-years) and ever exposure to chlorinated solvents were associated with decreased glioma risk and were statistically significant overall and for women. In analyses comparing participants with a high probability of exposure with the unexposed, no associations were statistically significant. Solvent-exposed participants with functional GST genes were not at increased risk of glioma.

CONCLUSIONS:

We observed no associations of glioma risk and chlorinated solvent exposure. Large pooled studies are needed to explore the interaction of genetic pathways and environmental and occupational exposures in glioma aetiology.

Temporal Variation in the Association between Benzene and Leukemia Mortality

David B. Richardson

Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina USA

BACKGROUND: Benzene is a human carcinogen. Exposure to benzene occurs in occupational and environmental settings.

OBJECTIVE: I evaluated variation in benzene-related leukemia with age at exposure and time since exposure.

METHODS: I evaluated data from a cohort of 1,845 rubber hydrochloride workers. Benzene exposure–leukemia mortality trends were estimated by applying proportional hazards regression methods. Temporal variation in the impact of benzene on leukemia rates was assessed via exposure time windows and fitting of a multistage cancer model.

RESULTS: The association between leukemia mortality and benzene exposures was of greatest magnitude in the 10 years immediately after exposure [relative rate (RR) at 10 ppm-years = 1.19; 95% confidence interval (CI), 1.10–1.29]; the association was of smaller magnitude in the period 10 to < 20 years after exposure (RR at 10 ppm-years = 1.05; 95% CI, 0.97–1.13); and there was no evidence of association \geq 20 years after exposure. Leukemia was more strongly associated with benzene exposures accrued at \geq 45 years of age (RR at 10 ppm-years = 1.11; 95% CI, 1.04–1.17) than with exposures accrued at younger ages (RR at 10 ppm-years = 1.01; 95% CI, 0.92–1.09). Jointly, these temporal effects can be efficiently modeled as a multistage process in which benzene exposure affects the penultimate stage in disease induction.

CONCLUSIONS: Further attention should be given to evaluating the susceptibility of older workers to benzene-induced leukemia.

KEY WORDS: benzene, cohort study, leukemia, mortality, Ohio. *Environ Health Perspect* 116:370–374 (2008). doi:10.1289/ehp.10841 available via <http://dx.doi.org/> [Online 2 January 2008]

In 1982 the International Agency for Research on Cancer (IARC) concluded there was sufficient evidence that benzene is carcinogenic to humans, with evidence predominantly related to associations between benzene and development of acute non-lymphocytic leukemia (IARC 1982). Subsequent epidemiologic studies have supported that conclusion (Hayes et al. 1997; Rinsky et al. 1987; Wong 1987; Yin et al. 1996). In addition, molecular and cytogenetic studies provide evidence of induction of chromosomal alterations by benzene that is likely to play a role in leukemogenesis (Smith and Zhang 1998; Zhang et al. 2007).

Despite its status as a recognized leukemogen, benzene exposure is common (IARC 1987). Benzene is an important raw material for the chemical industry and an occasional industrial solvent, as well as a component of gasoline (Hricko 1994). Smokers commonly experience protracted inhalation exposures to benzene as a component of cigarette smoke (Wallace et al. 1987). In addition, environmental exposures to benzene arise from sources such as gasoline vapor emissions and auto exhaust (Wallace 1996). Consequently, the identification of a factor that influences a person's susceptibility to benzene-induced leukemia has important public health implications, as does understanding the evolution over time of leukemia rates after benzene exposure.

Multistage theories of carcinogenesis predict that a person's susceptibility to benzene-induced leukemia will depend upon the age

at which exposure occurs, as the probability of transition through the stage (or stages) of the disease process unaffected by benzene exposure are assumed to be age dependent (Thomas 1988). Moreover, age-related physiologic changes might lead to changes in susceptibility to benzene's carcinogenic effects via changes in benzene uptake and its metabolism (Kim et al. 2006). Despite its plausibility as an effect measure modifier, the epidemiologic literature to date provides minimal information about whether susceptibility to benzene-induced leukemia varies with age at exposure.

Multistage cancer models also predict that effect of an increment of exposure on cancer risk may vary with time since exposure. Whereas some investigators have found that a simple metric of cumulative exposure adequately characterizes the exposure time–response relationship (Crump 1994, 1996), others have reported evidence of substantial variation in the impact of benzene exposure on leukemia risk with time since exposure (Finkelstein 2000; Hayes et al. 1997; Silver et al. 2002).

The analyses reported in the present article examine age at exposure and time since exposure as modifiers of the association between the leukemia mortality and occupational benzene exposure in a cohort of rubber hydrochloride workers. Previous analyses of these data have been used by the U.S. Occupational Safety and Health Administration (OSHA) to support the current permissible exposure limit for

benzene in the workplace and by the U.S. Environmental Protection Agency (EPA) as the basis for risk estimates for inhaled benzene (OSHA 1987; U.S. EPA 1985). The objective of these analyses was to use exposure time windows and a multistage model to evaluate temporal modifiers of the impact of benzene on leukemia rates.

Materials and Methods

This study is based upon the experience of workers employed in the manufacture of a natural rubber film (rubber hydrochloride) at two locations in Ohio. Natural rubber was dissolved in benzene and spread over a conveyor; the benzene was evaporated and recovered while the rubber film was stripped from the conveyor (Rinsky et al. 1987). Production at the first location commenced in 1939 and ceased in 1976; production at the second location began around 1937 and continued until 1965. All nonsalaried workers employed in a rubber hydrochloride department between 1 January 1940 and 31 December 1965 were included in these analyses.

Vital status was ascertained through 31 December 1996 via records of the Social Security Administration, Ohio Bureau of Motor Vehicles, and the National Death Index. If there was no death indication for a worker then they were assumed to be alive as of 31 December 1996. Information was obtained on underlying cause of death for deceased workers, coded according to the revision of the *International Classification of Diseases* (ICD) in effect at the time of death. These analyses focus on leukemia [ICD-6 and ICD-7 code 204 [World Health Organization

Address correspondence to D. Richardson, Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 USA. Telephone: (919) 966-2675. Fax: (919) 966-2089. E-mail: david.richardson@unc.edu

Supplemental Material is available online at <http://www.ehponline.org/docs/2008/10841/suppl.pdf>

I thank R. Rinsky, Cincinnati Children's Hospital Medical Center and S. Silver, National Institute for Occupational Safety and Health, for their support of these analyses, which make use of data derived from their previously published research.

This project was supported by grant K01-OH008635 from the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention.

The author declares he has no competing financial interests.

Received 4 September 2007; accepted 2 January 2008.

(WHO) 1948, 1957], ICD-8 codes 204-207 [U.S. Public Health Service 1968], ICD-9 codes 204-208 [WHO 1978]].

The exposure of interest was defined as cumulative benzene exposure, expressed in parts per million-year (ppm-year). Annual exposure rate estimates by plant, department, and job were developed by Rinsky et al. (2002, 1987) based on available air sampling data. Utterbach and Rinsky (1995) have reviewed the methods employed in this assessment of benzene exposure among rubber hydrochloride workers. The U.S. National Institute for Occupational Safety and Health provided a file that contained a plant, department, and job code, and start and finish dates, for each job held by each worker. Using this information, benzene exposure histories were computed for each worker as the product of the length of employment in each job in a year by the estimated benzene exposure rate for that job.

Statistical methods. Cox proportional hazards regression models were fitted to these data via the statistical program PECAN, with attained age as the primary time scale (Preston et al. 1993). Model covariates included a categorical indicator of birth cohort (classified as born before 1905, 1905 to < 1910, 1910 to < 1915, 1915 to < 1920, or after 1920), a binary indicator of sex, and a binary indicator of employment status (active employment status began when a person started employment and ended 1 week after the end of employment in order to allow for inaccuracies in personnel records regarding the day last employed) (Arrighi and Hertz-Picciotto 1994; Steenland and Stayner 1991; Steenland et al. 1996). The majority (99%) of workers of known race in this cohort was white, and no deaths due to leukemia were observed among nonwhite workers; therefore, race was not included as a covariate in these analyses. In analyses of cumulative exposure (expressed in 10-ppm-year increments) log-linear regression models were fitted, providing

an estimate of the log relative rate per 10 ppm-years; we report the anti-log of this estimate and discuss it as an estimate of the relative rate at 10 ppm-years. Ninety-five percent confidence intervals (CIs) were estimated via the likelihood method.

Cumulative exposure was treated as a time-varying explanatory variable that described the benzene exposures accrued prior to a person's entry into a risk set in the Cox regression analysis. The model with a single parameter for cumulative benzene exposure implies that the magnitude of the hazard ratio does not depend on when exposures occurred. Exposure time window analyses were conducted to assess whether the relationship between disease risk and benzene exposure depends on when exposures occurred (Checkoway et al. 1990; Richardson and Ashmore 2005; Thomas 1988). A model with three exposure time windows, defined *a priori*, described the association between leukemia rates and exposures accrued in the periods < 10 years, 10 to < 20 years, and ≥ 20 years prior to a person's entry into a risk set in the regression analysis (Rothman 1981). To assess variation in exposure effects with age at exposure, metrics of cumulative exposures accrued at < 45 and ≥ 45 years of age were examined (Richardson and Wing 1998). Each model was compared with a standard model of lifetime cumulative exposure by means of a likelihood ratio test (LRT); the difference between model deviances, described as an LRT statistic, can be interpreted using a chi-square distribution with degrees of freedom (df) equal to the difference in the numbers of model parameters.

Multistage models of carcinogenesis, of which the best known is the Armitage-Doll model, involve the mathematic expression of hypotheses about the process of carcinogenesis (Armitage and Doll 1954). Central to the Armitage-Doll model is the concept that cancer arises as the result of a single cell undergoing a series of transformations. The model

predicts that cancer incidence, I , will increase as an integer power of attained age, a , with the integer, depending on the number of stages, k , required for cancer induction. Specifically, the model posits the relationship $I = ca^{k-1}$, where c is a constant that is proportional to the product of the transition rates. When considering the effect of an environmental carcinogen, the transition rate from one rate-limiting step to the next is often assumed to be affected in a linear fashion by exposure. If exposure influences the transition rate for a single stage, $j < k$, this implies a linear relative rate model of the form RR (relative rate) = $1 + \delta_{j,k}Z$, where Z is a weighted cumulative exposure metric calculated for each person (Thomas 1988; Whittemore 1977). Specifically, if a denotes the attained age of members of a risk set enumerated for a Cox regression analysis, and a_0 is the age at which an increment of exposure occurs, then the weight assigned to that exposure increment is given by the expression, $w(a_0) = (1 + a^{k-1}) a_0^{j-1} (a-a_0)^{k-j-1}$. The weighted cumulative exposure metric Z represents the sum of weighted exposure increments accrued through age a .

Leukemia incidence rates increase approximately as a function of age to the fourth power, suggesting a process of carcinogenesis that involves five stages (Little et al. 1992; Ries et al. 2003). Therefore, a disease process that involves five stages was posited (i.e., $k = 5$) and weighted cumulative exposure metrics for each integer value of $j < k$ were calculated. Relationships between leukemia mortality and these weighted cumulative exposure metrics were evaluated, and fitted regression models were compared with reference to residual model deviance ($-2 \log$ likelihood). Alternative models with fewer than five stages and those with more than five stages were also evaluated. Regression analyses were conducted via the log-linear rate model as well as via the linear relative rate model.

Results

Table 1 shows the distribution of major characteristics among cases and noncases in the study cohort. A single leukemia death was observed among the females in the study cohort. Over one-third of the leukemia cases were ascertained among workers born before 1905, whereas nearly 60% of the noncases were born in the period 1920 or later. Leukemia cases were employed for a longer average duration than noncases, tended to start employment at older ages than noncases, and accrued higher average cumulative benzene exposures (144 ppm-years) than noncases (34 ppm-years). Two percent of the workers were hired before 1940, 19% were hired in the period 1940–1944, and the remainder were hired in 1945–1975.

Table 2 reports estimated RRs for categories of benzene exposure. The rate ratio for

Table 1. Characteristics [n (%)] of cohort of 1,845 rubber hydrochloride workers stratified by leukemia case status, Ohio, 1940–1996.

| Characteristic | Cases ($N = 17$) | Noncases ($N = 1,828$) |
|--|-----------------------|-----------------------------|
| Sex | | |
| Male | 16 (94) | 1,705 (93) |
| Female | 1 (6) | 123 (7) |
| Birth cohort | | |
| < 1905 | 6 (35) | 230 (13) |
| 1905 – < 1910 | 2 (12) | 131 (7) |
| 1910 – < 1915 | 3 (18) | 193 (11) |
| 1915 – < 1920 | 3 (18) | 226 (12) |
| < 1920 | 3 (18) | 1,048 (57) |
| Employment status | | |
| Employed | 2 (12) | 10 (1) |
| Terminated | 15 (88) | 1,818 (99) |
| Age at entry (years, mean \pm SD) | 41 \pm 11 | 32 \pm 11 |
| Age at exit (years, mean \pm SD) | 62 \pm 17 | 67 \pm 12 |
| Duration of employment (years, mean \pm SD) | 7 \pm 8 | 4 \pm 7 |
| Cumulative exposure (ppm-years, mean \pm SD) | 144 \pm 207 | 34 \pm 91 |

the contrast drawn between the categories 1 to < 50 ppm-years and < 1 ppm-year was below unity (Table 2). When considering contrasts drawn between 50 to < 250, 250 to < 500, and \geq 500 ppm-years and < 1 ppm-year, the rate ratios were greater than unity and increased in magnitude with increasing cumulative exposure level, although the associated 95% CIs were relatively wide for each exposure category, reflecting the small numbers of leukemia cases observed within each category.

There was a positive trend in the leukemia mortality rate with cumulative benzene exposure (Table 3). Table 3 also describes the association between leukemia and cumulative benzene exposure accrued in the periods < 10 years, 10 to < 20 years, and \geq 20 years prior. The largest magnitude of association was observed for benzene exposures accrued in the period < 10 years prior, whereas exposures received 10 to < 20 years previously exhibited a smaller, positive association with leukemia, and benzene exposures received \geq 20 years prior showed no association with leukemia. A model with three exposure time windows provided a substantially better fit to these data than a lifetime cumulative exposure model (LRT = 13.2, 2 df, p -value = 0.001).

Table 4 reports the association between cumulative benzene exposures accrued at younger (< 45 years) and older (\geq 45 years) ages and leukemia in the periods < 10 years, 10 to < 20 years, and \geq 20 years after exposure. When considering benzene exposures accrued at \geq 45 years of age, there was a positive association with leukemia mortality in the period shortly after exposure (< 10 years after exposure); there was minimal evidence of association within the period \geq 10 years after exposure. Benzene exposures accrued at younger ages exhibited little evidence of association with leukemia. The fit of this model with exposure time windows defined jointly by age at exposure and time since exposure was substantially better than the fit of a model for lifetime cumulative exposure (LRT = 16.9, 5 df, p -value = 0.005). Table 4 also reports estimates of the association between cumulative benzene exposures accrued at younger (< 45 years) and older (\geq 45 years) ages and leukemia, summarized over all periods of time since exposure. A model that included separate terms for two age-at-exposure time windows provided a slightly better fit to these data than the simpler, nested model that included a single parameter for cumulative benzene exposure accrued at all ages (LRT = 3.3, 1 df, p -value = 0.071).

Table 2. Estimated association between cumulative exposure to benzene and leukemia mortality among rubber hydrochloride workers, Ohio, 1940–1996.

| | Cumulative exposure to benzene (ppm-years) | | | | |
|--------------|--|---------------|----------------|-----------------|------------------|
| | < 1 | 1 to < 50 | 50 to < 250 | 250–500 | \geq 500 |
| RR (95% CI) | 1 | 0.8 (0.2–3.2) | 2.5 (0.6–10.2) | 10.5 (2.3–46.6) | 13.9 (0.7–116.1) |
| Deaths (no.) | 5 | 3 | 4 | 4 | 1 |

The results reported in Tables 3 and 4 are minimally impacted by inclusion of birth cohort, sex, or employment status as covariates; none of the parameter estimates on which the reported effect measures were based changed by > 10% on exclusion of these covariates. The linear relative rate model provided an equivalent fit to these data for analyses of lifetime cumulative exposure; however, the log-linear model fitted these data better for the exposure time window analyses. The cut point defining younger versus older age at exposure was chosen to broadly partition the ages at which exposures occur; there was minimal impact on relative rate estimates of selecting alternative cut points of 40 years or 50 years (results not shown).

In contrast to the exposure time window analyses presented above, which impose a piecewise constant model to describe temporal variation in exposure effects, the Armitage–Doll model implies a smooth time-varying exposure weighting function that jointly describes age at exposure and latency effects. Residual model deviances were compared for models in which benzene exposure acted upon the first, second, third, or fourth stage of a five-stage disease process (Table 5). A model under which the transition rate for the fourth stage was affected by benzene exposure resulted in the lowest residual deviance and therefore provided the best fit to these data. Figure 1A illustrates how the estimated effect of benzene exposure varies with time since exposure; the figure illustrates the natural log of the estimated relative rate of leukemia per 10 ppm-years for those 65 years of age (i.e., typical of the ages at which leukemia deaths occurred in this population). Consistent with observations from our exposure time window analyses, the modeled effect was largest for exposures that occurred in the prior decade and diminished rapidly with time since exposure. Figure 1B illustrates how the estimated effect of benzene exposure varies with age at exposure. As observed via time window analyses, the exposure effect was much smaller for exposures accrued prior to 45 years of age; the estimated effect of benzene exposure increased with age at exposure > 45 years of age. Multistage models were also fitted using a linear relative rate model; a model in which the transition rate for the penultimate stage was affected by benzene exposure provided the best fit to these data (Table 5). Evaluation of alternative models with as few as three stages, or as many as 15 stages, led to similar conclusions

(see Supplemental Material online at <http://www.ehponline.org/docs/2008/10841/suppl.pdf>); in all such models the best-fitting model is one in which benzene exposure acts at the penultimate stage.

Discussion

In the United States, the OSHA standard for benzene exposure is 1 ppm. The analyses in the present article suggest that accrual of benzene exposure at that level for a decade implies a modest increase in the relative rate of leukemia mortality, with the magnitude of the excess relative rate diminishing with time since exposure (Table 3). Because leukemia is a rare disease, this means that if a person is exposed to 1 ppm of benzene for a decade, it is still unlikely that they will develop leukemia. To understand the impact of benzene exposure on leukemia risk at a population level, however, the magnitude of the dose–response association and its variation over time must be accurately characterized. In this study population, the effect of benzene exposure on leukemia did not appear to persist indefinitely, but rather diminished with time since exposure. Of course, caution is warranted in drawing conclusions from an historical cohort study of a population in which working conditions differed substantially from those typical of contemporary work settings in the United States. Nonetheless, the findings of this historical cohort of U.S. workers may have substantial relevance for contemporary workers, both in the United States and abroad.

In prior analyses of this cohort, Crump (1994, 1996) investigated the hypothesis that the effect of benzene on leukemia risk diminishes with time since exposure by applying a set of time-dependent exposure weights with values informed *a priori* by latency patterns for leukemia after radiotherapy for ankylosing spondylitis. Crump reported that analyses using a simple metric of cumulative exposure fitted these data better than analyses using those exposure weights (Crump 1996). In the present paper, rather than assigning a set of

Table 3. Estimated relative rates (and associated 95% CIs) for leukemia mortality expressed as a trend with benzene exposure (10 ppm-years) and within time windows defined by time since exposure.

| | RR at 10 ppm-years (95% CI) |
|------------------------|-----------------------------|
| Cumulative exposure | 1.05 (1.02–1.08) |
| Time since exposure | |
| < 10 years prior | 1.19 (1.10–1.29) |
| 10 to < 20 years prior | 1.05 (0.97–1.13) |
| \geq 20 years prior | 1.00 (0.90–1.05) |
| Test of heterogeneity | |
| LRT, 2 df ^a | 13.1 |
| p -Value | 0.001 |

^aLRT comparing a model with terms for three exposure time windows to a model with one term for lifetime cumulative exposure.

exposure weights based on patterns observed in a study of radiation exposure effects, the method of exposure time–window analysis was used. The overall association between cumulative exposure and leukemia mortality (RR at 10 ppm-years = 1.05) is nearly identical to the estimate derived by Rinsky et al. (2002) via a log-linear Cox regression model; the evidence of heterogeneity of benzene exposure effects with time since exposure is consistent with previous observations reported by Silver et al. (2002) and Finkelstein (2000).

These findings suggest that the effect of benzene on leukemia mortality is jointly characterized as an effect of age at exposure and time since exposure. The temporal pattern is consistent with a multistage cancer model with benzene affecting a late stage in the induction of leukemia; the relative rate of leukemia per unit exposure increases with age at exposure and decreases with time since exposure (Thomas 1988). This conclusion is supported by analyses that involve fitting weighting expressions implied by the Armitage–Doll model. These weighted exposure metrics were evaluated via fittings of standard log-linear models as well as via fittings of linear relative rate models [the latter being the model form implied by the work of Whittemore (1977), whereas the former approach was consistent with the model form used in the exposure time–window analyses]. In these analyses a model with five stages was posited. Armitage and Doll intentionally used the word “stage” rather than mutation to allow for the possibility of nonmutational events leading to cancer induction (Doll 2004). They correctly maintained that the application of multistage models for cancer risk estimation offers a heuristic tool that allows an investigator to explore potentially complex dose–time–response patterns by imposing some relatively minor constraints based on biological expectations about the disease process. Although mutational events are clearly central to carcinogenesis, useful insights from these models may be obtained even if carcinogenesis is viewed more generally as resulting from a series of rate-limiting pathogenic events, with exposure influencing one or more transition rates (Hanahan and Weinberg 2000; Morrison 1979).

The validity of these findings depends, in part, on the validity of the benzene exposure estimates derived for this cohort. To the extent that the exposure measurement error conforms to a classical model, attenuation of the dose response would be expected. However, non-random measurement errors could lead to bias away from the null. Estimates of these historical benzene exposures used air monitoring results, which were relatively sparse for the early years of operation (Utterback and Rinsky 1995; Williams and Paustenbach 2003). In

theory, temporal variation in the magnitude of a benzene–leukemia association (e.g., diminished evidence of association with increasing time since exposure) could reflect increasing exposure misclassification for benzene exposure estimates for periods of employment further in the past. While it is difficult to assess such concerns, the observation in this cohort that the benzene–leukemia association diminished with time since exposure is consistent with patterns observed in other populations of benzene-exposed workers (Glass et al. 2004; Hayes et al. 1996), suggesting that the temporal patterns in this cohort are not simply an artifact of errors in exposure estimates.

Although the fitted models include a relatively small number of covariates, concerns about bias because of residual confounding are tempered by the fact that there are few leukemogens that are plausible strong confounders of the association under study. Cigarette smoking is a nonoccupational source of benzene exposure and could, in theory, confound our estimates of association between occupational benzene exposure and leukemia. However, given the relatively small

magnitude of association between smoking and leukemia mortality, high levels of correlation between occupational benzene exposure and smoking would be necessary to account for even modest dose–response trends for leukemia (Axelson and Steenland 1988; Siemiatycki et al. 1988).

The analyses in this article examined the broad category of all leukemia deaths. It is reasonable to posit that associations may vary in magnitude and temporal pattern by disease subtype. Although evaluation of heterogeneity in exposure–response analyses for different subtypes of leukemia is of interest because of small numbers of leukemia cases and the sparse information available from the death certificates, subtype-specific exposure–response analyses were not conducted. In addition, the use of mortality data in these analyses does not allow assessment of whether benzene exposure influences disease prognosis or incidence; therefore, it is possible that benzene exposures accrued proximate to death could influence mortality rates by reducing survival time rather than by increasing incidence rates. The relatively small number of

Table 4. Estimated association between leukemia mortality and cumulative exposure to benzene in exposure time windows cross-classified by age at exposure and time since exposure.

| | RR at 10 ppm-years (95% CI) | |
|------------------------|------------------------------|------------------------------|
| | Accrued at < 45 years of age | Accrued at ≥ 45 years of age |
| Cumulative exposure | 1.01 (0.92–1.09) | 1.11 (1.04–1.17) |
| Time since exposure | | |
| < 10 years prior | 0.78 (ND–1.23) | 1.22 (1.11–1.32) |
| 10 to < 20 years prior | 1.05 (0.89–1.22) | 1.03 (0.92–1.13) |
| ≥ 20 years prior | 1.01 (0.90–1.09) | 0.93 (0.55–1.10) |

ND, not determined (the 95% confidence bound was not determined via the likelihood method). LRT comparing model with six exposure time windows to the cumulative exposure model = 16.9, 5 df, *p*-value = 0.005.

Table 5. Residual deviances from fitting of log-linear and linear RR regression models.

| Stage affected by benzene (<i>j</i>) | Log-linear rate model | Linear RR model |
|--|-----------------------|-----------------|
| 1 | 211.23 | 209.5 |
| 2 | 209.76 | 206.9 |
| 3 | 204.74 | 203.4 |
| 4 | 193.60 | 200.1 |

Comparison of models in which a cumulative weighted benzene exposure metric was derived via a multistage model with five stages (i.e., *k* = 5), assuming a single stage, *j*, was affected by benzene exposure.

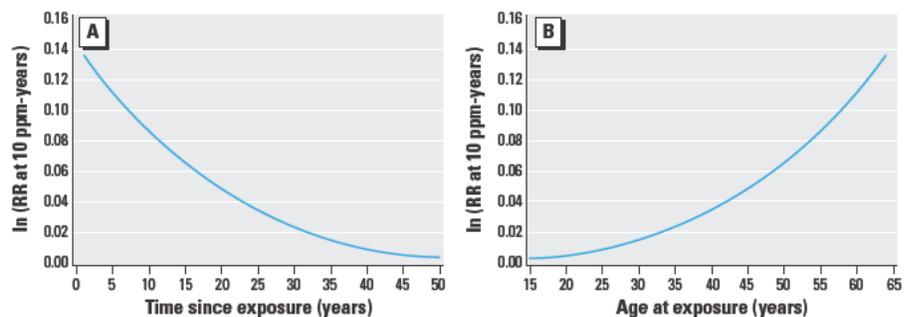


Figure 1. (A) Fitted time-varying exposure weighting function. Log relative rate (RR) of leukemia per 10 ppm-year benzene exposure by time since exposure for a person 65 years of age, rubber hydrochloride workers, Ohio, 1940–1996. (B) Fitted time-varying exposure weighting function. Log relative rate (RR) of leukemia per 10 ppm-year benzene exposure by age at exposure for a person 65 years of age, rubber hydrochloride workers, Ohio, 1940–1996.

leukemia deaths also suggests that model results are relatively sensitive to small changes in distribution of events; adding or subtracting a single case in the highest exposure category could lead to a substantial change in the estimates of the association between cumulative exposure and leukemia mortality. Last, the Armitage–Doll model, while often illustrated using mortality data (Armitage and Doll 1954), is posited as a model of disease incidence; it is likely that the conclusions obtained in these analyses would differ from those obtained via analyses of incidence data.

Since 1987, the Chinese Academy of Preventive Medicine has collaborated with the U.S. National Cancer Institute on a large-scale study of cancer among Chinese workers exposed to benzene (NCI-CAPM study) (Hayes et al. 1997). Although the NCI-CAPM study encompasses more leukemia cases than in this rubber hydrochloride cohort study, several concerns have been raised about the validity of the exposure estimates used in the previously reported analyses of the NCI-CAPM study (Hayes et al. 2001). Therefore, the rubber hydrochloride cohort examined in this article remains one of the important epidemiologic resources for benzene risk assessment.

The findings illustrate the importance of attention to dynamic changes in exposure–response patterns with temporal factors such as time since exposure and age at exposure. Failure to account for variation with time since exposure in the effect of an increment of benzene exposure on the relative rate of leukemia may lead to underestimation of the excess rate of leukemia in some risk periods (and overestimation of the excess rate of leukemia in other risk periods). In these analyses, the effect of an increment of benzene exposure on leukemia mortality appears promptly, diminishes with time since exposure, and is of greater magnitude for workers exposed at older ages than for those exposed at younger ages. These temporal patterns of association are consistent with a late-stage carcinogen and suggest that occupational protection efforts give particular consideration to the risks of benzene-induced leukemia faced by older workers. Further attention should be given to assessment of age at exposure in other benzene-exposed populations, specifically to the potentially greater susceptibility of older workers to benzene-induced leukemia.

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Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among U.S. veterans.

[Mashberg A](#), [Boffetta P](#), [Winkelman R](#), [Garfinkel L](#).

Author information

Abstract

BACKGROUND:

Independent carcinogenic effects of alcohol drinking and tobacco smoking as well as their interaction can be usefully studied in a population of heavy drinkers and smokers.

METHODS:

A hospital-based case-control study was conducted during 1972 to 1983 in a large Veterans hospital in East Orange, New Jersey. A total of 359 oral cavity-oropharynx cancer cases and 2280 controls were interviewed according to tobacco smoking, use of smokeless tobacco, alcoholic beverage, coffee and tea drinking, race, family origin, religion, and occupation as bartender.

RESULTS:

Odds ratio of oral cancer increased up to the level of 35 cigarettes per day and 21 whiskey equivalents per day: no further increase was found for higher level of exposure to either factor. A protective effect of quitting smoking was found, but the number of former smokers was small. No difference occurred in oral cancer risk according to type of alcoholic beverage drunk. An interaction effect compatible with a multiplicative model was found between the two exposures. Blacks were at lower risk than whites, and, in the latter group, individuals of Italian origin were at lower risk than individuals from northern or central European countries.

CONCLUSIONS:

Alcohol drinking and tobacco smoking were responsible for the majority of oral cancer cases in this population of US Veterans.

FULL TEXT

Environ Health Perspect. 2000 May; 108(Suppl 2): 161–176.

PMCID: PMC1637753

Research Article

Trichloroethylene and cancer: epidemiologic evidence.

[D Wartenberg](#), [D Reyner](#), and [C S Scott](#)

Environmental and Occupational Health Sciences Institute, UMDNJ--Robert Wood Johnson Medical School, Piscataway, NJ 08855, USA. dew@ehsi.rutgers.edu

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Trichloroethylene is an organic chemical that has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins. It has been shown to cause liver and kidney cancer in experimental animals. This article reviews over 80 published papers and letters on the cancer epidemiology of people exposed to trichloroethylene. Evidence of excess cancer incidence among occupational cohorts with the most rigorous exposure assessment is found for kidney cancer [relative risk (RR) = 1.7, 95% confidence interval (CI) 1.1–2.7], liver cancer (RR = 1.9, 95% CI 1.0–3.4), and non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9–2.3) as well as for cervical cancer, Hodgkin's disease, and multiple myeloma. However, since few studies isolate trichloroethylene exposure, results are likely confounded by exposure to other solvents and other risk factors. Although we believe that solvent exposure causes cancer in humans and that trichloroethylene likely is one of the active agents, we recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk. *Key words:* cancer, degreasers, dry cleaning, epidemiology, PERC, solvents, TCE, TCOH, tetrachloroethylene, trichloroethylene. — *Environ Health Perspect* 108(suppl 2):161–176 (2000).

<http://ehpnet1.niehs.nih.gov/docs/2000/suppl-2/161-176wartenberg/abstract.html>

From: (b) (6),
To: (b) (6),
Subject: Useful article-
Date: Tuesday, December 02, 2014 12:51:52 PM

Lancet. Aug 30, 2014; 384(9945): 755–765.

Published online Aug 30, 2014. doi: [10.1016/S0140-6736\(14\)60892-8](https://doi.org/10.1016/S0140-6736(14)60892-8)

PMCID: PMC4151483

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults

[Krishnan Bhaskaran](#), Dr, PhD,^{a,*} [Ian Douglas](#), PhD,^a [Harriet Forbes](#), MSc,^a [Isabel dos-Santos-Silva](#), Prof, PhD,^a [David A Leon](#), Prof, PhD,^a and

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Subject: useful article on second malignancies caused by radiation therapy for prostate ca
Date: Tuesday, September 09, 2014 2:48:41 PM

Secondary malignancies following radiotherapy for prostate cancer
Petros Sountoulides, Nikolaos Koletsas, Dimitris Kikidakis, Konstantinos Paschalidis and
Nikolaos Sofikitis; Ther Adv Urol (2010) 2(3) 119[1]125



DEPARTMENT OF VETERANS AFFAIRS
Veterans Benefits Administration
Washington, D.C. 20420

November 29, 2011

Director (00/21)
All VA Regional Offices

In Reply Refer To:
Training Letter 11-03 (Revised)

SUBJ: Processing Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune

This updated training letter incorporates multiple recommendations provided by other interested organizations, including the Department of Defense, Department of Justice, and Office of Management and Budget. It also reflects the Environmental Protection Agency's revised assessment of trichloroethylene (TCE), now characterized as "carcinogenic to humans" by all routes of exposure.

Purpose

Veterans who served at U.S. Marine Corps Base Camp Lejeune, North Carolina, were potentially exposed to contaminants present in the base water supply prior to 1987. The chemical compounds involved have been associated by various scientific organizations with the possible development of certain chronic diseases. However, many unanswered questions remain regarding the extent of base water contamination, the type and duration of exposure experienced by base personnel, and the likelihood that contaminant levels in the water supply were high enough to result in a particular disease.

While these issues are being studied, the Department of Veterans Affairs (VA) has determined that disability claims from Veterans who served at Camp Lejeune during this period deserve special handling to ensure fairness and consistency in claims processing. As a result, adjudication of these claims has been centralized at the Louisville, Kentucky, Regional Office with tracking measures initiated. Technical aspects related to processing these claims are outlined in Fast Letter 11-03, *Consolidation and Processing of Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune, North Carolina*.

This training letter was developed to provide additional background information on the Camp Lejeune situation, as well as to provide specific guidance for issues related to claims development and adjudication. The current guidance supersedes the initial release and the Camp Lejeune section of Training Letter 10-03, *Environmental Hazards in Iraq, Afghanistan, and Other Military Installations*.

Questions

Questions should be e-mailed to VAVBAWAS/CO/211/ENVIRO.

/S/

(b) (6),
Director
Compensation Service

Enclosures

Processing Disability Claims Based on Exposure to Contaminated Drinking Water at Camp Lejeune

I. Background

United States Marine Corps Base Camp Lejeune, NC, was established in 1941. In the early 1980s, it was discovered that two on-base water-supply systems were contaminated with the volatile organic compounds (VOCs) trichloroethylene (TCE), a metal degreaser, and perchloroethylene (PCE), a dry cleaning agent. The main source of TCE contamination was on-base industrial activities, while the main source of PCE was an off-base dry cleaning facility. Benzene, vinyl chloride, and other VOCs were also found to be contaminating the water-supply systems. These water systems served housing, administrative, and recreational facilities, as well as the base hospital. Department of the Navy estimates indicate that as many as 630,000 active duty personnel may have been exposed. The contaminated wells supplying the water systems were identified and shut down by February 1985. The Agency for Toxic Substances and Disease Registry (ATSDR), a branch of the Department of Health and Human Services, conducted a Public Health Assessment of Camp Lejeune in 1997, which did not determine whether base personnel experienced any long-term health effects from consumption of the contaminated water. However, the assessment indicated that the drinking water contaminants at Camp Lejeune created a “past public health hazard.” Follow up studies by ATSDR focused on potential birth defects experienced by mothers exposed to the drinking water. In 2008, as public awareness of Camp Lejeune increased, the Navy sent an informational outreach letter to those individuals who could be identified as having served there between 1957 and 1987. Apparently, the Navy felt that including individuals serving until 1987 would cover potential exposure from any residual contaminants present in the water beyond the well closings in 1985. The letter notified these former Servicemembers that “unregulated chemicals were discovered in some of the base drinking water systems” and encouraged them to participate in a registry so as to receive information from new health-related scientific studies initiated by the Navy. These studies involved the National Academy of Sciences’ National Research Council (NRC) and ATSDR.

Based on a congressional mandate, the Navy requested that NRC undertake a study to assess the potential long-term health effects for individuals who served at Camp Lejeune during the period of water contamination. In the resulting report, *Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects* (June 2009), NRC reviewed previous work done by ATSDR, including computerized water flow modeling, and concluded that additional studies may not produce definitive results because of the difficulties inherent in attempting to reconstruct past events and determine the amount of exposure experienced by any given individual. To address potential long-term health effects, NRC focused on diseases associated with TCE, PCE, and other VOCs. Based on analyses of scientific studies involving these chemicals, NRC provided an assessment of the potential association between certain diseases and exposure to the chemical contaminants.

The NRC analysis utilized categories of potential disease “health outcomes.” The categories included: (1) sufficient evidence of a causal relationship; (2) sufficient evidence of an association; (3) limited/suggestive evidence of an association; (4) inadequate/insufficient evidence to determine whether an association exists; and (5) limited suggestive evidence of no association. The analysis found that no diseases fell into the categories of sufficient evidence of a causal relationship or sufficient evidence of an association with the chemical contaminants. However, fourteen diseases were placed into the category of limited/suggestive evidence of an association. A number of diseases were also identified that fell into the category of inadequate/insufficient evidence to determine whether an association exists. NRC indicated that placement of diseases in these categories was based primarily on studies of highly exposed industrial workers, where the amount and duration of toxic chemical exposure greatly exceeded that experienced by individuals at Camp Lejeune.

The presentation of NRC’s disease list in this training letter is not meant to specifically associate these diseases with Veterans who served at Camp Lejeune. Rather, it reflects limited/suggestive evidence of an association between these diseases and the chemical compounds found to be in the Camp Lejeune water supply during the period of contamination. Limited/suggestive evidence of an association is defined as: “evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence.” U.S. and international scientific organizations have reviewed the available literature on the health effects of the identified chemical compounds found to be present in the water supply. These findings are summarized in Appendix B of this training letter. Disability compensation for any of these diseases under VA regulations must proceed under a case-by-case analysis, which requires evidence of a current disease, evidence of service at Camp Lejeune during the period of contamination, and a medical nexus between the two, justified with a rational scientific explanation.

ATSDR, with support from the Navy, is conducting additional studies to assess the human health risks associated with the Camp Lejeune water contamination. The suite of studies in progress and planned include: a continuation of water flow computer modeling studies to generate potential contaminant exposure rates and durations, a re-analysis of data collected on birth outcomes, studies on birth defects and childhood cancers, and further epidemiological studies based on mortality and health surveys that are in the process of being distributed to former Camp Lejeune residents. ATSDR’s pending studies, which include making use of computerized water flow modeling and the epidemiological mortality and health survey, have the potential to provide a higher level of exposure predictability and definable health outcomes than are possible at this time.

For additional information on the history of Camp Lejeune water contamination and the various governmental responses to it, see the Internet websites listed in Appendix A of this training letter.

II. Claims Processing

Evidence Development

Service connection for any disease alleged to have been caused by contaminated water at Camp Lejeune requires evidence of a current disease, evidence of service at Camp Lejeune during the period of contamination, and a medical nexus between the two, justified with a rational scientific explanation. Evidence development for water contaminant exposure requires obtaining verification of actual service at Camp Lejeune and as much detail as possible about that service, including the duration of that service. It also requires verifying, with medical evidence obtained through a VA medical examination or other authoritative medical source, whether a claimed current disease or disability is at least as likely as not the result of exposure to the chemical compounds present in the water at Camp Lejeune. A number of diseases are identified in Appendix B of this training letter that meet the limited/suggestive association criteria based on human and experimental animal studies. Manifestation of any of these diseases would be sufficient to initiate a VA medical examination and request an opinion regarding its relationship to Camp Lejeune service. However, this is not an exclusive list. Medical evidence provided by a Veteran indicating that some other disease may be related to the known water contaminants would also be sufficient to initiate a VA examination.

Verification of Service

Verification of service at Camp Lejeune will generally be available through military personnel and/or medical records. These can be obtained with standard development procedures, including a PIES O19 records request. When documents in the claims file do not provide sufficient information on Camp Lejeune service, it should be obtained through VCAA notification or direct contact with the Veteran. It is important to verify that service at Camp Lejeune occurred within the 1957 to 1987 timeframe. Additionally, when not specified in the records, efforts should be made to obtain the length of time served at Camp Lejeune, preferably the dates of arrival and departure. When feasible, it is also desirable to obtain the Veteran's work duty location and information regarding whether the Veteran resided on base or off base. There is some indication from ATSDR that certain base locations may have been associated with higher levels of water contamination. However, this has not yet been established with certainty. If the Veteran is claiming Camp Lejeune service but initial development does not show it, a PIES O18 request should be initiated to obtain complete service records, which might verify service through temporary duty orders or performance evaluations. Obtaining as complete a picture as possible of the Veteran's Camp Lejeune service will assist medical examiners with determining the likelihood of a nexus between water contaminant exposure and disease development.

Disease Manifestations

Scientific organizations, including NRC, have determined that some evidence is available that suggests the possible association between development of certain diseases and sufficiently high exposures to chemicals known to have contaminated the water at Camp Lejeune. However, where NRC recognizes associations, they are often based on experimental animal studies involving exposure dose rates generally considered to be in excess of the amount of exposure experienced by Camp Lejeune personnel. To date, there are no definitive scientific studies upon which to conclude that an individual who served at Camp Lejeune during the period of water contamination developed a particular disease as a result of that service. There are many unanswered questions regarding the levels of water contamination at various base locations, the amount and type of exposure experienced by any given Veteran who served there, and the probability that such contamination levels were sufficient to cause the health effects identified by NRC. Therefore, the question remains whether a Veteran's particular claimed disease resulted from the service at Camp Lejeune rather than from some other source. As a result, there are currently no "presumptive" diseases attributed to service at Camp Lejeune by statute, regulation, or VA policy. The listing of diseases in this training letter does not imply that any Camp Lejeune Veteran who is diagnosed with one of the listed diseases developed that disease as a result of the Camp Lejeune service. The listed diseases are only meant to serve as a guide for determining when a VA examination should be scheduled. It is the VA medical examination process that will determine, on a case-by-case basis, whether one of the listed diseases is at least as likely as not the result of Camp Lejeune service.

As noted above, each of the chemical compounds present in the contaminated water has been shown by toxicologic or epidemiologic studies to be associated with some form of negative health outcome. Appendix B of this training letter provides an overview of each contaminant and the diseases potentially associated with it. Appendix C of this training letter provides a list of Internet websites containing scientific analyses of the contaminants. Although certain disease manifestations may be associated with one of the specific contaminants found in the water and not associated with another, it is currently impossible to determine which contaminants, if any, were in the Camp Lejeune water consumed or used by a particular Veteran. Therefore, until scientific evidence shows otherwise, it will be assumed by VA that any given Veteran-claimant who served at Camp Lejeune was potentially exposed in some manner to the full range of chemicals known to have contaminated the water there between 1957 and 1987.

Requesting VA Medical Examinations

Service connection for any disability claimed to have resulted from contaminated water exposure at Camp Lejeune requires sufficient medical evidence that the disability is related to that exposure. This medical evidence will generally come from a competent and qualified medical examiner who provides an opinion, justified with a rational scientific explanation, establishing a medical nexus between the claimed disability and the exposure. NRC has determined that the diseases listed in Appendix B of this training letter are associated in a limited/suggestive manner with the chemical contaminants in the

water at Camp Lejeune. However, this does not mean that service connection can automatically be established for a Camp Lejeune Veteran claiming one of these diseases. It is up to a competent medical authority, based on each Veteran's individual case, to determine whether it is at least as likely as not that the claimed disease or disability has resulted from the contaminant exposure at Camp Lejeune. Sufficient medical evidence to establish the required nexus may come from a private physician or other competent private medical authority. In such cases, the claim may be adjudicated without further development if the level of disability can also be ascertained from the available evidence. If the level of disability cannot be ascertained, a VA medical examination is needed to establish the basis for a disability rating. However, in the majority of cases, an initial VA medical examination will be required to establish both service connection and the level of disability.

VA regulations at 38 C.F.R. § 3.159(c)(4) serve as the basis for requesting medical examinations and opinions in claims based on Camp Lejeune service. Under these regulations, an examination should be requested when the claim: (1) contains competent lay or medical evidence of a current diagnosed disability or persistent or recurrent symptoms of disability; (2) establishes that the veteran suffered an event, injury, or disease in service; and (3) indicates that the claimed disability or symptoms may be associated with the established event, injury, or disease in service. These requirements establish a relatively low threshold for requesting medical examinations for Camp Lejeune Veterans. The first requirement is met when a Veteran provides any credible lay or medical evidence showing a current diagnosis or symptoms of a disease or disability. The second is met when service at Camp Lejeune between 1957 and 1987 is verified. The third is met when the claimed disease or disability is included among, but not limited to, the diseases described in Appendix B of this training letter because these have a limited/suggestive association with exposure to the water contaminants. Other claimed diseases or disabilities may also trigger a VA examination request if they are supported by credible medical evidence or an opinion provided by a competent medical authority indicating a possible association with one of the known water contaminants. However, certain claimed conditions, such as those based on a musculoskeletal *injury*, may not be sufficiently reasonable, or as likely as not from a scientific standpoint, to justify requesting an examination for determining its relationship to a chemical compound. On the other hand, additional consideration would be required if a musculoskeletal *disease* was involved because the contaminants are linked to disease processes.

When examinations are requested, it should be kept in mind that these claims represent a unique situation for VA medical examiners. They must determine, on a case-by-case basis, whether a particular claimed condition is linked to contaminated water exposure. In order to assist them with their assessment and determination, the regional office must provide them with the Appendices to this training letter listed below. These replace the Camp Lejeune "Fact Sheet" intended for VA examiners found in Training Letter 10-03.

Appendix A, *Internet websites related to the issue of contaminated water at Camp Lejeune*,

Appendix B, *Diseases potentially associated with exposure to contaminants present in the Camp Lejeune water supply between 1957 and 1987,*

Appendix C, *Websites describing potential health effects of exposure to chemical contaminants present in the water supply of Camp Lejeune between 1957 and 1987, and*

Appendix D, *Notice to Examiners Evaluating Claims Based on Service at Camp Lejeune.*

This information is intended to provide the VA examiners with an adequate basis for providing a reasoned opinion. This opinion is a critical element for evaluating the claim. Therefore, if the examiner fails to provide a reasoned opinion and resorts to a statement such as “an opinion cannot be made without resort to mere speculation,” the examination should be returned as inadequate.

Rating Decisions

The VA medical examination report and opinion, or in some cases a private medical examination report and opinion, will serve as the basis for the rating decision. If the examiner determines that it is at least as likely as not that the claimed condition resulted from exposure to the known water contaminants, service connection can be granted and a disability percentage assigned based on the examiners assessment of symptom severity. The rating narrative should provide the Veteran with a clear explanation for all decisions made. Upon completion of the rating decision, it is important to ensure that all tracking procedures outlined in Fast Letter 11-03 have been followed.

Appendix A

Internet websites related to the issue of contaminated water at Camp Lejeune

US Marine Corps Site for Camp Lejeune Contaminated Water

<https://clnr.hqi.usmc.mil/clwater/index.html>

NRC Report on Water Contamination at Camp Lejeune

http://books.nap.edu/catalog.php?record_id=12618

US Navy Funding of ATSDR Camp Lejeune Studies

http://www.navy.mil/search/display.asp?story_id=51453

ATSDR Home Page for Camp Lejeune

<http://www.atsdr.cdc.gov/sites/lejeune/index.html>

ATSDR Feasibility Assessment for Future Studies of Camp Lejeune

http://www.atsdr.cdc.gov/sites/lejeune/docs/feasibility_assessment_Lejeune.pdf

Appendix B

Diseases potentially associated with exposure to contaminants present in the Camp Lejeune water supply between 1957 and 1987

I. National Research Council

The National Academy of Sciences' National Research Council (NRC) published its *Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects*, in 2009. This report included a review of studies addressing exposure to Trichloroethylene (TCE), and Tetrachloroethylene or Perchloroethylene (PCE), as well as a mixture of the two, and a discussion of disease manifestations potentially associated with such exposure. Fourteen disease conditions were identified as having limited/suggestive evidence of an association with TCE, PCE, or a solvent mixture exposure. They include:

- esophageal cancer
- lung cancer
- breast cancer
- bladder cancer
- kidney cancer
- adult leukemia
- multiple myeloma
- myelodysplastic syndromes
- renal toxicity
- hepatic steatosis
- female infertility
- miscarriage, with exposure during pregnancy
- scleroderma
- neurobehavioral effects

NRC uses the category “limited/suggestive evidence of an association” when the evidence is “limited by the inability to rule out chance and bias, including confounding, with confidence” [see online report page 6, Box 1]. More specifically, the NRC “concluded that the epidemiological studies give some reason to be concerned that sufficiently high levels of the chemical may cause the disease, but the studies do not provide strong evidence that they actually do so” [see page 7]. While the NRC noted that animal testing showed adverse health effects of TCE and PCE, it also noted that the “highest levels of either TCE or PCE measured in the mixed-water samples at Camp Lejeune were much lower than the lowest dose that caused adverse effects in the most sensitive strains and species of laboratory animals. The lower levels of exposure may be of some concern for effects on neurotoxicity and immunotoxicity, but further research is needed to evaluate the specific effects of TCE and PCE and whether they are relevant to humans” [see page 9].

The National Research Council's report also contained a listing of disease conditions classified as having inadequate/insufficient evidence to determine whether an association existed. This listing can be found in the report, which is available on the Internet and can be accessed in Appendix C of this training letter.

II. Other Scientific Organizations

Assessments of potential long-term health effects resulting from exposure to TCE and PCE, as well as benzene and vinyl chloride, are available from a number of scientific sources. Among the reliable sources are the Chemical Abstract Services (CAS) of the American Chemical Society, the Agency for Toxic Substances and Disease Registry (ATSDR), and the Environmental Protection Agency (EPA). Succinct "substance profiles" are available from CAS, each with a statement of "carcinogenicity" for the chemical compound evaluated. More extensive analyses of the compounds of interest are provided by ATSDR's "toxic substance portal" and EPA's "integrated risk information system" (IRIS).

Regarding the reliability of this group of assessments, a distinction is not always made between potential health effects due to inhalation versus ingestion and dermal contact. The contaminants involved are volatile organic compounds and are most commonly encountered by humans in the air rather than dissolved in water, as was the case at Camp Lejeune. However, any of the exposure routes may have occurred.

The health assessments provided by the scientific organizations are summarized below for each contaminant. Their Internet websites, which contain detailed analyses and explanations, are provided in Appendix C of this training letter.

Trichloroethylene (TCE), according to CAS, "is reasonably anticipated to be a human carcinogen" based on limited evidence from human studies and sufficient evidence from experimental animal studies. It has been associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma. According to ATSDR, drinking small amounts of trichloroethylene for long periods may cause liver and kidney damage, impaired immune system function, and impaired fetal development in pregnant women, although the extent of some of these effects is not yet clear. Additionally, animal studies suggest that high levels are associated with liver, kidney, and lung cancer.

EPA revised its assessment of TCE on September 28, 2011, and characterized it as "carcinogenic to humans" by all routes of exposure.

Tetrachloroethylene or Perchloroethylene (PCE), according to CAS, “is reasonably anticipated to be a human carcinogen” based on limited evidence from human studies and sufficient evidence from experimental animal studies. It has been associated with esophageal and cervical cancer and non-Hodgkin’s lymphoma. According to ATSDR, pregnant women may be affected, and the results of animal studies, conducted with amounts much higher than those to which most people are exposed, show that tetrachloroethylene can cause liver and kidney damage.

Benzene, according to CAS, “is known to be a human carcinogen” based on sufficient evidence from human studies. It is primarily associated with increased risk for lymphatic and hematopoietic cancers, total leukemia, and specific histologic types of leukemia, including chronic lymphocytic leukemia, as well as acute myelogenous leukemia. According to ATSDR, epidemiological studies and case reports provide clear evidence of a causal relationship between occupational exposure to benzene and the occurrence of acute nonlymphocytic leukemia, particularly the myeloid cell type or acute myelogenous leukemia. Some studies also provide suggestive evidence of an association with non-Hodgkin’s lymphoma and multiple myeloma. According to EPA’s current IRIS report, benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies. Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia and also suggest evidence for chronic nonlymphocytic leukemia and chronic lymphocytic leukemia. Other neoplastic conditions that are associated with an increased risk in humans include hematologic neoplasms, blood disorders such as preleukemia and aplastic anemia, Hodgkin's lymphoma, and myelodysplastic syndrome.

Vinyl Chloride, according to CAS, “is known to be a human carcinogen” based on sufficient evidence from human studies. It is primarily associated with liver cancer, especially angiosarcoma of the liver, as well as cancer to a lesser extent at other tissue sites including the brain, lung, lymphatic system, and hematopoietic system. According to ATSDR, vinyl chloride is a known human and animal carcinogen. It has been associated with both an increased incidence of hepatic angiosarcomas and hepatotoxicity. According to EPA’s current IRIS report, studies demonstrate a statistically significant elevated risk of liver cancer, specifically angiosarcomas, from vinyl chloride exposure. There is also a possible association with brain, soft tissue, and nervous system cancer, as well as cancers of the hematopoietic and lymphatic systems.

Appendix C

Internet websites describing potential health effects of exposure to chemical contaminants present in the water supply of Camp Lejeune between 1957 and 1987

Trichloroethylene (TCE)

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s180tce.pdf>

ATSDR

<http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=172&tid=30>

EPA

<http://www.epa.gov/iris/subst/0199.htm>

NRC

http://books.nap.edu/catalog.php?record_id=12618

Tetrachloroethylene or Perchloroethylene (PCE)

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s169tetr.pdf>

ATSDR

<http://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=264&tid=48>

EPA

<http://www.epa.gov/iris/subst/0106.htm>

NRC

http://books.nap.edu/catalog.php?record_id=12618

Benzene

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s019benz.pdf>

ATSDR

<http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=40&tid=14>

EPA

<http://www.epa.gov/iris/subst/0276.htm#reforal>

Vinyl Chloride

American Chemical Society

<http://ntp.niehs.nih.gov/ntp/roc/elevnth/profiles/s186viny.pdf>

ATSDR

<http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=282&tid=51>

EPA

<http://www.epa.gov/iris/subst/1001.htm>

ATSDR Summary for all contaminants

http://www.atsdr.cdc.gov/sites/lejeune/tce_pce.html

Appendix D

Notice to Examiners Evaluating Claims Based on Service at Camp Lejeune

Examiner,

The water supply at Camp Lejeune, North Carolina, was contaminated between 1957 and 1987 with a number of chemical compounds that have been associated by scientific organizations with the potential for developing certain diseases. These include a limited/suggestive association for trichloroethylene (TCE) and tetrachloroethylene, also known as perchloroethylene (PCE), as well as benzene, and vinyl chloride. The Veteran you are examining has verified service at Camp Lejeune during that period and is claiming service connection for (specify disease or diseases claimed). Please evaluate the available evidence, determine whether it is at least as likely as not that the claimed disease is related to the Veteran's exposure to contaminated water while serving at Camp Lejeune, and provide a medical rationale for that determination.

For assistance, we are providing a document that identifies diseases which have a limited/suggestive association with exposure to the known contaminants in the Camp Lejeune water supply between 1957 and 1987. We are also providing a list of Internet websites from scientific organizations, which analyze the potential long-term health effects of exposure to the contaminants. The web addresses can be copied and pasted into a search engine such as Google in order to access them.

Please conduct any required tests and consider any evidence in the file, or obtained by you, which identifies the duration or extent of contaminated water exposure experienced by the Veteran. Information on how long the Veteran served at Camp Lejeune, and whether the Veteran lived off base, should be considered. Unfortunately, there are many unanswered questions regarding potential exposure to contaminants at Camp Lejeune. They include: the levels of water contamination at various base locations, the amount and duration of exposure experienced by any given Veteran who served there, and the scientific probability that a Veteran's particular claimed disease resulted from service at Camp Lejeune and not from some other source.

[Purchase IF](#), [Stafford J](#), [Paddle GM](#). Vinyl chloride: an assessment of the risk of occupational exposure. [Food Chem Toxicol](#). 1987 Feb;25(2):187-202.

Abstract

There is little doubt that exposure to high levels of VCM as a consequence of occupation can result in an increased incidence of ASL. A review of 20 epidemiological studies involving about 45,000 workers occupationally exposed to VCM showed that neoplasms of the liver showed an increase in incidence in the majority of studies. For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and haemopoietic system, buccal cavity, and pharynx, cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies. In view of the increased incidence of breast neoplasms in rodents exposed to VCM, the studies of Chaizze et al. (1980), who did not confirm these findings in humans, are of importance. The register of ASL cases now contains records of 99 persons with confirmed ASL and occupational exposure to VCM. The average latent period between first exposure to VCM and death from ASL is 21.9 years. The majority of cases occurred in autoclave workers, who are recognized as having been exposed to extremely high levels. Although precise estimates of exposure are not available for the periods of most interest, the pattern of cases roughly suggests that extremely high exposures were necessary for the induction of ASL. For example, ASL cases tended to occur in larger numbers in some plants than in others, a finding that can be explained most easily by differences in exposure patterns. There is an extensive series of animal studies on the carcinogenicity of VCM. Some of these precede the epidemiological studies confirming the association between VCM exposure and ASL in man. ASL and neoplasms of a number of other organs have been induced in laboratory rodents by VCM. Estimation of the exposure levels likely to cause a lifetime risk of ASL of 10^{-6} on the basis of these data give extremely low levels (down to 3.9×10^{-7} ppb) which appear to be unrealistic estimates for man. Part of the reason for this is that laboratory studies have shown that VCM is metabolized in the liver (and elsewhere in the body) to the reactive metabolites chloroethylene oxide and chloroacetaldehyde. The rate of conversion is limited at high levels of exposure giving inaccurate estimates of the slope of the dose-response relationship.

Tetrachloroethylene Exposure and Bladder Cancer Risk: A Meta-Analysis of Dry-Cleaning-Worker Studies.

[Vlaanderen J](#)¹, [Straif K](#)², [Ruder A](#)³, [Blair A](#)⁴, [Hansen J](#)⁵, [Lynge E](#)⁶, [Charbotel B](#)⁷, [Loomis D](#)², [Kauppinen T](#)⁸, [Kyyronen P](#)⁹, [Pukkala E](#)¹⁰, [Weiderpass E](#)¹¹, [Guha N](#)².

Abstract

BACKGROUND: In 2012, the International Agency for Research on Cancer classified tetrachloroethylene, used in the production of chemicals and the primary solvent used in dry cleaning, as *probably carcinogenic to humans* based on *limited* evidence of an increased risk of bladder cancer in dry cleaners.

OBJECTIVES:

We assessed the epidemiological evidence for the association between exposure to tetrachloroethylene and bladder cancer from published studies estimating occupational exposure to tetrachloroethylene or in workers in the 'dry cleaning' industry.

METHODS: Random-effects meta-analyses were carried out separately for occupational exposure to tetrachloroethylene and employment as a dry cleaner. We qualitatively summarized exposure-response data because of the limited number of studies available.

RESULTS:

The meta-relative risk (mRR) among tetrachloroethylene exposed workers was 1.08 (95% CI: 0.82, 1.42; 3 studies; 463 exposed cases). For employment as dry cleaner the overall mRR was 1.47 (95% CI: 1.16, 1.85; 7 studies; 139 exposed cases) and for smoking-adjusted studies 1.50 (95% CI: 0.80, 2.84; 4 case-control studies).

CONCLUSIONS:

Our meta-analysis demonstrates an increased risk of bladder cancer in dry cleaners, reported in both cohort and case-control studies, and some evidence for an exposure-response relationship. Although dry cleaners incur mixed exposures, tetrachloroethylene could be responsible for the excess risk of bladder cancer because it is the primary solvent used and it is the only chemical commonly used by dry cleaners that is currently identified as a potential bladder carcinogen. Relatively crude exposure assessment approaches in the studies of 'tetrachloroethylene exposed workers' may have attenuated the relative risks

Occupational trichloroethylene exposure and kidney cancer risk: a meta-analysis.

[Karami S](#), [Lan Q](#), [Rothman N](#), [Stewart PA](#), [Lee KM](#), [Vermeulen R](#), [Moore LE](#).

Source

National Cancer Institute, Division of Cancer Epidemiology and Genetics, Occupational and Environmental Epidemiology Branch, 6120 Executive Blvd, EPS 8102, Rockville, MD 20852, USA.

Abstract

OBJECTIVES:

Inconsistent epidemiological findings, debate over interpretation, and extrapolation of findings from animal studies to humans have produced uncertainty surrounding the carcinogenicity of trichloroethylene (TCE) exposure in occupational settings. We updated meta-analyses of published case-control and cohort studies exploring occupational TCE exposure and kidney cancer risk, incorporating new analytical results from three recently published cohort studies and a case-control study.

METHODS:

PubMed MEDLINE was searched for studies published from 1950 to 2011 assessing occupational exposure to chlorinated solvents, degreasers or TCE. All cohort (N=15) and case-control (N=13) studies included in analyses were stratified by assessment of occupational exposure to TCE specifically and to any chlorinated solvent.

RESULTS:

Significantly elevated summary estimates were observed for cohort studies (relative risk (RR) 1.26, 95% CI 1.02 to 1.56; p heterogeneity=0.65), case-control studies (OR 1.35, 95% CI 1.17 to 1.57; p heterogeneity=0.41), and cohort and case-control studies combined (RR 1.32, 95% CI 1.17 to 1.50, p heterogeneity=0.63) that specifically assessed TCE exposure after excluding outlier studies that contributed to heterogeneity. Non-significantly elevated summary estimates were generally observed for studies of workers exposed to chlorinated solvents but who were not assessed for TCE specifically.

CONCLUSIONS:

Regardless of study design, significant and stronger estimates were only observed in studies specifically assessing occupational exposure to TCE. Estimates were lower in studies assessing occupational exposure to chlorinated solvents. This updated meta-analysis supports an association between occupational TCE exposure and kidney cancer and provides evidence that exposure misclassification may weaken estimates assessing exposure to the broader class of chlorinated solvents.

PMID:

23000822

[PubMed - indexed for MEDLINE]

A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia.

[Alexander DD](#), [Mink PJ](#), [Mandel JH](#), [Kelsh MA](#).

Source

Exponent-Health Sciences, 185 Hansen Court, Suite 100, Wood Dale, IL 60191, USA.
dalexander@exponent.com

Abstract

BACKGROUND:

Trichloroethylene (TCE) has been widely used as an industrial solvent and degreasing agent.

AIMS:

We conducted a meta-analysis of epidemiologic studies of occupational TCE exposure and multiple myeloma (MM) or leukaemia.

METHODS:

We identified a total of eight cohort or case-control studies that enumerated a TCE-exposed study population and presented relative risk (RR) estimates for MM (n = 7) and/or leukaemia (n = 7). The individual studies included aerospace or aircraft workers (n = 3 studies), workers from a transformer manufacturing plant (n = 1 study) and workers from numerous occupations who, based on biomonitoring or extensive industrial hygiene exposure measurements, were likely exposed to TCE (n = 4). We used random effects models to calculate summary relative risk estimates (SRRE). In addition, we examined heterogeneity across studies and the relative influence of each individual study on the overall meta-analysis.

RESULTS:

No association was observed for MM (SRRE = 1.05, 95% CI: 0.80-1.38; P value for heterogeneity = 0.94) or leukaemia (SRRE = 1.11, 95% CI: 0.93-1.32; P value for heterogeneity = 0.50), based on TCE-exposed subgroup meta-analyses. Study-specific RR estimates for MM ranged between 0.57 and 1.62. RRs for leukaemia ranged between 1.05 and 1.15 in five studies, while one study reported a 2-fold increased RR and another study reported an inverse association of 0.60. All confidence intervals (CIs) for study-specific estimates included 1.0.

CONCLUSIONS:

The results of this meta-analysis do not support an etiologic association between occupational TCE exposure and risk of MM or leukaemia.

[Paulu C](#), [Aschengrau A](#), [Ozonoff D](#). Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers. [Environ Health Perspect](#). 1999 Apr;107(4):265-71.

Full text: <http://web.ebscohost.com/ehost/detail?vid=3&sid=9c017e1b-41b2-4e27-ac9d-1938ec4a4bfd%40sessionmgr110&hid=108&bdata=JnNpdGU9ZWlhvc3QtbGl2ZQ%3d%3d#db=mnh&AN=10090704>

Abstract:

We conducted a population-based case-control study to evaluate the relationship between cancer of the colon-rectum (n = 326), lung (n = 252), brain (n = 37), and pancreas (n = 37), and exposure to tetrachloroethylene (PCE) from public drinking water. Subjects were exposed to PCE when it leached from the vinyl lining of drinking-water distribution pipes. Relative delivered dose of PCE was estimated using a model that took into account residential location, years of residence, water flow, and pipe characteristics. Adjusted odds ratios (ORs) for lung cancer were moderately elevated among subjects whose exposure level was above the 90th percentile whether or not a latent period was assumed [ORs and 95% confidence intervals (CIs), 3.7 (1.0-11.7), 3.3 (0.6-13.4), 6.2 (1.1-31.6), and 19.3 (2.5-141.7) for 0, 5, 7, and 9 years of latency, respectively]. The adjusted ORs for colon-rectum cancer were modestly elevated among ever-exposed subjects as more years of latency were assumed [OR and CI, 1.7 (0.8-3.8) and 2.0 (0.6-5.8) for 11 and 13 years of latency, respectively]. These elevated ORs stemmed mainly from associations with rectal cancer. Adjusted ORs for rectal cancer among ever-exposed subjects were more elevated [OR and CI, 2.6 (0.8-6.7) and 3.1 (0.7-10.9) for 11 and 13 years of latency, respectively] than were corresponding estimates for colon cancer [OR and CI, 1.3 (0.5-3.5) and 1.5 (0.3-5.8) for 11 and 13 years of latency, respectively]. These results provide evidence for an association between PCE-contaminated public drinking water and cancer of the lung and, possibly, cancer of the colon-rectum.

From: (b) (6),
To: (b) (6),
Subject: smoking and breast cancer risk: new article:
Date: Thursday, January 23, 2014 9:39:20 AM

Cancer Epidemiol Biomarkers Prev.
<<http://www.ncbi.nlm.nih.gov/pubmed/24420985>> 2014 Jan;23(1):37-46. doi:
10.1158/1055-9965.EPI-13-1081.

The surgeon general report on smoking and health 50 years later: breast cancer and the cost of increasing caution.

Glantz SA <http://www.ncbi.nlm.nih.gov/pubmed?term=Glantz%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=24420985>,
Johnson KC <http://www.ncbi.nlm.nih.gov/pubmed?term=Johnson%20KC%5BAuthor%5D&cauthor=true&cauthor_uid=24420985>.

(b) (6), could you put this on the share point?

Thanks

(b)
(6)

FULL TEXT

[N Engl J Med](#). 2015 Feb 12;372(7):631-40. doi: 10.1056/NEJMsa1407211.

Smoking and mortality--beyond established causes.

[Carter BD](#)¹, [Abnet CC](#), [Feskanich D](#), [Freedman ND](#), [Hartge P](#), [Lewis CE](#), [Ockene JK](#), [Prentice RL](#), [Speizer FE](#), [Thun MJ](#), [Jacobs EJ](#).

Abstract

BACKGROUND:

Mortality among current smokers is 2 to 3 times as high as that among persons who never smoked. Most of this excess mortality is believed to be explained by 21 common diseases that have been formally established as caused by cigarette smoking and are included in official estimates of smoking-attributable mortality in the United States. However, if smoking causes additional diseases, these official estimates may significantly underestimate the number of deaths attributable to smoking.

METHODS:

We pooled data from five contemporary U.S. cohort studies including 421,378 men and 532,651 women 55 years of age or older. Participants were followed from 2000 through 2011, and relative risks and 95% confidence intervals were estimated with the use of Cox proportional-hazards models adjusted for age, race, educational level, daily alcohol consumption, and cohort.

RESULTS:

During the follow-up period, there were 181,377 deaths, including 16,475 among current smokers. Overall, approximately 17% of the excess mortality among current smokers was due to associations with causes that are not currently established as attributable to smoking. These included associations between current smoking and deaths from renal failure (relative risk, 2.0; 95% confidence interval [CI], 1.7 to 2.3), intestinal ischemia (relative risk, 6.0; 95% CI, 4.5 to 8.1), hypertensive heart disease (relative risk, 2.4; 95% CI, 1.9 to 3.0), infections (relative risk, 2.3; 95% CI, 2.0 to 2.7), various respiratory diseases (relative risk, 2.0; 95% CI, 1.6 to 2.4), breast cancer (relative risk, 1.3; 95% CI, 1.2 to 1.5), and prostate cancer (relative risk, 1.4; 95% CI, 1.2 to 1.7). Among former smokers, the relative risk for each of these outcomes declined as the number of years since quitting increased.

CONCLUSIONS: A substantial portion of the excess mortality among current smokers between 2000 and 2011 was due to associations with diseases that have not been formally established as caused by smoking. These associations should be investigated further and, when appropriate, taken into account when the mortality burden of smoking is investigated. (Funded by the American Cancer Society.).

Solvents and Parkinson disease: A systematic review of toxicological and epidemiological evidence.

[Lock EA](#), [Zhang J](#), [Checkoway H](#).

Source

Liverpool John Moores University, School of Pharmacy and Biomolecular Sciences, Byrom Street, Liverpool, UK. Electronic address: e.lock@ljamu.ac.uk.

Abstract

Parkinson disease (PD) is a debilitating neurodegenerative motor disorder, with its motor symptoms largely attributable to loss of dopaminergic neurons in the substantia nigra. The causes of PD remain poorly understood, although environmental toxicants may play etiologic roles. Solvents are widespread neurotoxicants present in the workplace and ambient environment. Case reports of parkinsonism, including PD, have been associated with exposures to various solvents, most notably trichloroethylene (TCE). Animal toxicology studies have been conducted on various organic solvents, with some, including TCE, demonstrating potential for inducing nigral system damage. However, a confirmed animal model of solvent-induced PD has not been developed. Numerous epidemiologic studies have investigated potential links between solvents and PD, yielding mostly null or weak associations. An exception is a recent study of twins indicating possible etiologic relations with TCE and other chlorinated solvents, although findings were based on small numbers, and dose-response gradients were not observed. At present, there is no consistent evidence from either the toxicological or epidemiologic perspective that any specific solvent or class of solvents is a cause of PD. Future toxicological research that addresses mechanisms of nigral damage from TCE and its metabolites, with exposure routes and doses relevant to human exposures, is recommended. Improvements in epidemiologic research, especially with regard to quantitative characterization of long-term exposures to specific solvents, are needed to advance scientific knowledge on this topic.

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PMID:

232

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Subject: some articles
Date: Wednesday, January 22, 2014 3:00:33 PM
Attachments: [EAS](#)

Attachments:

Moore renal cell ca risk factors.pdf (516838 Bytes)
Karami TCE kidney cancer OEM 2012.full.pdf (560836 Bytes)
Theis renal ca and smoking BMCCancer 2008.pdf (809240 Bytes)
Nevai modifiable risk factors kidney cancer UrolOncol 2012.pdf (230596 Bytes)
smoking and esophageal ca.pdf (339210 Bytes)
veterans oral cancer.pdf (703694 Bytes)
Occupational and Env Exposures with Testic Germ Cell Tumours.pdf (639414 Bytes)

From: (b) (6), [REDACTED]
To: (b) (6), [REDACTED]
Cc: (b) (6), [REDACTED]
Subject: Suggested articles for Sharepoint
Date: Monday, March 24, 2014 11:09:06 AM

Suggesting the following articles for inclusion on the CLCW Sharepoint:

1. Qureshi, A., Ramsey, D., Kramer, J. Whitehead, L., El-Serag, H. (2013). Occupational Exposure and the Risk of Barrett's Esophagus: A Case-Control Study. *Dig Dis Sci.* 2013 Jul;58(7): 1967-75. Doi: 10.1007/s10620-013-2572-6. Epub 2013 Feb 5.
2. Pohl, H., Wrobel, K., Bojarski, C., Voderholzer, W., Sonnenberg, A., Rosch, T. & Baumgart, D. (2013). Risk Factors in the Development of Esophageal Adenocarcinoma. *The American Journal of Gastroenterology*, 2013 Feb; 108(2): 200-7. Doi: 10.1038/ajg.2012.387. Epub 2012 Dec 18.

PubMed

Abstract

Full text links



See 1 citation found by title matching your search:

Lancet. 2014 Aug 30;384(9945):755-65. doi: 10.1016/S0140-6736(14)60892-8. Epub 2014 Aug 13.

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults.

Bhaskaran K¹, Douglas I², Forbes H², dos-Santos-Silva I², Leon DA², Smeeth L³.

Author information

Abstract

BACKGROUND: High **body-mass index** (BMI) predisposes to several **site-specific cancers**, but a large-scale systematic and detailed characterisation of patterns of **risk** across all common **cancers** adjusted for potential confounders has not previously been undertaken. We aimed to investigate the links between BMI and the most common **site-specific cancers**.

METHODS: With primary care data from individuals in the Clinical Practice Research Datalink with BMI data, we fitted Cox models to investigate associations between BMI and **22** of the most common **cancers**, adjusting for potential confounders. We fitted linear then non-linear (spline) models; investigated effect modification by sex, menopausal status, smoking, and age; and calculated population effects.

FINDINGS: 5·24 million individuals were included; 166,955 developed **cancers** of interest. BMI was associated with 17 of **22 cancers**, but effects varied substantially by site. Each 5 kg/m² increase in BMI was roughly linearly associated with **cancers** of the uterus (hazard ratio [HR] 1·62, 99% CI 1·56-1·69; p<0·0001), gallbladder (1·31, 1·12-1·52; p<0·0001), kidney (1·25, 1·17-1·33; p<0·0001), cervix (1·10, 1·03-1·17; p=0·00035), thyroid (1·09, 1·00-1·19; p=0·0088), and leukaemia (1·09, 1·05-1·13; p≤0·0001). BMI was positively associated with liver (1·19, 1·12-1·27), colon (1·10, 1·07-1·13), ovarian (1·09, 1·04-1·14), and postmenopausal breast **cancers** (1·05, 1·03-1·07) overall (all p<0·0001), but these effects varied by underlying BMI or individual-level characteristics. We estimated inverse associations with prostate and premenopausal breast cancer **risk**, both overall (prostate 0·98, 0·95-1·00; premenopausal breast cancer 0·89, 0·86-0·92) and in never-smokers (prostate 0·96, 0·93-0·99; premenopausal breast cancer 0·89, 0·85-0·94). By contrast, for lung and oral cavity cancer, we observed no association in never smokers (lung 0·99, 0·93-1·05; oral cavity 1·07, 0·91-1·26): inverse associations overall were driven by current smokers and ex-smokers, probably because of residual confounding by smoking amount. Assuming causality, 41% of uterine and 10% or more of gallbladder, kidney, liver, and colon **cancers** could be attributable to excess weight. We estimated that a 1 kg/m² population-wide increase in BMI would result in 3790 additional annual UK patients developing one of the ten **cancers** positively associated with BMI.

INTERPRETATION: BMI is associated with cancer **risk**, with substantial population-level effects. The heterogeneity in the effects suggests that different mechanisms are associated with different cancer sites and different patient subgroups.

FUNDING: National Institute for Health Research, Wellcome Trust, and Medical Research Council.

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Comment in

The obesity and cancer link. [Ann Oncol. 2015]

Overweight and obesity are linked to 10 common **cancers** and more than 12,000 **UK** cases. [BMJ. 2014]

[Fat people have common **cancers**]. [MMW Fortschr Med. 2014]

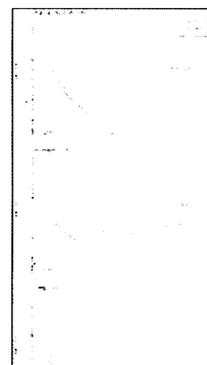
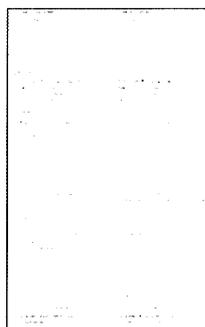
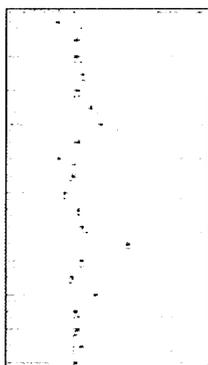
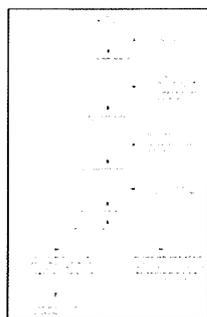
Obesity: a certain and avoidable cause of cancer. [Lancet. 2014]

[Obesity and cancer]. [Soins. 2014]

PMID: 25129328 [PubMed - indexed for MEDLINE] PMCID: PMC4151483 **Free PMC Article**



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Ann Oncol. 2013 Mar;24(3):807-16. doi: 10.1093/annonc/mds508. Epub 2012 Oct 26.

Alcohol drinking and all cancer mortality: a meta-analysis.

Jin M¹, Cai S, Guo J, Zhu Y, Li M, Yu Y, Zhang S, Chen K.

Author information

Abstract

BACKGROUND: Epidemiological studies have suggested an inconsistent relationship between **alcohol drinking** and risk of all **cancer mortality**. As far as we know, no **meta-analysis** has been conducted to explore this issue.

PATIENTS AND METHODS: We carried out a PubMed search to find relevant articles published before April 2012 in English. Categorical and dose-response meta-analyses were conducted to identify the impact of **alcohol drinking** on all **cancer mortality**. Potential sources of heterogeneity were detected by meta-regression and stratification analyses. Sensitivity and cumulative meta-analyses were also carried out.

RESULTS: Eighteen independent cohort studies met the inclusion criteria. Compared with non/occasional drinkers, the pooled relative risks (RRs) were 0.91 [95% confidence interval (CI) 0.89-0.94] for light, 1.02 (95% CI 0.99-1.06) for moderate, and 1.31 (95% CI 1.23-1.39) for heavy drinkers. Former drinkers presented a higher risk (RR = 1.32, 95% CI 1.15-1.50) than current drinkers (RR = 1.06, 95% CI 0.98-1.16). There was a J-shaped relationship between all **cancer mortality** and **alcohol** consumption in males but not in females.

CONCLUSIONS: This **meta-analysis** confirms the health hazards of heavy **drinking** (≥ 50 g/day) and benefits of light **drinking** (≤ 12.5 g/day). Large-sample, well-designed, prospective epidemiological studies, especially on heavy **drinking** among women, should be developed in future.

Comment in

Re: light **drinking** has positive public health consequences. [*Ann Oncol.* 2013]

Heavy consumption of **alcohol**: a risk factor for **cancer** deaths? [*Natl Med J India.* 2013]

Light **drinking** has positive public health consequences. [*Ann Oncol.* 2013]

PMID: 23104725 [PubMed - indexed for MEDLINE] [Free full text](#)



Publication Types, MeSH Terms

PubMed

Abstract

Full text links



See 1 citation found by title matching your search:

Cancer Res. 2014 Jun 1;74(11):3076-83. doi: 10.1158/0008-5472.CAN-13-2430.

Breast cancer risk after occupational solvent exposure: the influence of timing and setting.

Ekenqa CC¹, Parks CG², D'Aloisio AA², DeRoo LA³, Sandler DP².

Author information

Abstract

Organic solvents are ubiquitous in **occupational** settings where they may contribute to risks for carcinogenesis. However, there is limited information on organic solvents as human **breast** carcinogens. We examined the relationship between **occupational exposure** to solvents and **breast cancer** in a prospective study of 47,661 women with an **occupational** history in the Sister Study cohort. **Occupational solvent exposure** was categorized using self-reported job-specific **solvent** use collected at baseline. Multivariable Cox regression analyses were used to assess **breast cancer risk**, adjusting for established **breast cancer risk** factors. A total of 1,798 women were diagnosed with **breast cancer** during follow-up, including 1,255 invasive cases. Overall the **risk** of invasive **breast cancer** was not associated with lifetime **exposure** to solvents [HR, 1.04; 95% confidence interval (CI), 0.88-1.24]. Parous women who worked with solvents before their first full-term birth had an increased **risk** of estrogen receptor-positive invasive **breast cancer** compared with women who never worked with solvents (HR, 1.39; 95% CI, 1.03-1.86). A significantly elevated **risk** for estrogen receptor-positive invasive **breast cancer** was associated with **solvent exposure** among clinical laboratory technologists and technicians (HR, 2.00; 95% CI, 1.07-3.73). **Occupational exposure** to solvents before first birth, a critical period of **breast** tissue differentiation, may result in increased vulnerability for **breast cancer**. Our findings suggest a need for future studies in this area to focus on **exposure** time windows and **solvent** types in different **occupational** settings.

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PMID: 24879566 [PubMed - indexed for MEDLINE] PMCID: PMC4059370 [Available on 2015-06-01]



Publication Types, MeSH Terms, Substances, Grant Support

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JAMA Internal Med

JAMA Intern Med. 2014 Dec;174(12):1922-8. doi: 10.1001/jamainternmed.2014.5219.

Estimation of cigarette smoking-attributable morbidity in the United States.

Rostron BL¹, Chang CM¹, Pechacek TF².

Author information

Abstract

IMPORTANCE: Cigarette smoking has been found to harm nearly every bodily organ and is a leading cause of preventable disease, but current estimates of **smoking-attributable morbidity** by condition for the **United States** are generally unavailable.

OBJECTIVE: To estimate the burden of major medical conditions attributable to **cigarette** smoking in the **United States**.

DESIGN, SETTING, AND PARTICIPANTS: The disease burden of smoking was estimated using population-attributable risk calculations, taking into account the uncertainty of estimates. Population estimates came from 2009 US Census Bureau data and smoking prevalence, disease prevalence, and disease relative risk estimates came from National Health Interview Survey data for surveyed adults from 2006 through 2012. National Health and Nutrition Examination Survey spirometry data obtained from medical examination of surveyed adults from 2007 through 2010 was used to adjust for underreporting of chronic obstructive pulmonary disease.

EXPOSURES: Smoking status was assessed from self-reported National Health Interview Survey data.

MAIN OUTCOMES AND MEASURES: The number of adults 35 years and older who had had a major **smoking-attributable** disease by sex and condition and the total number of these conditions were estimated for the **United States** in 2009.

RESULTS: Using National Health Interview Survey data, we estimated that 6.9 million (95% CI, 6.5-7.4 million) US adults had had a combined 10.9 million (95% CI, 10.3-11.5 million) self-reported **smoking-attributable** medical conditions. Using chronic obstructive pulmonary disease prevalence estimates obtained from National Health and Nutrition Examination Survey self-reported and spirometry data, we estimated that US adults had had a combined 14.0 million (95% CI, 12.9-15.1 million) **smoking-attributable** conditions in 2009.

CONCLUSIONS AND RELEVANCE: We estimate that US adults have had approximately 14 million major medical conditions that were attributable to smoking. This figure is generally conservative owing to the existence of other diseases and medical events that were not included in these estimates. **Cigarette** smoking remains a leading cause of preventable disease in the **United States**, underscoring the need for continuing and vigorous smoking-prevention efforts.

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Environ Health. 2014 Feb 19;13(1):10. doi: 10.1186/1476-069X-13-10.



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Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

Bove FJ¹, Ruckart PZ, Maslia M, Larson TC.

Author information

Abstract

BACKGROUND: Two drinking water systems at U.S. Marine Corps Base **Camp Lejeune**, North Carolina were contaminated with solvents during 1950s-1985.

METHODS: We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at **Camp Lejeune** or **Camp Pendleton**, California during this period. **Camp Pendleton's** drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between **Camp Lejeune** (N = 154,932) and **Camp Pendleton** (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the **Camp Lejeune** cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS: There were 8,964 and 9,365 deaths respectively, in the **Camp Lejeune** and **Camp Pendleton** cohorts. Compared to **Camp Pendleton**, **Camp Lejeune** had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the **Camp Lejeune** cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; log₁₀ β = 0.06, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; β = 0.00005, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; β = 0.00203, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship (β = 0.0011, 95% CI: 0.0002, 0.0020).

CONCLUSION: The study found elevated HRs at **Camp Lejeune** for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposures at the base.

PubMed

Abstract

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See 1 citation found by title matching your search:

Environ Health Perspect. 2014 Apr;122(4):325-34. doi: 10.1289/ehp.1307359. Epub 2014 Feb 14.

Human health effects of tetrachloroethylene: key findings and scientific issues.

Guyton KZ¹, Hogan KA, Scott CS, Cooper GS, Bale AS, Kopylev L, Barone S, Makris SL, Glenn B, Subramaniam RP, Gwinn MR, Dzubow RC, Chiu WA.

Author information

Abstract

BACKGROUND: The U.S. Environmental Protection Agency (EPA) completed a toxicological review of **tetrachloroethylene** (perchloroethylene, PCE) in February 2012 in support of the Integrated Risk Information System (IRIS).

OBJECTIVES: We reviewed **key findings** and **scientific issues** regarding the **human health effects** of PCE described in the U.S. EPA's Toxicological Review of **Tetrachloroethylene** (Perchloroethylene).

METHODS: The updated assessment of PCE synthesized and characterized a substantial database of epidemiological, experimental animal, and mechanistic studies. **Key scientific issues** were addressed through modeling of PCE toxicokinetics, synthesis of evidence from neurological studies, and analyses of toxicokinetic, mechanistic, and other factors (tumor latency, severity, and background rate) in interpreting experimental animal cancer **findings**. Considerations in evaluating epidemiological studies included the quality (e.g., specificity) of the exposure assessment methods and other essential design features, and the potential for alternative explanations for observed associations (e.g., bias or confounding).

DISCUSSION: Toxicokinetic modeling aided in characterizing the complex metabolism and multiple metabolites that contribute to PCE toxicity. The exposure assessment approach—a **key** evaluation factor for epidemiological studies of bladder cancer, non-Hodgkin lymphoma, and multiple myeloma—provided suggestive evidence of carcinogenicity. Bioassay data provided conclusive evidence of carcinogenicity in experimental animals. Neurotoxicity was identified as a sensitive noncancer **health** effect, occurring at low exposures: a conclusion supported by multiple studies. Evidence was integrated from **human**, experimental animal, and mechanistic data sets in assessing adverse **health effects** of PCE.

CONCLUSIONS: PCE is likely to be carcinogenic to humans. Neurotoxicity is a sensitive adverse **health** effect of PCE.

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[Environ Health](#). 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.



Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

[Bove FJ](#)¹, [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

Author information

Abstract

BACKGROUND: Two drinking water systems at U.S. Marine Corps Base **Camp Lejeune**, North Carolina were contaminated with solvents during 1950s-1985.

METHODS: We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at **Camp Lejeune** during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 **Camp Pendleton** workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between **Camp Lejeune** and **Camp Pendleton** workers and assess the effects of estimated cumulative contaminant exposures within the **Camp Lejeune** cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at **Camp Lejeune**. The confidence interval (CI) indicated precision of effect estimates.

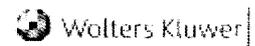
RESULTS: Compared to **Camp Pendleton**, **Camp Lejeune** workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the **Camp Lejeune** cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION: The study found elevated HRs in the **Camp Lejeune** cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the **Camp Lejeune** cohort died by end of follow-up, producing small numbers of cause-specific deaths and wide CIs. Additional follow-up would be necessary to comprehensively assess drinking water exposure effects at the base.

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See 1 citation found by title matching your search:

[J Occup Environ Med.](#) 2013 Feb;55(2):198-208. doi: 10.1097/JOM.0b013e3182728eab.

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#)¹, [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Author information

Abstract

OBJECTIVE: To evaluate the association between **exposure to chlorinated solvents** and cancer.

METHODS: We conducted a **case-control study** of **occupational exposures** and cancer in **Montreal, Quebec, Canada**, including 3730 cancer cases and 533 population controls.

Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six **chlorinated solvents** with 11 sites of cancer.

RESULTS: The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS: There was little evidence of associations between **chlorinated solvents** and cancer. Limited power precludes strong inferences about absence of **risk**. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

PMID: 23147555 [PubMed - indexed for MEDLINE]



Publication Types, MeSH Terms, Substances, Grant Support

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See 1 citation found by title matching your search:

QJM. 2015 Mar;108(3):205-12. doi: 10.1093/qjmed/hcu195. Epub 2014 Sep 9.

The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis.

Cheungpasitporn W¹, Thongprayoon C², O'Corragain OA², Edmonds PJ², Ungprasert P², Kittanamongkolchai W², Erickson SB².

Author information

Abstract

BACKGROUND: The objective of this **meta-analysis** was to evaluate the association between a history of **kidney stones** and **kidney cancer**.

METHODS: A literature search was performed from inception until June 2014. Studies that reported odds ratios or hazard ratios comparing the **risk** of renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of the upper urinary tract in **patients** with the history of **kidney stones** versus those without the history of **kidney stones** were included. Pooled **risk** ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

RESULT: Seven studies were included in our analysis to assess the association between a history of **kidney stones** and RCC. The pooled RR of RCC in **patients** with **kidney stones** was 1.76 (95% CI, 1.24-2.49). The subgroup analysis found that the history of **kidney stones** was associated with increased RCC **risk** only in males (RR, 1.41 [95% CI, 1.11-1.80]), but not in females (RR, 1.13 [95% CI, 0.86-1.49]). Five studies were selected to assess the association between a history of **kidney stones** and TCC. The pooled RR of TCC in **patients** with **kidney stones** was 2.14 (95% CI, 1.35-3.40).

CONCLUSION: Our study demonstrates a significant increased **risk** of RCC and TCC in **patients** with prior **kidney stones**. However, the increased **risk** of RCC was noted only in male **patients**. This finding suggests that a history of **kidney stones** is associated with **kidney cancer** and may impact clinical management and **cancer** surveillance.

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PMID: 25208892 [PubMed - in process]



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((Trichloroethylene[Title] AND cancer: epidemiologic evidence[Title

Abstract

Full text links

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Environ Health Perspect. 2000 May;108 Suppl 2:161-76.

Trichloroethylene and cancer: epidemiologic evidence.

Wartenberg D¹, Reyner D, Scott CS.

Author information

Abstract

Trichloroethylene is an organic chemical that has been used in dry cleaning, for metal degreasing, and as a solvent for oils and resins. It has been shown to cause liver and kidney **cancer** in experimental animals. This article reviews over 80 published papers and letters on the **cancer** epidemiology of people exposed to **trichloroethylene**. Evidence of excess **cancer** incidence among occupational cohorts with the most rigorous exposure assessment is found for kidney **cancer** (relative risk [RR] = 1.7, 95% confidence interval [CI] 1.1-2.7), liver **cancer** (RR = 1.9, 95% CI(1.0-3.4), and non-Hodgkin's lymphoma (RR = 1.5, 95% CI 0.9-2.3) as well as for cervical **cancer**, Hodgkin's disease, and multiple myeloma. However, since few studies isolate **trichloroethylene** exposure, results are likely confounded by exposure to other solvents and other risk factors. Although we believe that solvent exposure causes **cancer** in humans and that **trichloroethylene** likely is one of the active agents, we recommend further study to better specify the specific agents that confer this risk and to estimate the magnitude of that risk.

Comment in

Errors in TCE analysis. [Environ Health Perspect. 2001]

The a posteriori probability of a kidney **cancer** cluster attributed to **trichloroethylene** exposure. [Environ Health Perspect. 2002]

Carcinogenicity of **trichloroethylene**. [Environ Health Perspect. 2002]

Meta-analyses of TCE carcinogenicity. [Environ Health Perspect. 2000]

PMID: 10807550 [PubMed - indexed for MEDLINE] PMCID: PMC1637753 **Free PMC Article**



Publication Types, MeSH Terms, Substances, Grant Support

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Secondary malignancies following radiotherapy for prostate cancer.

[Sountoulides P¹](#), [Koletsas N](#), [Kikidakis D](#), [Paschalidis K](#), [Sofikitis N](#).

[Author information](#)

Abstract

Human exposure to sources of radiation as well as the use of radiation-derived therapeutic and diagnostic modalities for medical reasons has been ongoing for the last 60 years or so. The carcinogenetic effect of radiation either due to accidental exposure or use of radiation for the treatment of cancer has been undoubtedly proven during the last decades. The role of radiation therapy in the treatment of patients with prostate cancer is constantly increasing as less-invasive treatment modalities are sought for the management of this widely, prevalent disease. Moreover the wide adoption of screening for prostate cancer has led to a decrease in the average age that patients are diagnosed with prostate cancer. Screening has also resulted in the diagnosis of low-grade, less-aggressive prostate cancers which would probably never lead to complications or death from the disease. Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer. Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal. Care should be given to the long-term follow up of patients under radiation therapy for prostate cancer, while the indications for its use in certain cases should be reconsidered.

KEYWORDS:

brachytherapy; prostate cancer; radiation therapy; secondary bladder cancer

Secondary malignancies following radiotherapy for prostate cancer.

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Abstract

Human exposure to sources of radiation as well as the use of radiation-derived therapeutic and diagnostic modalities for medical reasons has been ongoing for the last 60 years or so. The carcinogenetic effect of radiation either due to accidental exposure or use of radiation for the treatment of cancer has been undoubtedly proven during the last decades. The role of radiation therapy in the treatment of patients with prostate cancer is constantly increasing as less-invasive treatment modalities are sought for the management of this widely, prevalent disease. Moreover the wide adoption of screening for prostate cancer has led to a decrease in the average age that patients are diagnosed with prostate cancer. Screening has also resulted in the diagnosis of low-grade, less-aggressive prostate cancers which would probably never lead to complications or death from the disease. Radiotherapy for prostate cancer has been linked to the late occurrence of second malignancies both in the true pelvis and outside the targeted area due to low-dose radiation scatter. Secondary malignancies following prostate irradiation include predominantly bladder cancer and, to a lesser extent, colon cancer. Those secondary radiation-induced bladder tumors are usually aggressive and sometimes lethal. Care should be given to the long-term follow up of patients under radiation therapy for prostate cancer, while the indications for its use in certain cases should be reconsidered.

KEYWORDS:

brachytherapy; prostate cancer; radiation therapy; secondary bladder cancer

FULL TEXT

Skeletal Plasmacytoma: Progression of disease and impact of local treatment; an analysis of SEER database

Muhammad U Jawad and Sean P Scully*

Journal of Hematology & Oncology 2009, **2**:41 doi:10.1186/1756-8722-2-41

Abstract

Background

Previous reports suggest an as yet unidentifiable subset of patients with plasmacytoma will progress to myeloma. The current study sought to establish the risk of developing myeloma and determine the prognostic factors affecting the progression of disease.

Methods

Patients with plasmacytoma diagnosed between 1973 and 2005 were identified in the SEER database (1164 patients). Patient demographics and clinical characteristics, treatment(s), cause of death, and survival were extracted. Kaplan-Meier, log-rank, and Cox regression were used to analyze prognostic factors.

Results

The five year survival among patients initially diagnosed with plasmacytoma that later progressed to multiple myeloma and those initially diagnosed with multiple myeloma were almost identical (25% and 23%; respectively). Five year survival for patients with plasmacytoma that did not progress to multiple myeloma was significantly better (72%). Age > 60 years was the only factor that correlated with progression of disease ($p = 0.027$).

Discussion

Plasmacytoma consists of two cohorts of patients with different overall survival; those patients that do not progress to systemic disease and those that develop myeloma. Age > 60 years is associated with disease progression. Identifying patients with systemic disease early in the treatment will permit aggressive and novel treatment strategies to be implemented.

From: (b) (6)
Cc: (b) (6)
Subject: renal and bladder ca and impaired kidney function
Date: Monday, June 02, 2014 8:20:20 AM

Medscape
Impaired Kidney Function Linked to Higher Renal Cancer Risk

Diedtra Henderson
May 30, 2014

-

Impaired kidney function, as measured by depressed glomerular filtration rates (GFR), is associated with a significantly higher risk of being diagnosed with renal and urothelial cancers, according to a retrospective cohort study.

William T. Lowrance, MD, MPH, from the Huntsman Cancer Institute, University of Utah, Division of Urology, Salt Lake City, and colleagues report the findings of their study, powered by Kaiser Permanente Northern California records for 1.19 million adult patients with no history of cancer and known kidney function, in an article published online May 29 in the Journal of the American Society of Nephrology.

The number of patients diagnosed with chronic kidney disease (CKD) is rising, Dr. Lowrance and coauthors note, with an estimated 11.5% of US residents registering diminished estimated GFR (eGFR) levels. To determine whether the level of kidney function was associated with a higher risk for subsequent cancer, the research team analyzed data from the regional cancer registry, looking for heightened risk for a wide variety of cancers. The patients were more likely to be older, people of color, poorer, and current or former smokers.

The researchers identified 76,809 incident cancers during the 5-plus years of follow-up, with the strongest correlations found between reduced kidney function and increased risk for renal and urothelial cancers.

The researchers adjusted for confounders including age, gender, race, socioeconomic status, comorbidities, proteinuria, hematuria, and body mass index. When eGFR rates ranged between 45 and 59 mL/minute/1.73 m², incident diagnosed renal cancer rate increased by 1.39 (95% confidence interval [CI], 1.22 - 1.58). That hazard ratio inched up to 1.81 (95% CI, 1.51 - 2.17) for eGFR ranging from 30 to 44 mL/minute/1.73 m². And when eGFR dropped to less than 30 mL/minute/1.73 m², risk for renal cancer rate soared to 2.28 (95% CI, 1.78 - 2.92), and there also was a 48% increased rate of urothelial cancer.

The authors found no similarly heightened risk for breast, colorectal, lung, or prostate cancer.

"Our findings reveal the association of CKD and cancer risk is site-specific for renal and urothelial cancers, and does not appear to be associated with an individual's overall cancer risk," the authors

write. Although the study team asserts that their findings could more effectively target cancer screening recommendations for patients with CKD, an accompanying editorial says the cancer associations are "smaller than that generally considered acceptable for screening purposes."

J Am Soc Nephrol. Published online May 29, 2014. Abstract

Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review.

[Moore LE](#), [Wilson RT](#), [Campleman SL](#).

Author information

Abstract

Malignant kidney tumors account for approximately 2% of all new primary cancer cases diagnosed in the United States, with an estimated 30,000 cases occurring annually. Although a variety of agents, chemical and biological, have been implicated as causal agents in the development of renal cell carcinoma (RCC), the etiology remains enigmatic. The strongest association has been developed between cigarette smoking and renal cancer however consistent, positive associations between RCC and obesity, diabetes, and hypertension have also been reported. In addition, more recent investigations of familial kidney cancer syndromes indicate that a strong genetic component contributes to RCC development. Several genes have been identified through investigation of familial kidney cancer syndromes. This review article describes recent trends in RCC incidence and the currently identifiable etiological causes that account for approximately half of the RCC cases diagnoses. The remainder of this review then focuses on additional risk factors that have thus far not been well examined but may be helpful in explaining the increasing incidence trends and the geographic or racial variation observed nationally and worldwide.

Smoking, environmental tobacco smoke, and risk of renal cell cancer: a population-based case-control study.

[Theis RP](#), [Dolwick Grieb SM](#), [Burr D](#), [Siddiqui T](#), [Asal NR](#).

[Author information](#)

Abstract

BACKGROUND:

Kidney and renal pelvis cancers account for 4% of all new cancer cases in the United States, among which 85% are renal cell carcinomas (RCC). While cigarette smoking is an established risk factor for RCC, little is known about the contribution of environmental tobacco smoke (ETS) to RCC incidence. This study assesses the role of smoking and ETS on RCC incidence using a population-based case-control design in Florida and Georgia.

METHODS:

Incident cases (n = 335) were identified from hospital records and the Florida cancer registry, and population controls (n = 337) frequency-matched by age (+/- 5 years), gender, and race were identified through random-digit dialing. In-person interviews assessed smoking history and lifetime exposure to ETS at home, work, and public spaces. Home ETS was measured in both years and hours of exposure. Odds ratios and 95% confidence intervals were calculated using logistic regression, controlled for age, gender, race, and BMI.

RESULTS:

Cases were more likely to have smoked 20 or more pack-years, compared with never-smokers (OR: 1.35, 95% CI: 0.93 - 1.95). A protective effect was found for smoking cessation, beginning with 11-20 years of cessation (OR: 0.39, 95% CI: 0.18-0.85) and ending with 51 or more years of cessation (OR: 0.11, 95% CI: 0.03-0.39) in comparison with those having quit for 1-10 years. Among never-smokers, cases were more likely to report home ETS exposure of greater than 20 years, compared with those never exposed to home ETS (OR: 2.18; 95% CI: 1.14-4.18). Home ETS associations were comparable when measured in lifetime hours of exposure, with cases more likely to report 30,000 or more hours of home ETS exposure (OR: 2.37; 95% CI: 1.20-4.69). Highest quartiles of combined home/work ETS exposure among never-smokers, especially with public ETS exposure, increased RCC risk by 2 to 4 times.

CONCLUSION:

These findings confirm known associations between smoking and RCC and establish a potential etiologic role for ETS, particularly in the home. Differences in methods of retrospective measurement of lifetime smoking and ETS exposure may contribute to discrepancies in measures of associations across studies, and should be addressed in future research.

FULL TEXT

[Int Arch Occup Environ Health](#). 2006 Mar;79(3):251-8. Epub 2005 Oct 12.

Reproductive history, occupational exposures, and thyroid cancer risk among women textile workers in Shanghai, China.

[Wong EY¹](#), [Ray R](#), [Gao DL](#), [Wernli KJ](#), [Li W](#), [Fitzgibbons ED](#), [Feng Z](#), [Thomas DB](#), [Checkoway H](#).

Author information

Abstract

OBJECTIVES:

Thyroid cancer risk has been previously associated with increased age at first pregnancy and history of miscarriage. Occupational risk factors for thyroid cancer, with the exception of radioactive iodine, have not been well investigated. We conducted a case-cohort study nested in a cohort of 267,400 female textile workers in Shanghai, China, who had been followed for cancer incidence during 1989-1998.

METHODS:

The analysis included 130 incident thyroid cases and 3,187 subcohort non-cases. Reproductive history was determined by questionnaire at baseline. Historical exposures were reconstructed from work history and information on factory processes and exposures. Cox proportional hazards analysis was performed to estimate hazard ratios (HR) for reproductive factors and occupational exposures.

RESULTS:

Associations were observed between thyroid cancer and employment in jobs with 10 or more years of benzene exposure (HR 6.43, 95% CI: 1.08, 38) and formaldehyde exposure (HR 8.33, 95% CI: 1.16, 60). Administration workers also had an increased risk (HR 1.56, 95% CI: 1.08, 2.25). No associations between examined reproductive factors and thyroid cancer were observed in this study.

CONCLUSIONS:

Despite statistically imprecise risk estimates, the findings suggest potential associations with some occupational chemical exposures in this cohort of textile workers.

Brownson R, Reif J, Keefe T, Ferguson S, Pritzl J. Risk Factors for Adenocarcinoma of the Lung. Am J Epi 125(1): 25-34.

RISK FACTORS FOR ADENOCARCINOMA OF THE LUNG

1. [ROSS C. BROWNSON^{1,3}](#),
2. [JOHN S. REIF¹](#),
3. [THOMAS J. KEEFE¹](#),
4. [STANLEY W. FERGUSON²](#) and
5. [JANE A. PRITZL²](#)

[±](#) Author Affiliations

1. ¹*Department of Microbiology and Environmental Health Colorado State University, Fort Collins, CO.*
 2. ²*Colorado Department of Health Denver, CO.*
 1. ³Reprint requests to Dr. Ross C. Brownson at current address: Cancer Epidemiology and Control Program, Division of Environmental Health and Epidemiology Services, Missouri Department of Health, P. O. Box 1268, Columbia, MO 65205.
- Received March 28, 1986.

Brownson R, Reif J, Keefe T, Ferguson S, Pritzl J. Risk Factors for Adenocarcinoma of the Lung. Am J Epi 125(1): 25-34.

[Oxford Journals](#)

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[American Journal of Epidemiology](#)

[Volume 125, Issue 1](#)

Pp. 25-34.

Abstract

The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979–1982 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio (OR) = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age-and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval (CI) = 0.39–2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% CI = 0.97–5.12). The results suggest the need to develop cell type-specific etiologic hypotheses.

Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3490374/>

[Clin Epidemiol.](#) 2012;4:1-11. doi: 10.2147/CLEP.S16747. Epub 2012 Jan 5.

Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates.

[Leitzmann MF](#), [Rohrmann S](#).

Source

Department of Epidemiology and Preventive Medicine, Regensburg University Medical Center, Regensburg, Germany.

Abstract

At present, only three risk factors for prostate cancer have been firmly established; these are all nonmodifiable: age, race, and a positive family history of prostate cancer. However, numerous modifiable factors have also been implicated in the development of prostate cancer. In the current review, we summarize the epidemiologic data for age, location, and selected behavioral factors in relation to the onset of prostate cancer. Although the available data are not entirely consistent, possible preventative behavioral factors include increased physical activity, intakes of tomatoes, cruciferous vegetables, and soy. Factors that may enhance prostate cancer risk include frequent consumption of dairy products and, possibly, meat. By comparison, alcohol probably exerts no important influence on prostate cancer development. Similarly, dietary supplements are unlikely to protect against the onset of prostate cancer in healthy men. Several factors, such as smoking and obesity, show a weak association with prostate cancer incidence but a positive relation with prostate cancer mortality. Other factors, such as fish intake, also appear to be unassociated with incident prostate cancer but show an inverse relation with fatal prostate cancer. Such heterogeneity in the relationship between behavioral factors and nonadvanced, advanced, or fatal prostate cancers helps shed light on the carcinogenetic process because it discerns the impact of exposure on early and late stages of prostate cancer development. Inconsistent associations between behavioral factors and prostate cancer risk seen in previous studies may in part be due to uncontrolled detection bias because of current widespread use of prostate-specific antigen testing for prostate cancer, and the possibility that certain behavioral factors are systematically related to the likelihood of undergoing screening examinations. In addition, several genes may modify the study results, but data concerning specific gene-environment interactions are currently sparse. Despite large improvements in our understanding of prostate cancer risk factors in the past two decades, present knowledge does not allow definitive recommendations for specific preventative behavioral interventions.



NIH Public Access

Author Manuscript

Expert Opin Med Diagn. Author manuscript; available in PMC 2013 July 01.

Published in final edited form as:

Expert Opin Med Diagn. 2012 July 1; 6(4): 323–333. doi:10.1517/17530059.2012.686996.

Risk Factors of Follicular Lymphoma

Shuangge Ma, Ph.D [Associate Professor]

School of Public Health, Yale University

Abstract

Introduction—Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of malignancies with over thirty different subtypes. Follicular lymphoma (FL) is the most common form of indolent NHL and the second most common form of NHL overall. It has morphologic, immunophenotypic and clinical features significantly different from other subtypes. Considerable effort has been devoted to the identification of risk factors for etiology and prognosis of FL. These risk factors may advance our understanding of the biology of FL and have an impact on clinical practice.

Areas covered—The epidemiology of NHL and FL is briefly reviewed. For FL etiology and prognosis separately, we review clinical, environmental and molecular (including genetic, genomic, epigenetic and others) risk factors suggested in the literature.

Expert opinion—A large number of potential risk factors have been suggested in recent studies. However, there is a lack of consensus, and many of the suggested risk factors have not been rigorously validated in independent studies. There is a need for large-scale, prospective studies to consolidate existing findings and discover new risk factors. Some of the identified risk factors are successful at the population level. More effective individual-level risk factors and models remain to be identified.

Keywords

Follicular lymphoma; Etiology; Non-Hodgkin lymphoma; Prognosis; Risk factor

1. Introduction

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of malignancies of lymphocyte origin. It usually arises or is present in lymphoid tissues, such as lymph nodes, spleen and

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#)¹, [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Author information

Abstract

OBJECTIVE:

To evaluate the association between exposure to chlorinated solvents and cancer.

METHODS:

We conducted a case-control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer.

RESULTS:

The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS:

There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma.

From: (b) (6)
To: (b) (6)
Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::
Date: Tuesday, May 05, 2015 4:13:35 PM

This is the someone I sent you a month ago..

From: (b) (6)

Sent: Tuesday, April 14, 2015 12:33 PM

To: (b) (6)

Subject: RE: <http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

I think this document is useful for reading but cannot be used as a reference as 1) it is "Draft" form and 2) there are now many more recent documents which have a different perspective on this, such as USDHHS RoC.

(b)
(6)

From: (b) (6)

Sent: Tuesday, May 05, 2015 2:37 PM

To: (b) (6)

Subject: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

These are still in draft form, and not officially sanctioned, but check them out:

<http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

<http://www.atsdr.cdc.gov/toxprofiles/tp18.pdf>

From: (b) (6)
To: (b) (6)
Subject: RE: good article for the sharepoint: breast ca and environmental exposures
Date: Monday, May 12, 2014 12:45:23 PM

<http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2014/5/ehp.1307455.pdf>

From: (b) (6)
Sent: Monday, May 12, 2014 5:39 AM
To: (b) (6)
Subject: RE: CLCW: vacation

Thanks (b) (6),

I will make note of it. I hope you are planning to do something fun.

(b) (6)

From: (b) (6)
Sent: Friday, May 09, 2014 11:24 AM
To: (b) (6)
Subject: RE: CLCW: vacation

Hi (b) (6),

I will be on vacation May 26-June 2.

Thanks

(b) (6)

From: (b) (6)
Sent: Thursday, May 08, 2014 11:50 AM
To: (b) (6)
Cc: (b) (6)
Subject: CLCW: data extraction.

(b) (6),

I want to have (b) (6) start working a few of the cases in your queue. I am giving him : S6110 prostate cancer, B0664 bladder cancer. He will provide the data extraction file via email upon completion.

Thanks,

(b) (6)
Office of Disability & Medical Assessment
Department of Veterans Affairs
810 Vermont Ave. NW

Washington, DC 20420
202.461.1703 office
(b) (6) blackberry



Please consider your environmental responsibility before printing this e-mail & any documents

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: RF for follicular lymphoma
Date: Monday, December 22, 2014 2:38:13 PM

Let's add to the library if not already entered.

thanks

From: (b) (6)
Sent: Monday, December 22, 2014 10:40 AM
To: (b) (6)
Cc: (b) (6)
Subject: RF for follicular lymphoma

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3384553/pdf/nihms374241.pdf>

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: Suggested articles for Sharepoint
Date: Monday, March 24, 2014 11:13:19 AM

Additional article also suggested for uploading.

Spechler, S. (2013). Barrett Esophagus and Risk of Esophageal Cancer A Clinical Review. *JAMA* 2013 Aug 14. 310 (6): 627-36. Doi: 10.1001/jama.2013.226450.

From: (b) (6)
Sent: Monday, March 24, 2014 11:09 AM
To: (b) (6)
Cc: (b) (6)
Subject: Suggested articles for Sharepoint

Suggesting the following articles for inclusion on the CLCW Sharepoint:

1. Qureshi, A., Ramsey, D., Kramer, J. Whitehead, L., El-Serag, H. (2013). Occupational Exposure and the Risk of Barrett's Esophagus: A Case-Control Study. *Dig Dis Sci.* 2013 Jul;58(7): 1967-75. Doi: 10.1007/s10620-013-2572-6. Epub 2013 Feb 5.
2. Pohl, H., Wrobel, K., Bojarski, C., Voderholzer, W., Sonnenberg, A., Rosch, T. & Baumgart, D. (2013). Risk Factors in the Development of Esophageal Adenocarcinoma. *The American Journal of Gastroenterology*, 2013 Feb; 108(2): 200-7. Doi: 10.1038/ajg.2012.387. Epub 2012 Dec 18.

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: Camp Lejeune studies and updates
Date: Monday, December 09, 2013 8:24:52 PM
Attachments: [EAS](#)

The occ med list serv interpretation you mentioned below seems to relate to an earlier survey of parents that took place in 1999-2002.

There are updates on the ATSDR website of a more recent survey of parents that started in 2005:

“Page last updated: December 5, 2013”

[“Birth Defects and Childhood Cancers Study
<<http://www.atsdr.cdc.gov/sites/lejeune/update.html>>](#)

The current study is entitled *Exposure to Volatile Organic Compounds in Drinking Water and Specific Birth Defects and Childhood Cancers, United States Marine Corps Base Camp Lejeune, North Carolina*. Interviews of parents started in April 2005.”

“In 2005 ATSDR began a full study of specific birth defects and childhood cancers in children born to mothers who lived on base any time during their pregnancies from 1968-1985.”

(b) (6)

From: (b) (6)
Sent: Monday, December 09, 2013 8:56 AM
To: (b) (6)
Cc: (b) (6)
Subject: RE: Camp Lejeune studies and updates

Here is the occ med listserv interpretation of the study, which is a bit different from that noted in the AP. I'd be curious to hear Wendy's interpretation of the study.

Birth Defects and Childhood Cancers Study

Exposure to Contaminated Drinking Water and Specific Birth Defects and Childhood Cancers at Marine Corps Base Camp Lejeune, North Carolina

Study Purpose

The purpose of this study was to determine if maternal exposures to the drinking water contaminants at Camp Lejeune increased the risk of neural tube defects (NTDs), oral clefts, and childhood hematopoietic cancers. This study also examined whether children exposed to contaminated drinking water during the first year of life had an increased risk of childhood cancers. Drinking water at Camp Lejeune was

contaminated with volatile organic compounds (VOCs) including trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, 1,2-dichloroethylene (DCE) and vinyl chloride from the 1950s through 1985.

What Was Studied

The Agency for Toxic Substances and Disease Registry (ATSDR) surveyed the parents of 12,598 children during 1999-2002 to identify potential cases of birth defects and childhood cancers. ATSDR asked parents if their child had a birth defect or developed a childhood cancer. To be eligible for the survey, the mother had to reside on base some time during her pregnancy and children had to be born between 1968-1985.

The survey's participation rate was approximately 76% (ATSDR 2003). Survey participants reported 106 cases: 35 NTDs, 42 oral clefts, and 29 childhood hematopoietic cancers. ATSDR made extensive efforts to obtain medical information from health providers to confirm reported cases. ATSDR was able to confirm 15 NTDs, 24 oral clefts, and 13 cancers. Only confirmed cases from the survey were eligible for the study.

Based on the survey results, the study focused on NTDs (spina bifida and anencephaly), oral clefts (cleft lip and cleft palate), and childhood hematopoietic cancers (leukemia and non-Hodgkin's lymphoma [NHL]) diagnosed before 20 years of age.

Features of this Study

Due to the lack of exposure information, ATSDR used extensive water modeling to reconstruct exposures before 1987. This study is unique because it used this water modeling to thoroughly examine associations between monthly exposures to VOCs in drinking water at the residence and the risk of developing specific birth defects and childhood cancers. Most previous studies that have evaluated these associations have done so at the broad water system level versus drinking water at the residence.

Conclusion and Key Results

ATSDR's study results suggested associations between TCE and benzene in Camp Lejeune drinking water and NTDs.

- In this study, these effects were seen in children born from 1968-1985 whose mothers were exposed to contaminated drinking water in their residences at Camp Lejeune.
- During the first trimester of pregnancy, the risk of a NTD increased with increasing levels of exposure to TCE.
 - o This finding is consistent with a previous study conducted in New Jersey, which found similar risk of NTDs when exposed to TCE during the first trimester.

- Investigators observed an association between NTDs and first trimester exposure to benzene. ATSDR was unable to evaluate whether increasing levels of exposure to benzene were associated with increased risk of NTDs because of small numbers of exposed cases.

ATSDR's study results suggested weaker associations between 1st trimester exposure to PCE, vinyl chloride, and 1,2- DCE and childhood hematopoietic cancers such as leukemia.

- These associations are weaker than those found for NTDs.
- Researchers did not observe an increased risk for these cancers with increasing levels of exposure to the chemicals.

The study found no evidence suggesting any other associations between outcomes and exposures.

- For childhood cancers, ATSDR also looked at exposures during the second and third trimesters, the entire pregnancy as a whole, and exposures in the first year of life. The investigators did not see any associations between these chemicals with these time periods.
- Exposure to contaminants in Camp Lejeune drinking water did not increase the risk of oral clefts.

Additional Resources

- Journal Article (provisional)
<<http://www.ehjournal.net/content/12/1/104/abstract>>

From: (b) (6)
Sent: Saturday, December 07, 2013 12:18 PM
To: (b) (6)
(b) (6) E.
Cc: (b) (6)
Subject: Camp Lejeune studies and updates

Hi, All

updates about Camp Lejeune Studies were posted on Dec 5, 2013 re: adverse pregnancy outcomes (birth defects and childhood cancers) and male breast cancer

<<http://www.atsdr.cdc.gov/sites/lejeune/activities.html>>

Also from the Associated Press is the following:

“RALEIGH, N.C. (AP) — A long-awaited study by the U.S. Centers for Disease Control and Prevention confirms a link between tainted tap water at a U.S. Marine Corps base in North Carolina and increased risk of serious birth defects and childhood cancers.

The study released late Thursday by the CDC's Agency for Toxic Substances & Disease Registry surveyed the parents of 12,598 children born at Camp Lejeune between 1968 and 1985, the year drinking-water wells contaminated with chemicals from a leaky fuel depot and a dry cleaner were closed.

The study concludes that babies born to mothers who drank the tap water while pregnant were four times more likely than normal to have such serious birth defects as spinal bifida. Babies whose mothers were exposed also had an elevated risk of such childhood cancers as leukemia”

Keep in contact and Best to all during the Holiday season!

(b)
(6)

(b) (6) [REDACTED], Syracuse VAMC)

Attachments:

image001.png (298 Bytes)

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: CLCW: Library
Date: Sunday, February 22, 2015 9:46:42 PM

Thanks, (b) (6) .

(b) (6) , chat?

As I'm struggling with these I've created myself a directory at home with disease, subdisease, the most recent case anonymized, and specific references. So, for example, I have subfolders for squamous and for adeno ca of the esophagus. Lets chat.

From: (b) (6)
Sent: Tuesday, February 17, 2015 12:36 PM
To: (b) (6)
Cc: (b) (6)
Subject: CLCW: Library

(b) (6) : Thank you for your comments and suggestions concerning improving the organization of the SharePoint Library. I look forward to receiving input from you and (b) (6) for improvements.

(b) (6)
Office of Disability & Medical Assessment
Department of Veterans Affairs
810 Vermont Ave NW
Washington, DC 20420
202.461.1703 office
(b) (6) blackberry



Please consider your environmental responsibility before printing this e-mail & any documents

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: cml 6.1.2014
Date: Tuesday, June 17, 2014 11:56:52 AM

Hi guys, there is evidence that CML is related to obesity (2—3 fold increase in rates);

FYI

(b) (6)

Cancer Epidemiol Biomarkers Prev. 2009 May ; 18(5): 1501–1506. doi:10.1158/1055-9965.EPI-09-0028.

Obesity, Weight Gain, and Risk of Chronic Myeloid Leukemia

Sara S. Strom, Yuko Yamamura, Hagop M. Kantarjian, and Jorge E. Cortes-Franco

Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas (SSS, YY); Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas (HK, JC)

From: (b) (6)
Sent: Monday, June 16, 2014 7:17 PM
To: VHA CO CLCW SME
Subject: cml 6.1.2014

Fyi CML

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: RE: FYI October 2014 draft ATSDR TOXICOLOGIC PROFILES are available online fo PCE and TCE::
Date: Wednesday, May 06, 2015 11:50:47 AM

I will look into this further:

The Mattei article seems to be an abstract or a publication of an oral presentation: It is not likely peer reviewed and is therefore suspect;

(b) (6)

0139 OCCUPATIONAL EXPOSURE TO CHLORINATED
SOLVENTS AND LUNG CANCER: RESULTS FROM THE
ICARE STUDY

1Francesca Mattei, 1Florence Guida, 1Marie Sanchez, 1Sylvie C n e, 2Jo lle F votte,

3Daniele Luce, 1Isabelle St cker. 1Inserm, CESP Centre for Research in
Epidemiology and

Population Health, U1018, Environmental Epidemiology of Cancer Team, Villejuif,

France; 2Inserm, CESP Centre for Research in Epidemiology and Population Health,

U1018, Epidemiology of Occupational and Social Determinants of Health Team,
Villejuif,

France; 3UMRESTTE (Unit  Mixte de Recherche  pid miologique Et de Surveillance en

Transport, Travail Et Environnement), University Claude Bernard, Lyon, France

10.1136/oemed-2014-102362.52

Objectives We aimed to investigate the role of occupational
exposure to chlorinated solvents in the aetiology of lung cancer.

Method ICARE is a multicenter population-based case-control
study conducted in France between 2001 and 2006. Information
on subjects lifelong work history was collected by face to face
interviews using standardised questionnaires. Occupational exposures

were assessed using job-exposure matrices (JEM) relative to five chlorinated solvents including trichloroethylene (TCE), methylene chloride, perchloroethylene (PER), chloroform and carbon tetrachloride. Solvents were studied separately and since overlapping among exposures analyses for combined solvents exposure were performed. In the questionnaire, subjects also had to report if they were exposed to TCE or other substances (PER was among them). Odds ratios (ORs) were computed using unconditional logistic regression models adjusted for classical risk factors.

Results A total of 2926 cases (2276 men and 650 women) and 3555 controls (2780 men and 775 women) were included. A statistically significant positive association for lung cancer risk was observed in both men (OR 1.47, 95% CI: 1.00–2.17) and in women (OR 3.86, 95% CI: 1.36 -11.01) exposed to PER combined with TCE and/or methylene chloride. In contrast, no statistically significant associations were found for TCE or other solvent combinations. Finally for subjects, who reported the exposure to PER, the ORs were 3.25 (95% CI: 1.23, 8.59) and 3.12 (95% CI: 0.50, 19.28) among men and women respectively.

Conclusions The results of this study suggest that PER alone or in combination with TCE and/or methylene chloride may increase the risk of lung cancer.

From: (b) (6)

Sent: Wednesday, May 06, 2015 6:25 AM

To: (b) (6)

Cc: (b) (6)

Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

What do you guys think about these studies? Do we know anything about the degree of exposure? I would think we'd want to include that.

(b) (6)

Compensation & Pension

Environmental Health Clinician

DMA Subject Matter Expert Panel

VISN 11 Primary MRO

Ann Arbor VAMC

734-769-7100 x (b) (6) (office)

(b) (6) (cell)

(b) (6)

From: (b) (6)

Sent: Tuesday, May 05, 2015 4:02 PM

To: (b) (6)

Cc: (b) (6)

Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

Do you want to study or use the below?

A multicenter case-control study in France in 2014 sampling occupational exposure to PCE and TCE found a positive association for lung cancer risk in men (OR 1.47, 95% CI: 1.00-2.17) (26), and after adjustment for exposure to asbestos, they observed a positive, significant association with lung cancer for men and women exposed to a combination of perchloroethylene (PCE), and trichloroethylene (27). Two case-control studies in Quebec found indications of an increased risk of lung cancer associated with occupational exposure to perchloroethylene (OR(any exposure) 2.5, 95% CI 1.2 to 5.6; OR(substantial exposure) 2.4, 95% CI 0.8 to 7.7) (28)

26; Occup Environ Med. 2014 Jun;71 Suppl 1:A17. doi: 10.1136/oemed-2014-102362.52.

0139 Occupational exposure to chlorinated solvents and lung cancer: results from the ICARE study.

Mattei F1, Guida F1, Sanchez M1, C  n  e S1, F  votte J2, Luce D3, St  cker I1.

27; Occup Environ Med. 2014 Oct;71(10):681-9. doi: 10.1136/oemed-2014-102182. Epub 2014 Jul 11.

Exposure to chlorinated solvents and lung cancer: results of the ICARE study.

Mattei F1, Guida F1, Matrat M2, Cenée S1, Cyr D3, Sanchez M1, Radoi L4, Menvielle G5, Jellouli F6, Carton M3, Bara S7, Marrer E8, Luce D9, Stücker I1.

28: Occup Environ Med. 2013 Feb;70(2):81-5. doi: 10.1136/oemed-2012-101155. Epub 2012 Oct 26.

Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montreal, Canada. Vizcaya D1, Christensen KY, Lavoué J, Siemiatycki J.

From: (b) (6)
Sent: Tuesday, May 05, 2015 12:42 PM
To: (b) (6)
Subject: RE: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

You don't need to look at the lung cancer template. I fixed all the references and some other things. Unless you want to but know that I did make some changes.

From: (b) (6)
Sent: Tuesday, May 05, 2015 3:37 PM
To: (b) (6)
Subject: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::

These are still in draft form, and not officially sanctioned, but check them out:

<http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

<http://www.atsdr.cdc.gov/toxprofiles/tp18.pdf>

Parkinson's References, Case Control Studies

3.14.2013

Gallegos-Arreola MP, Figuera LE, Ortiz GG, Jiménez-Gil FJ, Ramírez-Vega J, Ruíz-Sandoval JL, Puebla-Pérez AM, Troyo-Sanroman R, García-Ortiz JE, Sanchez-Corona J, Zúñiga-González GM. Apolipoprotein E genotypes in Mexican patients with Parkinson's disease. *Dis Markers*. 2009;27(5):225-30.

Firestone JA, Lundin JI, Powers KM, Smith-Weller T, Franklin GM, Swanson PD, Longstreth WT Jr, Checkoway H. Occupational factors and risk of Parkinson's disease: A population-based case-control study. *Am J Ind Med*. 2010 Mar;53(3):217-23.

Tanner CM, Ross GW, Jewell SA, Hauser RA, Jankovic J, Factor SA, Bressman S, Deligtisch A, Marras C, Lyons KE, Bhudhikanok GS, Roucoux DF, Meng C, Abbott RD, Langston JW. Occupation and risk of parkinsonism: a multicenter case-control study. *Arch Neurol*. 2009 Sep;66(9):1106-13.

Dick FD, De Palma G, Ahmadi A, Osborne A, Scott NW, Prescott GJ, Bennett J, Semple S, Dick S, Mozzoni P, Haites N, Wettinger SB, Mutti A, Otelea M, Seaton A, Soderkvist P, Felice A; Geoparkinson Study Group. Gene-environment interactions in parkinsonism and Parkinson's disease: the Geoparkinson study. *Occup Environ Med*. 2007 Oct;64(10):673-80. Epub 2007 Apr 20.

Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, Semple S, Dick S, Counsell C, Mozzoni P, Haites N, Wettinger SB, Mutti A, Otelea M, Seaton A, Söderkvist P, Felice A; Geoparkinson study group. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup Environ Med*. 2007 Oct;64(10):666-72. Epub 2007 Mar 1.

Pezzoli G, Canesi M, Antonini A, Righini A, Perbellini L, Barichella M, Mariani CB, Tenconi F, Tesei S, Zecchinelli A, Leenders KL. Hydrocarbon exposure and Parkinson's disease. *Neurology*. 2000 Sep 12;55(5):667-73.

De Palma G, Mozzoni P, Mutti A, Calzetti S, Negrotti A. Case-control study of interactions between genetic and environmental factors in Parkinson's disease. *Lancet*. 1998 Dec 19-26;352(9145):1986-7.

Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. *Neurotoxicology*. 1998 Aug-Oct;19(4-5):709-12.

Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P, Joerg J, Oertel WH, Ulm G, Schneider E. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology*. 1996 May;46(5):1275-84.

PARKINSON'S DISEASE AND ORGANIC SOLVENTS

Human studies: epidemiology

Trichloroethylene (TCE) has been widely used in the workplace, in drycleaning and degreasing, and in environmental exposures, including in typewriter fluids, adhesives, paints, carpet cleaners, spot removers. In 1977 FDA banned its use as an anesthetic and decaffeinating agent.

Since 1981, a robust body of literature has explored the relationship between exposure to organic solvents and Parkinson's disease (PD). At least nine case control studies explored the relationship of solvents, pesticides and PD. Six showed a clear relationship between exposure to organic solvents and the development of disease. The "better" the exposure assessment techniques the more likely associations are to be evident. Two studies failed to distinguish pesticide from solvent exposure and found only elevated risks associated with pesticides. One study failed to find an increased risk of PD after exposure to solvents. Two studies identified interactions between specific genetic markers and the risk for Parkinson's disease

Several formal cohort studies failed to show an increased rate of disease, but PD is only rarely the actual cause of death so that these are not ideal approaches to identifying such relationships. The one cross-sectional study conducted in the workplace identified a strong relationship between the degree of exposure to trichloroethylene and PD or, at lower levels of exposure, early signs of basal ganglion involvement

Mechanistic studies of solvents in general and TCE in particular identified ways that general damage in dopaminergic neurons in the brainstem.

Few studies provide approximate exposure data, much less information allowing precise dose estimates. The most pertinent and useful study was conducted by Goldman et al: the World War II Veterans Twins study. An exposure to TCE of at least one hour a day or 2% of the work day for at least six months was associated with a six-fold risk of disease; PERC in that same exposure definition was associated with a 10-fold risk.

Toxicology, Exposures, and Dose Extrapolation

The Environmental Protection Agency (EPA) considers the amounts that can be "safely" consumed each day for a lifetime without concerns for adverse health effects, i.e., the reference dose (RfD) for each of the agents as listed below. The source is EPA's Integrated Risk Information System (IRIS). That dose incorporates a safety factor listed in column 2. Similarly, the Agency for Toxic Substances and Disease Registry provides No Adverse Observed Effect Level (NOAEL) and the Lowest Observed Adverse Effect Level (LOAEL) for each of the four contaminants of concern. The table below summarizes the EPA IRIS doses and the associated safety factors. In general, these safety factors take into consideration extrapolation of dose effects from animals to humans and inter-subject variability.

| | RFD (+) in mg/kg/day | Safety factor |
|--------------------------|----------------------|---------------|
| Trichloroethylene (TCE) | 0.0005 | 1,000 |
| Perchloroethylene (PERC) | 0.006 | 1,000 |
| Benzene | 0.004 | 300 |
| Vinyl Chloride | 0.003 | 1,000 |

*: animal data, as no human data are available

For Trichloroethylene, acute levels of interest for neurological outcomes as NOAEL and LOAELs are, respectively, 100 vs 200 mg/kg/day. For intermediate duration, a LOAEL of 200 mg/kg/day exists for “less serious effects, but no NOAEL exists. No data are available for chronic ingestion exposures.

For Perchloroethylene, acute levels of interest for neurological outcomes exist for humans only as LOAEL at 100 mg/kg/day. No animal data and no data on intermediate or chronic doses associated with adverse neurological exist.

For Benzene, 10 mg/kg/day and 30 mg/kg/day represent respectively NOAEL and LOAELs for intermediate duration (15 – 365 days) of doses associated with adverse neurological exist. Chronic exposure to 100 mg/kg/day was not associated with adverse neurological health effects.

For Vinyl chloride,

Use of the calculation spreadsheet provides an estimate of the likely doses and sets them into a relation with RfD and Toxprofile specific data

Competing exposures

Additional pertinent considerations include other known risk factors for Parkinson’s disease. Smoking is known to be protective, with consistent relative risks of 0.5 – 0.6; similarly, coffee drinking reduces the risk. No explanation exists for these two factors.

Several other exposures are known to increase the risk of Parkinson’s disease, most prominently, managanese, carbon monoxide, and pesticides. Carbon monoxide represents a known risk factor, but that onset of disease is relatively prompt after over-exposure. Common events leading to onset include suicidal gestures with combustion products, “accidental” overexposures from use of internal combustion (indoor chain saws, gas-powered buffers, and entrainment of grill exhaust). Manganese in mining and manufacturing and in welding is clearly associated with disease.

Examiners should make efforts to identify an acute onset of disease (CO) or exposures to pesticides (farming, pesticide application) or welding. Smoking may reduce the risk for Parkinson's disease for an unknown reason

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Community Cancer Assessment in Response to Long-Time Exposure to Perchlorate and Trichloroethylene in Drinking Water

Abstract

In response to concerns about cancer stemming from drinking water contaminated with ammonium perchlorate and trichloroethylene, we assessed observed and expected numbers of new cancer cases for all sites combined and 16 cancer types in a California community (1988 to 1998). The numbers of observed cancer cases divided by expected numbers defined standardized incidence ratios (SIRs) and 99% confidence intervals (CI). No significant differences between observed and expected numbers were found for all cancers (SIR, 0.97; 99% CI, 0.93 to 1.02), thyroid cancer (SIR, 1.00; 99% CI, 0.63 to 1.47), or 11 other cancer types. Significantly fewer cases were observed than expected for cancer of the lung and bronchus (SIR, 0.71; 99% CI, 0.61 to 0.81) and the colon and rectum (SIR, 0.86; 0.74 to 0.99), whereas more cases were observed for uterine cancer (SIR, 1.35; 99% CI, 1.06 to 1.70) and skin melanoma (SIR, 1.42; 99% CI, 1.13 to 1.77). These findings did not identify a generalized cancer excess or thyroid cancer excess in this community.

From: (b) (6)
To: (b) (6)
Subject: Please circulate to SME's
Date: Wednesday, April 02, 2014 11:42:21 AM
Attachments: [EAS](#)

Thanks

Topic: ASTDR Mortality Study of Marines at Camp Lejeune and Camp Pendleton

Review of: Bove FJ, Ruckart PZ, Maslia M, et.al. Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC base camp LeJeune: a retrospective cohort study. *Environmental Health* 2014, 13:10.

Issue:

- Contaminated drinking water was discovered in the 1980s at Camp Lejeune; there are concerns about long term health effects
- The Department of Veterans Affairs (VA) is responsible for the provision of care for Veterans who lived at Camp Lejeune. Additionally, VA is responsible for payment of care for 15 specific conditions for family members of Veterans who lived at Camp Lejeune.
- On February 19, 2014 the Agency for Toxic Substances and Disease Registry (ASTDR), a branch of the CDC, published a mortality study of Marines and sailors who lived at Camp Lejeune during the time of the water contamination.

Analysis:

- Since 1991, ATSDR has been performing health surveillance of former residents of Camp Lejeune. These studies have been funded by the Navy, totaling more than \$40 million.
- The research question of the mortality study was to determine if exposure of Marine and Navy personnel to contaminated drinking water at Camp Lejeune increased the risk of mortality from cancers and other chronic diseases”.
- The mortality rate of 154,932 Marines at Camp Lejeune was compared to mortality rates of 154,969 Marines at Camp Pendleton. Mortality rates were also compared to the general US population.
- By the end of the study period about 6% (n=9,000) of the Marines in **both** groups died.
- Multiple comparisons were performed on the data, with only three statistically significant findings:
 - Both groups of Marines were significantly healthier than the general population. Both group of Marines had decreased mortality for all causes and for all cancers. It is expected that Marines would be healthier than the general population (healthy soldier effect)
 - The Camp Lejeune Marines had a significant increase in prostate cancer death (18 deaths) compared to the US population, but **NOT** compared to the Camp Pendleton group
 - The Camp Lejeune Marines had a 10% increase in mortality from all cancers, compared to the Camp Pendleton group.

Methodological Flaws

- ATSDR concludes that there were “elevated risks” for several types of cancer and amyotrophic lateral sclerosis. This is misleading, and not supported by data. These results were **NOT** statistically significant.
 - Although risk estimates between two populations may differ from each other in magnitude (i.e., one risk estimated being “elevated” over another), it **does not** mean that they are statistically and meaningfully different from each from an epidemiological perspective. You must use statistical testing to interpret if the difference in magnitude is meaningful. The authors did not use statistical significance testing (p-values testing the null hypothesis of no difference) to interpret these differences, and therefore, there is limited confidence in the conclusions.
 - Another method that is commonly used to test for significance in population statistics is to examine the 95% confidence intervals for the two risk estimates. If the 95% confidence intervals for each of the two risk estimates overlap, it can be deduced that those two risk estimates do not differ significantly (although one may be larger in magnitude). Table 4 demonstrates this.
- The authors state “We did not use statistical significance testing to interpret findings”. It is methodologically suspect that in a study sample this large (N=20,000), statistical testing was not performed, since statistical significance (p-values) is largely a function of sample size.
 - Multiple comparisons were performed (which lead to chance associations) without any corrections for p-values (Bonferroni corrections should have been performed).
 - The 95% confidence intervals for almost all comparisons were unstable and not significant, due to the small number of deaths from each condition.
 - Table 5, which compares the risk of specific cause mortality between Camp Pendleton and Camp Lejeune (which is the best table to assess if cause specific mortality is different between the “exposed” and “unexposed” cohort) reports **all non-significant results**. All p-values are not significant, and all 95% confidence intervals include 1 (which means no association).
 - Data on major confounders was not collected.
 - Data on confounders was limited to administrative data from DMDC, which is known to have errors, namely for race.
 - For example, alcohol consumption and hepatitis C status are greatest predictors of liver cancer, and should have been controlled for in any analysis of liver cancer mortality.
 - Exposure data is based on a theoretical model, which makes several assumptions, years after the exposure occurred. No scientific body, outside of ATSDR, has validated this exposure model. This can result in major bias.
 - Results from one study cannot be considered scientific proof. Replication or concordance with other studies of the same exposure in a different population is needed to make a statement on certainty of results.
 - *Environmental Health* is not a high profile journal--its impact factor is 2.71. It is an open access, online journal. Authors pay to have their studies published in it. It is possible that other journals would have questioned these methodological issues and not selected this paper for publication.

- ATSDR published a similar study of birth defects in the same journal in December of 2013. The same flaws were present in that report and the data did not support the conclusions.

Implications:

- ATSDR will release four more studies in the upcoming year.
- ATSDR has refused to share study results prior to publication with DoD or VA; however, they do share their results with the new media early.
- This study may have direct impact on disability compensation. Congress and Veterans groups are likely to pressure VA for make a presumption of service connection for the diseases in the mortality study and birth defect study, even though the epidemiological/statistical methodology is flawed, producing **potentially** misleading results.

Review by the Office of Public Health, VHA

Reviewer: (b) (6)

March 3, 2014

Article link: <http://www.jstor.org/stable/3552700>

[Lynge E](#), [Anttila A](#), [Hemminki K](#).. Organic solvents and cancer. [Cancer Causes Control](#). 1997 May;8(3):406-19.

Organic Solvents and Cancer

Abstract

Epidemiologic evidence on the relationship between organic solvents and cancer is reviewed. In the 1980s, more than a million persons were potentially exposed to some specific solvents in the United States; in Canada, 40 percent of male cancer patients in Montreal had experienced exposure to solvents; in the Finnish population, one percent was regularly exposed. There is evidence for increased risks of cancer following exposure to: trichloroethylene (for the liver and biliary tract and for non-Hodgkin's lymphomas); tetrachloroethylene (for the esophagus and cervix -- although confounding by smoking, alcohol, and sexual habits cannot be excluded -- and non-Hodgkin's lymphoma); and carbon tetrachloride (lymphohematopoietic malignancies). An excess risk of liver and biliary tract cancers was suggested in the cohort with the high exposure to methylene chloride, but not found in the other cohorts where an excess risk of pancreatic cancer was suggested. 1,1,1-trichloroethane has been used widely, but only a few studies have been done suggesting a risk of multiple myeloma. A causal association between exposure to benzene and an increased risk of leukemia is well-established, as well as a suggested risk of lung and nasopharynx cancer in a Chinese cohort. Increased risks of various gastrointestinal cancers have been suggested following exposure to toluene. Two informative studies indicated an increased risk of lung cancer, not supported by other studies. Increased risks of lymphohematopoietic malignancies have been reported in some studies of persons exposed to toluene or xylene, but not in the two most informative studies on toluene. Occupation as a painter has consistently been associated with a 40 percent increased risk of lung cancer. (With the mixed exposures, however, it is not possible to identify the specific causative agent[s].) A large number of studies of workers exposed to styrene have evidenced no consistent excess risk of all lymphohematopoietic malignancies, although the most sensitive study suggested an excess risk of leukemia among workers with a high exposure.

Organic Solvents as Risk Factor for Autoimmune Diseases: A Systematic Review and Meta-Analysis

Carolina Barragán-Martínez, Cesar A. Speck-Hernández, Gladis Montoya-Ortiz, Rubén D. Mantilla, Juan-Manuel Anaya, Adriana Rojas-Villarraga*

Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia

[FULL TEXT](#)

Abstract

Background: Genetic and epigenetic factors interacting with the environment over time are the main causes of complex diseases such as autoimmune diseases (ADs). Among the environmental factors are organic solvents (OSs), which are chemical compounds used routinely in commercial industries. Since controversy exists over whether ADs are caused by OSs, a systematic review and meta-analysis were performed to assess the association between OSs and ADs.

Methods and Findings: The systematic search was done in the PubMed, SCOPUS, SciELO and LILACS databases up to February 2012. Any type of study that used accepted classification criteria for ADs and had information about exposure to OSs was selected. Out of a total of 103 articles retrieved, 33 were finally included in the meta-analysis. The final odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by the random effect model. A sensitivity analysis confirmed results were not sensitive to restrictions on the data included. Publication bias was trivial. Exposure to OSs was associated to systemic sclerosis, primary systemic vasculitis and multiple sclerosis individually and also to all the ADs evaluated and taken together as a single trait (OR: 1.54; 95% CI: 1.25–1.92; p-value, 0.001).

Conclusion: Exposure to OSs is a risk factor for developing ADs. As a corollary, individuals with non-modifiable risk factors (i.e., familial autoimmunity or carrying genetic factors) should avoid any exposure to OSs in order to avoid increasing their risk of ADs.

Citation: Barragán-Martínez C, Speck-Hernández CA, Montoya-Ortiz G, Mantilla RD, Anaya J-M, et al. (2012) Organic Solvents as Risk Factor for Autoimmune

Diseases: A Systematic Review and Meta-Analysis. PLoS ONE 7(12): e51506. doi:10.1371/journal.pone.0051506

Editor: Sudha Chaturvedi, Wadsworth Center, United States of America

Received July 12, 2012; Accepted November 1, 2012; Published December 19, 2012

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permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This project did not have any specific funding, but the work was supported by the School of Medicine and Health Sciences, Universidad del Rosario.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: adrirojas@gmail.com

From: (b) (6)
To: (b) (6)
Subject: male and female breast cancer are the same condition-reference
Date: Thursday, January 23, 2014 11:44:06 AM

Appl Clin Genet. 2011; 4: 145–158.

Published online 2011 November 14. doi: 10.2147/TACG.S13226
<<http://dx.doi.org/10.2147%2FTACG.S13226>>

PMCID: PMC3681186

Inherited and acquired alterations in development of breast cancer

Piera Rizzolo <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Rizzolo%20P%5Bauth%5D>>, Valentina Silvestri <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Silvestri%20V%5Bauth%5D>>, Mario Falchetti <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Falchetti%20M%5Bauth%5D>>, and Laura Ottini <<http://www.ncbi.nlm.nih.gov/pubmed/?term=Ottini%20L%5Bauth%5D>>

“Overall, current epidemiologic and pathologic data, such as age-frequency distribution, age-specific incidence rate patterns, and prognostic factor profiles, suggest that male breast cancer is similar to postmenopausal female breast cancer. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3681186/#b2-tacg-4-145>> It is generally accepted that breast cancer may represent the same disease entity in both genders, and common hormonal, genetic, and environmental risk factors are involved in the pathogenesis of breast cancer in women and men.”

(b) (6), could you put this on the share point?

1. Epidemiology and risk factors for breast cancer [UpToDate]

Authors

Mary E Costanza, MD

Wendy Y Chen, MD, MPH

Section Editor

Daniel F Hayes, MD

Deputy Editor

Don S Dizon, MD, FACP

Disclosures

All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

Literature review current through: Dec 2012. |**This topic last updated:** Jan 29, 2012.

ENVIRONMENTAL EXPOSURES — Organochlorines include polychlorinated biphenyls (PCB's), dioxins, and organochlorine pesticides such as DDT. These compounds are weak estrogens, highly lipophilic, and capable of persisting in body tissues for years. However, most large studies have failed to find an association [[207,208](#)].

[207] Calle EE, Frumkin H, Henley SJ, et al. Organochlorines and breast cancer risk. *CA Cancer J Clin* 2002; 52:301.

[208] Willett WC, Rockhill B, Hankinson SE, et al. factors in the causation of breast cancer. In: *Diseases of the Breast*, Harris JR, Lippman ME, Morrow M, Osborne CK (Eds), Lippincott, Williams and Wilkins, Philadelphia 2004. p.255.

RISK FACTORS FOR MALE BREAST CANCER — Men are more than one hundred times less likely to get breast cancer than women. Risk factors for male breast cancer include Klinefelter's syndrome, testicular and liver pathology, a family history of breast cancer, and BRCA2 mutations. (See "[Male breast cancer](#)".)

Male breast cancer [UpToDate]

Author

William J Gradishar, MD

Section Editors

Daniel F Hayes, MD

Anees B Chagpar, MD, MSc, MA, MPH, FACS, FRCS(C)

Deputy Editors

Don S Dizon, MD, FACP

Rosemary B Duda, MD, MPH, FACS

Disclosures

All topics are updated as new evidence becomes available and our [peer review process](#) is complete.

Literature review current through: Dec 2012. |**This topic last updated:** Nov 15, 2012.

INTRODUCTION — Male breast cancer (MBC) is rare in contrast to female breast cancer, which is the most common cancer and second leading cause of cancer deaths in women [1]. Although MBC shares many similarities with cancer of the female breast, there are also important differences [2].

EPIDEMIOLOGY AND RISK FACTORS — In the United States, approximately 2140 new cases of MBC are diagnosed annually, and 450 deaths occur; this represents less than 0.5 percent of all cancer deaths in men annually [1]. By contrast, in Tanzania and areas of central Africa, breast cancer accounts for up to 6 percent of cancers in men [3].

In the United States, the ratio of female to male breast cancer is approximately 100:1 in whites, but lower (70:1) in blacks [2,3]. Blacks also have a poorer prognosis, even after adjustment for clinical, demographic, and treatment factors. (See '[Racial disparities](#)' below.)

The median age of onset of MBC is 65 to 67, approximately 5 to 10 years older than in women [2,4-9]. Like female breast cancer, the incidence of MBC has been increasing; one report suggests that incidence has increased 26 percent over the past 25 years [10].

Risk factors — Although the majority of men with breast cancer have no identifiable risk factors, several have been identified, many related to hormone levels. Many of these risk factors are the same as in women, including family history, Jewish ancestry, obesity, low levels of physical activity, prior chest wall irradiation, and benign breast disease [3,11]. (See "[Epidemiology and risk factors for breast cancer](#)".)

[3] Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. *Int J Cancer* 1993; 53:538.

[11] Brinton LA, Richesson DA, Gierach GL, et al. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* 2008; 100:1477.

Other risk factors that are modestly unique to men include never being married, gynecomastia, and a history of testicular or liver pathology [3], a history of a bone fracture after age 45 [11], and Klinefelter's syndrome:

- Gynecomastia, which is most often drug-related ([table 1](#)), may be associated with the development of male breast cancer because of shared hormonal risk factors. (See

"Epidemiology and pathogenesis of gynecomastia" and "Causes and evaluation of gynecomastia".)

- Testicular conditions associated with an increased risk of MBC include orchitis, undescended testes (cryptorchidism) and testicular injury [4,8,12]. Among the chronic liver diseases that are associated with MBC are cirrhosis, alcoholic liver disease, and schistosomiasis [13-17].
- Klinefelter syndrome is a rare condition resulting from the inheritance of an additional X chromosome [4,18-20]. The Klinefelter syndrome consists of atrophic testes, gynecomastia, high serum concentrations of gonadotropins (follicle-stimulating hormone, luteinizing hormone), and low serum testosterone levels; the net effect is a high ratio of estrogen-to-testosterone. (See "Causes of primary hypogonadism in males".)

Few carefully conducted epidemiologic studies have been undertaken given the rarity of both Klinefelter syndrome and male breast cancer. The largest cohort study of 3518 men who were cytogenetically diagnosed with Klinefelter syndrome found 19- and 58-fold increases in incidence and mortality, respectively, compared to the general population, with particularly high risks among 47,XXY mosaics [21].

Additional studies are needed to clarify which patients with Klinefelter syndrome are at a high risk of developing MBC and to define the contribution of possible predisposing factors, including altered endogenous hormones. The role of breast cancer screening in men with Klinefelter syndrome is unclear. Although the relative risk of breast cancer is increased, the absolute risk is still much lower than it is in women. Although routine mammography is not advocated for all affected men, the importance of patient education, self examination, and regular physician examinations are stressed [21].

Several of the risk factors for MBC involve imbalance in estrogenic versus androgenic influences (ie, relative estrogen excess or lack of androgen) [3,4]. As an example, men with liver disease have increased production of androstenedione from the adrenal glands, enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol [22]. On the other hand, androgens may convey a protective effect on breast tissue by inhibiting cell proliferation. The association of MBC with prolactinoma, a condition often associated with low plasma testosterone levels, is consistent with this hypothesis [23,24].

It is hypothesized that relative changes in endogenous hormones may play a causative role in MBC. However, abnormalities in peripherally detectable hormone levels have not been detected in affected men [25]. Furthermore, other conditions associated with an increased estrogen-to-testosterone ratio such as obesity, thyroid disease, use of marijuana, and exogenous estrogen use (eg, transsexuals, treatment of prostate cancer) have a less certain relationship to MBC [4,12].

2. Abstract:

The etiology of male breast cancer is largely unknown, reflecting its relative rarity. Although a number of previous studies have suggested relationships with a variety of medical conditions, the results have largely derived from case-control studies and may reflect recall biases. Within the large U.S. Veterans Affairs computerized medical care system database, we had the opportunity to access 26 million hospital discharge records over the period 1969-1996 and to relate various documented medical conditions to the risk of subsequent male breast cancer. This allowed us to calculate relative risks (RR) and 95% confidence intervals (CI) for male breast cancer associated with conditions occurring one or more years after initial hospitalization, adjusted for age, race, calendar year, duration of follow-up, and number of hospital visits. Among 4,501,578 men aged 18-100 years, a total of 642 cases of primary male breast cancer were identified (523 among whites, 119 among blacks). Medical conditions that were significantly related to risk were diabetes (RR 1.30, 95% CI 1.05-1.60), obesity (1.98, 1.55-2.54), orchitis/epididymitis (1.84, 1.10-3.08), Klinefelter syndrome (29.64, 12.26-71.68), and gynecomastia (5.86, 3.74-9.17). Additionally, among black patients, cholelithiasis emerged as a significant risk predictor (3.45, 1.59-7.47). Diseases that have previously been related to male breast cancer risk that were not supported by our study results included thyroid diseases, smoking-related conditions, liver cirrhosis, prostatic hyperplasia, and fractures. After adjustment for obesity, the association with diabetes disappeared, but that with gynecomastia persisted. In multivariate models that simultaneously considered all important medical predictors of risk, significant risks were seen for Klinefelter syndrome (16.83, 6.81-41.62), gynecomastia (5.08, 3.21-8.03), obesity (1.91, 1.50-2.44), and orchitis/epididymitis (1.80, 1.08-3.01). These results support previous speculations that male breast cancer is influenced not only by tissue at risk, but also by hormonal and inflammatory factors.

Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database.

Brinton LA - *Breast Cancer Res Treat* - 01-JAN-2010; 119(1): 185-92

3. Abstract:

BACKGROUND: The overall incidence of male breast cancer is around 1% of all breast cancers and is on the rise. In this review we aim to present various aspects of

male breast cancer with particular emphasis on incidence, risk factors, pathophysiology, treatment, prognostic factors, and outcome. **METHODS:** Information on all aspects of male breast cancer was gathered from available relevant literature on male breast cancer from the MEDLINE database over the past 32 years from 1975 to 2007. Various reported studies were scrutinized for emerging evidence. Incidence data were also obtained from the IARC, Cancer Mondial database. **CONCLUSION:** There is a scenario of rising incidence, particularly in urban US, Canada and UK. Even though more data on risk factors is emerging about this disease, more multi-institutional efforts to pool data with large randomized trials to show treatment and survival benefits are needed to support the existing vast emerging knowledge about the disease.

Citation:

Male breast cancer: is the scenario changing.

Contractor KB - *World J Surg Oncol* - 01-JAN-2008; 6: 58

Etiology and risk factors

The definite etiology of MBC is unknown. Factors such as alteration in hormonal milieu, family history and genetic alterations are known to influence its occurrence. Various studies have shown that conditions that alter the estrogen-testosterone ratio in males predispose to breast cancer [14,15]. Among these conditions the strongest association is with Klinefelter's syndrome. Males with this condition have a fifty times increased risk and accounts for 3% of all MBC [16]. Conditions, which are associated with increased estrogen levels, like cirrhosis [17,18] and exogenous administration of estrogen (either in transsexuals or as therapy for prostate cancer) have been implicated as causative factors [19-22]. Also, androgen deficiency due to testicular disease like mumps, undescended testes, or testicular injury, has been linked to the occurrence of breast cancer in men [23,24]. Occupational exposure to heat and electromagnetic radiation, causing testicular damage and further leading to the development of MBC is also postulated [25,26]. An inherited predisposition for breast cancer is noticed in males-analogous to that in females [27-31]. A positive family history of a first-degree female relative having breast cancer is seen in up to 15–20% patients [32]. This increased risk is conferred by mutations in the breast cancer susceptibility genes (BRCA1 and BRCA2). Mutations in both the BRCA1 and BRCA2 genes are linked to female breast cancer. Genetic studies in males however, have shown that germline mutations in BRCA2 alone account for the majority of hereditary breast cancer [33-36].

No link between BRCA1 and familial breast cancer has been noticed in one study [37], whereas other studies have suggested a possible link [38,39]. The Cambridge study showed that 8% of patients had BRCA2 mutations and all the carriers had a family history of breast, ovarian, prostate or pancreatic cancer [40]. The highest prevalence of BRCA2 mutation in MBC has been noted in Iceland where 40% have the mutation [41]. Several case reports have linked MBC with other genetic disorders like Cowden syndrome [42] and Hereditary Non-Polyposis Colonic Cancer (HNPCC) [43]. It has been recently reported that male breast cancer may also predispose to increased risk of developing a second cancer of the stomach, skin and breast [44].

A strong racial predilection is noted in MBC, with studies establishing a high-risk for Jews. Among them, the Sephardic Jews present at a younger age with advanced stage disease whereas the Ashkenazi Jews have an increased lifetime risk of suffering from the disease [45,46]. Gynecomastia, present in 6–38% of MBC patients has also been implicated as a risk factor [47,48] and some studies have shown positive correlation between the two [49]. An interesting study in the US comparing incidence, pathology and outcomes in male and female breast cancer in a defined population showed more black males than white males to be affected. Also black men with breast cancer had more involved axillary lymph nodes and higher stage than whites at presentation [50]. This is in stark contrast to the high incidence of male breast cancer preponderance in whites as shown in another recently reported study in the US which showed higher incidence in white males, although black males were more not likely to see an oncologist for consideration of chemotherapy and had higher mortality associated with the disease (hazard ratio = 3.29; 95% CI, 1.10 to 9.86) [51]. Reports have shown that an association of MBC and gynecomastia could also represent a chance occurrence as 35–40% of healthy men have clinical or histological gynecomastia [52].

Alcohol has been variably linked as a causative factor in the genesis of MBC. A large Swedish study has not shown any such correlation [53], although it has been implicated as a causal agent in other studies [54]. A case control study conducted in Europe has shown that for alcohol intakes of less than 60 grams per day, the relative risk of MBC is comparable to that in females,

and it continues to increase at high consumption levels [55]. Other risk factors mentioned in various studies are low socioeconomic status, obesity, pacemakers, tuberculosis and hyperthyroidism [56,57]. A meta analysis of 7 case-control studies revealed that the risk of MBC to be significantly increased in males with the following characteristics; never married, benign breast disease, gynecomastia, Jewish or history of breast cancer in a first-degree relative [58-61].

4. Abstract:

OBJECTIVES: Male breast cancer is a rare disease of largely unknown aetiology. In addition to genetic and hormone-related risk factors, a large number of environmental chemicals are suspected of playing a role in breast cancer. The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men may help to identify mammary carcinogens in the environment.

METHODS: Occupational risk factors for male breast cancer were investigated in a multi-centre case-control study conducted in eight European countries which included 104 cases and 1901 controls. Lifetime work history was obtained during in-person interviews. Occupational exposures to endocrine disrupting chemicals (alkylphenolic compounds, phthalates, polychlorinated biphenyls (PCBs) and dioxins) were assessed on a case-by-case basis using expert judgement.

RESULTS: Male breast cancer incidence was particularly increased in motor vehicle mechanics (OR 2.1, 95% CI 1.0 to 4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers, and furniture manufacture workers. The OR for exposure to alkylphenolic compounds above the median was 3.8 (95% CI 1.5 to 9.5). This association persisted after adjustment for occupational exposures to other environmental oestrogens.

CONCLUSION: These findings suggest that some environmental chemicals are possible mammary carcinogens. Petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer.

Citation:

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.

Villeneuve S - *Occup Environ Med* - 01-DEC-2010; 67(12): 837-44

5. Abstract:

Most risk factors for male breast cancer have been derived from retrospective studies that may reflect selective recall. In the prospective National Institutes of Health-AARP Diet and Health Study, we studied 324 920 men, among whom 121 developed breast cancer. Men who reported a first-degree relative with breast cancer had an increased risk of breast cancer (relative risk [RR] = 1.92, 95% confidence interval [CI] = 1.19 to 3.09). Among the medical conditions examined, a new finding emerged regarding increased male breast cancer risk associated with a history of a bone fracture (RR = 2.20, 95% CI = 1.24 to 3.91). Obesity was positively related to risk (RR = 1.79, 95% CI = 1.10 to 2.91, for body mass indices of ≥ 30 vs < 25 kg/m²) and physical activity inversely related, even after adjustment for body mass index. Smokers were at somewhat elevated risk, although trends with smoking characteristics were inconsistent. Alcohol consumption was not related to risk. The identified risk factors show some commonalities with female breast cancer and indicate the importance of hormonal mechanisms. Differences in risk factors may reflect unique mechanisms associated with androgens and their ratio to bioavailable estrogens.

Citation:

Prospective evaluation of risk factors for male breast cancer.

Brinton LA - *J Natl Cancer Inst* - 15-OCT-2008; 100(20): 1477-81

Johansen Taber, Katherine A (11/2010). "Male breast cancer: risk factors, diagnosis, and management (Review)". *Oncology reports*(1021-335X), 24(5), p.1115.

Table I. Risk factors for MBC (3,4,7,13-41).

Known presence of *BRCA* mutation
History of *BRCA*-suggestive cancer, either in self or family
Estrogen exposure/androgen insufficiency
Klinefelter syndrome
Testicular abnormality
Obesity
Liver cirrhosis
Exogenous estrogen therapy
Radiation exposure
Occupational exposure
High ambient temperature

Occupational risks. Men who work in high-temperature environments, such as blast furnaces, steel works, and rolling mills have a higher risk for breast cancer, probably due to testicular failure resulting from long-term exposure to high ambient temperatures (4,29). In a 1988 Swedish study, those who worked in the soap and perfume industry showed an almost eight-fold increase in risk for MBC, likely because during the 1950s and 1960s this industry made estrogen containing cosmetic creams, increasing workers' exposure to exogenous estrogens (35). Occupational carcinogen exposure, such as that found in gasoline and exhaust fumes, has also been implicated in increasing risk for breast cancer (4,36).

6. Abstract:

Male breast cancer (MaleBC) is a rare disease, accounting for <1% of all male tumors. During the last few years, there has been an increase in the incidence of this disease, along with the increase in female breast cancer (FBC). Little is known about the etiology of MaleBC: hormonal, environmental and genetic factors have been reported to be involved in its pathogenesis. Major risk factors include clinical disorders carrying hormonal imbalances, radiation exposure and, in particular, a positive family history (FH) for BC, the latter suggestive of genetic susceptibility. Rare mutations in high-penetrance genes (BRCA1 and BRCA2) confer a high risk of BC development; low-penetrance gene mutations (i.e. CHEK-2) are more common but involve a lower risk increase. About 90% of all male breast tumors have proved to be invasive ductal carcinomas, expressing high levels of hormone receptors with evident therapeutic returns. The most common clinical sign of BC onset in men is a painless palpable retroareolar lump, which should be evaluated by means of mammography, ultrasonography and core biopsy or fine needle aspiration (FNA). To date, there are no published data from prospective randomized trials supporting a specific therapeutic approach in MaleBC. Tumor size together with the number of axillary nodes involved are the main prognostic factors and should guide the treatment choice. Locoregional approaches include surgery and radiotherapy (RT), depending upon the initial clinical presentation. When systemic treatment (adjuvant, neoadjuvant and metastatic) is delivered, the choice between hormonal and or chemotherapy (CT) should depend upon the clinical and biological features, according to the FBC management guidelines. However great caution is required because of high rates of age-related comorbidities. 2009 Elsevier Ireland Ltd. All rights reserved.

Citation:

Male breast cancer.

Ottini L - *Crit Rev Oncol Hematol* - 01-FEB-2010; 73(2): 141-55

7. Madeira, Marcelo (2011). "A case report of male breast cancer in a very young patient: what is changing?". *World journal of surgical oncology(1477-7819)*, 9(1), p.16.
-

Background

Breast cancer in men is rare, and it accounts for about 1% of all malignant breast neoplasm cases [1,2]. The estimated incidence is 1 case for each 100,000 men. In the United States, about 1,910 new cases were diagnosed in 2009, and 440 of these cases resulted in death [3]. Among the histologic types, invasive ductal carcinoma is the most prevalent breast cancer in males, with an incidence varying from 65 to 95% [2,4].

Male breast cancer has unimodal age-frequency distribution with a peak incidence at 71 years old. Conversely, female breast cancer has a bimodal age-frequency distribution with early-onset and late-onset peak incidences at 52 and 72 years old, respectively [5].

This study examined a 25-year-old man without important risk factors who was diagnosed with invasive ductal carcinoma. Although it is rare, there have been instances of breast cancer in younger males [6]. We evaluated the main aspects of the epidemiology of breast neoplasm in men and the best approach for treatment.

Discussion

There is a close relation between the BRCA2 gene mutation and male breast cancer. It has also been observed, however, that some cases involve BRCA1 participation [14-16]. Other conditions that have been associated with the occurrence of breast neoplasms in men are cirrhosis [17], testicular trauma, obesity, radiation therapy exposure, and the use of exogenous estrogen [18]. In addition to the very young age of the patient in the present report, this patient did not have a family, hormonal, or genetic history that could justify the high risk for breast cancer. Although gynecomastia has been suggested to be present in 6-38% of breast cancer cases in men [19], it was not evident in our patient.

It is fundamental to consider the history of breast tumors in first-degree relatives because that can be an indicator for increased breast cancer risk. Indeed, genetic diseases such as Klinefelter's syndrome and Cowden's disease have been shown to be related to breast cancer in men [1].

Conclusions

Invasive ductal carcinoma in young men is extremely rare; the peak incidence is around the seventh decade of life. Risk factors for male breast cancer include genetic factors and hormonal abnormalities. Despite an absence of a familial history of breast cancer, hormonal abnormalities, or a genetic disease, the male patient in the present study developed breast cancer at a very young age. The causative factors in this patient were unable to be definitively identified. The pathophysiology of breast cancer in males is not adequately understood. As more cases of breast cancer in young male patients are investigated, we may be able to gain a better understanding of the mechanism.

8. Review

Male breast cancer

Sandhu NP - *Journal of Men's Health* - September, 2012; 9(3); 146-153

Nicole P. Sandhu, MD, PhD^{a,□}

Marie Brid Mac Bride, MB, BCh^b

Christina A. Dilaveri, MD^b

Lonzetta Neal, MD^b

David R. Farley, MD^c

Charles L. Loprinzi, MD^d

Dietlind L. Wahner-Roedler, MD^b

Karthik Ghosh, MD, MS^b

^a Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA

^b Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA

^c Division of Gastroenterologic and General Surgery, Mayo Clinic, Rochester, MN, USA

^d Division of Medical Oncology, Mayo Clinic, Rochester, MN, USA

* Corresponding author.

E-mail address: sandhu.nicole@mayo.edu

Manuscript received January 13, 2012 , accepted March 15, 2012

PII S1875-6867(12)00055-3

Abstract

Male breast cancer is rare, and many patients and health care providers are not familiar with this entity. Although the underlying causes are not well understood, certain populations are at higher risk, including certain gene mutation carriers, men with Klinefelter syndrome, and

certain ethnic groups. Male breast cancer typically presents at a later stage than female breast cancer. A palpable mass is the most common presentation, but nipple discharge or other nipple changes may be seen. Because the number of affected individuals is small, prospective trials have not been conducted; thus, treatment recommendations are typically taken from large trials involving female breast cancer populations. Although outcomes in male breast cancer were previously thought to be worse than female breast cancer outcomes, it appears that they are similar. Questions regarding the most effective surgical and adjuvant therapies remain. Mastectomy with axillary lymph node evaluation, adjuvant hormonal therapy, and chemotherapy are commonly used. Providers of health care to male patients must be aware of the possibility of breast cancer and appropriately evaluate any suspicious changes.

Introduction

Breast cancer is rare in men, accounting for less than 1% of all breast cancers diagnosed annually in the United States [1]. The American Cancer Society estimates that, in 2012, 2,190 new cases of breast cancer will be diagnosed in men, with 410 deaths attributable to male breast cancer (MBC) [2]. Many are at an advanced stage (stage III or greater) at the time of diagnosis [3]. Therefore, health care providers must be aware of the potential for men to develop breast cancer.

This article reviews risk factors, clinical features, diagnostic strategies, management, and follow-up recommendations after treatment for MBC.

Epidemiology

The incidence of MBC has increased since 1975, but the reasons are not known. It is unlikely to be due to improved detection; male patients, even in higher-risk groups, typically do not undergo breast cancer screening. Surveillance, Epidemiology, and End Results data from 1973 to 2006 showed the incidence of MBC to be about 1 case per 100,000 men in 1973 compared with 1.25 per 100,000 in 2006 [2]. According to the American Cancer Society, the annual incidence rate of MBC is 1.09 per 100,000 men compared with 68.73 per 100,000 women in the United States [4]. This is somewhat higher than the National Cancer Institute statistic, but still quite uncommon. The lifetime risk of MBC is 1 in 1,000 compared with 1 in 8 for women [2]. As in women, breast cancer is most often identified in older men.

Hormonal imbalance

A relative increase in endogenous estrogens relative to testosterone may be a risk factor for MBC. Klinefelter syndrome (XXY), in which affected men have a 50-fold increased risk of MBC, is associated with testicular dysgenesis, elevated gonadotropins, and low testosterone levels [24, 25]. Undescended testes, orchitis, and orchiectomy also increase the risk of MBC [26, 27]. Conditions associated with relative estrogen excess (e.g., hepatic cirrhosis) have also been associated with increased incidence of MBC [28, 29].

Obesity causes imbalanced estrogen-to-testosterone ratios. Men with body mass index (BMI) higher than 30 kg/m² have a higher risk of MBC (RR = 1.79; 95% CI = 1.10–2.91) than those with a BMI of <25 kg/m². The risk of MBC is also elevated in men with a history of bone fracture occurring after the age of 45 years (RR = 2.2; 95% CI = 1.24–3.91) [7]. The authors concluded that the association between bone fractures and MBC may be attributable to declining testosterone levels, a risk factor for osteoporosis in men, associated with increasing age. Physical activity may be protective against MBC because a current physical activity routine was associated with a statistically significant lower risk of developing MBC (RR = 0.49; 95% CI = 0.28–0.87) [7]. This relationship may have been associated with weight, as obese patients are less likely to exercise.

Environmental exposures

An increased incidence of MBC was found in male patients who worked in blast furnaces, steel mills, and rolling mills, suggesting that high environmental temperature could damage testicular health and predispose men to breast cancer [35]. A case–control study [36] demonstrated similar findings, but careful analysis failed to reveal a definite association with high ambient temperature based on a job-exposure matrix. Other environmental exposures, for example, chemical exposures from occupations like working in the soap and perfume industries, may also be associated with MBC [37]. Overall, the role of environmental and workplace exposures in MBC warrants further research.

9. Abstract:

BACKGROUND: We report our findings on a hospital-based retrospective pilot cohort with case-controls study, which we carried out to examine genetic, environmental, and occupational risk factors in men with breast cancer.

METHODS: 86 men with breast cancer were diagnosed in eight VA medical centers that agreed to collaborate on this project. A case-control analysis was conducted on a subset of the male breast cancer cases (n = 44) and age- and ethnicity-matched controls (n = 77). We compared host characteristics, comorbidities, and medications intake between cases and controls by using Chi-square analysis and Fisher's exact test.

RESULTS: The descriptive analysis showed that the majority of veterans with male breast cancer were non-Hispanic white (60%), older than 65 years at diagnosis (56%), and more likely estrogen receptor positive (45%). World War II veterans represented the largest group (22%), followed by the Vietnam era veterans (10%). Thirty-three percent reported a positive family history of cancer, while 18% had another primary cancer diagnosis. Prior alcohol (43%) and tobacco use (56%) was substantial among these patients. Twenty percent of patients were overweight or obese and 55% had comorbid diseases with heart disease being the most prevalent, followed by diabetes mellitus. The case-control analysis yielded a significantly greater proportion of cases with gynecomastia (p < 0.0001), a positive family history of cancer (p =

0.0028), history of antibiotic use ($p = 0.0112$), and history of tobacco use ($p = 0.0143$) compared to controls.

CONCLUSION: The findings of this hospital-based pilot study indicate case-control differences in gynecomastia and family history of cancer. The pilot study lacked sufficient power to determine a true association between the variables of interest and warrants a large-scale collaborative study between the VA medical centers.

Citation:

A pilot study of male breast cancer in the Veterans Affairs healthcare system.

Satram-Hoang S - *J Environ Pathol Toxicol Oncol* - 01-JAN-2010; 29(3): 235-44

Despite the increasing incidence of male breast cancer, it remains an uncommon cancer, accounting for less than 1% of all cancers in men. Because of the rarity of this cancer, randomized and prospective data are lacking. All studies are based on a small series of patients.

Only prospective national clinical trials through cooperative groups would further enhance our understanding of the biology and treatment of this uncommon disease.

10. Lynn, Karen (12/2010). "Rare male breast cancer has similarities to female disease". *MLO. Medical laboratory observer(0580-7247)*, 42(12), p.34.

Like female breast cancer, male breast cancer often is related to estrogen hormonal levels. In men, the risk increases when estrogen levels are abnormally high. Testicular abnormalities in development (e.g., undescended testes, congenital inguinal hernia, or testicular injury) may change the estrogen-level balance. Infertility and Klinefelter's syndrome (the XXY condition) also seem to increase a man's risk of getting breast cancer. Like women, if a man has a history of breast cancer in his family, or if he was treated with radiation for lymphoma to the chest area, his chances of developing this disease increase.^-^^

Another factor that increases a man's chances of getting breast cancer includes advanced age. The median age for diagnosis is age 67 for men and age 62 for women." Alcohol abuse and liver disease are also associated with increased risk for male breast cancer. Various causes of liver damage affect the liver's ability to metabolize steroid hormones, which is why obesity is also a known risk factor. "Just because a man has an increased risk does not mean he will get cancer," Zarka notes.

11. **Male breast cancer: a multicentric study.** - Culell P - *Breast J* - 01-MAR-2007; 13(2): 213-5

Male breast cancer (MBC) average is about 0.2% of all cancers and 1% of breast carcinomas. The etiology of MBC is obscure, although an excess risk has been associated with Klinefelter syndrome, testicular disorders, benign breast disease including gynecomastia, use of exogenous estrogens, radiation, and a family history of male or female breast cancer; obesity may increase the risk of MBC, possibly through hormonal mechanisms, while dietary factors, physical activity, and socioeconomic status deserve further investigation

12. White, Jonathan (2011). "Male breast carcinoma: increased awareness needed". *Breast cancer research : BCR(1465-5411)*, 13(5), p.219

13. **Abstract:**

Male breast cancer is a very rare disease with an incidence of about 0.5-1% comparing with the one of female breast cancer but relatively little is known about its cause. Treatment strategies for breast cancer in males are derived from studies performed among females. The probable reasons behind the frequent, late diagnoses presented at stages III or IV might be the lack of awareness. The rarity of the disease precludes large prospective randomized clinical trials. This study reviews male breast cancer and its risk factors, recommendations for diagnosis and the management of patients with male breast cancer.

Citation:

Male breast carcinoma: epidemiology, risk factors and current therapeutic approaches.
Zygianni AG - *Asian Pac J Cancer Prev* - 01-JAN-2012; 13(1): 15-9

14. Gynecomastia
Narula HS - *Endocrinol Metab Clin North Am* - 01-JUN-2007; 36(2): 497-519

Fortunately, breast cancer is rare in men; approximately 1400 men are diagnosed with invasive breast cancer in the United States each year—1 percent of the risk of developing breast cancer in

women. Men with a family history of breast cancer in female relatives have a 2.5 times increased risk of developing breast cancer, however, and those with an inherited germline BRCA2 mutation are at a 100-fold greater risk of developing a breast malignancy. With the exception of KS, gynecomastia does not increase the risk of future development of breast carcinoma [89]. Men with breast cancer seem to have a prognosis similar to women with the same stage of cancer at the time of diagnosis [89].

Introduction

Breast cancer is predominantly a female disease with 49,492 cases (invasive and non-invasive) diagnosed in the UK in 2006 [1]. According to data from the International Agency for Research on Cancer, this is broadly in line with figures from other western nations [2]. Tremendous strides in our understanding of breast cancer have been made over the past two decades and, when detected early, breast cancer is one of the most curable and treatable of all cancers. Male breast cancer is much less frequent with 334 cases diagnosed in the UK in 2006 [1], accounting for just under 1% of all breast cancers.

Risk factors for male breast cancer

Owing to the rarity of male breast cancer, establishing precise risk factors for the disease has proved challenging. Male and female breast cancers share many common risk factors; for example, advancing age and previous family history. In terms of male breast cancer, data from the Breast Cancer Linkage Consortium showed that men harbouring *BRCA2* mutations have a relative risk of 80 for developing breast cancer [3] - making *BRCA2* the strongest known gene associated with male breast cancer [4,5]. Androgen receptor mutations have also been reported [6]. Some suggested risk factors associated with male breast cancer are summarised in Table 1[4-8].

Table 1

Suggested risk factors for male breast cancer

Risk factor

Explanation

| | |
|-----------------------------|---|
| BRCA2 | <i>BRCA2</i> mutations are associated with most inherited MBC |
| Klinefelter syndrome | Hereditary condition characterised by the 47XXY karyotype, which is consistently associated with MBC |
| Androgen receptor mutation | Germline mutations in <i>AR</i> predispose to MBC |
| CYP17 | Encodes cytochrome P450c17 α , an enzyme involved in oestrogen and androgen biosynthesis |
| Cowden syndrome | Autosomal-dominant cancer susceptibility syndrome caused by germline mutation in the <i>PTEN</i> gene |
| CHEK2 | CHEK2*1100delC variants may increase risk of MBC by 10-fold |
| Endogenous oestrogen levels | Increased oestrogen levels as a result of obesity, male-female transsexuals and liver cirrhosis are all associated with MBC |
| Testicular disorders | Cryptorchidism, mumps orchitis, orchiectomy, congenital inguinal hernia and testicular injury are associated with MBC |
| Physical inactivity | Lack of exercise is associated with increased risk of MBC |

Data obtained from [3-7]. These references include comprehensive discussion on other considered risk factors for male breast cancer (MBC). CHEK, cell-cycle checkpoint kinase.

White *et al. Breast Cancer Research* 2011 **13**:219 doi:10.1186/bcr2930

This Reference is from a patient education handout:

The exact cause of breast cancer is not known. It is believed that breast cancer occurs due to many factors. Men are at a higher risk of developing breast cancer if they have:

- Other family members who have had breast cancer.
- Changes in certain genes (such as BRCA1 or BRCA2).
- A history of radiation exposure, such as treatment for another type of cancer.
- Higher than normal levels of the hormone estrogen in their bodies. This may be due to:
- Unknown origins.
- Treatment with estrogen-containing drugs.
- Cirrhosis of the liver.
- Being overweight (*obese*).

- Klinefelter's syndrome (*chromosome abnormality*).
- Large intake of alcohol.
- Abnormalities of the testicles:
 - Past history of mumps.
 - Undescended testicle.
 - Surgical removal of the testicles.
- Certain occupational exposures (not proven, but may be associated with male breast cancer). Such exposures may include:
 - High temperatures.
 - Gasoline fumes.

15. *Semper Fi: Always Faithful*; Burki TK - *Lancet Oncol* - April, 2012; 13(4); 344

“There is one thing of which there is no doubt: the water at the Camp Lejeune Marine base in North Carolina, USA, was contaminated. It was poisoned from 1957 to 1987; perhaps a million people were exposed to it. Firemen describe hydrants disgorging water that reeked of gasoline. The Marine Corps itself documented the improper disposal of cleaning solvents, while other documents outlined a fuel spill of 1·1 million gallons. The water contained more than 20 times the safe levels of tetrachloroethylene and a scarcely credible 280 times the safe level of trichloroethylene, both of which are carcinogenic. There were a host of other chemicals present too, including benzene.

How many people became sick is still unclear. We know of a cluster of cases of male breast cancer, the cemetery has high numbers of children, and efforts to contact those who lived on the base are turning up more and more people with serious health problems. A website dedicated to providing information on the contamination states that those exposed to the water—Marines, sailors, families, and civilian employees—have subsequently developed liver cancer, kidney cancer, breast cancer, bladder cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, leukaemia, and non-Hodgkin lymphoma.

Master Sergeant Jerry Ensminger trained some 2000 recruits during his time with the Marine Corps, which began in 1970. He lived on Camp Lejeune. It was there that his daughter Janey was born in 1975. Janey died from leukaemia before she reached her tenth birthday. Today the Janey Ensminger Act, which would force the military to provide health care for those affected by their exposure to the toxic water of Camp Lejeune, sits before Congress. It is testament to the tireless campaigning of her indefatigable father (and others). Their quest forms the subject of Rachel Libert and Tony Hardmon's slender documentary *Semper Fi: Always Faithful*.

Ensminger is a gruff man, greying at the temples. There is something of the American outdoorsman to him: diligent, well-mannered, and keen on hunting. His attempt to hold the military to account for Camp Lejeune has fully occupied his retirement. He has been joined in his efforts by the sensitive Mike Pantain, who was born on Camp Lejeune and diagnosed with male breast cancer in 2007, and the elderly and reclusive Major Tom Townsend. We accompany Ensminger et al on trips to Washington, DC, and interviews with environmental experts. It is an

endeavour that often appears hopeless, but Ensminger is unyielding, trawling through endless documents, traversing the country, and hearing testimony from those whose health has been wrecked.

In all this, the military appears obstructive, non-committal, and resistant to outside scrutiny. Most offensively, it seems to be dragging its feet in notifying former residents of Camp Lejeune. But *Semper Fi*'s impact is weakened by the fact that it does not contain any fresh interviews with military personnel or politicians. There is plenty of footage of select committee activity, but Libert and Hardmon remain firmly embedded in Ensminger's unit. It means the film lacks a little balance—we do not really get a feel for the context in which Ensminger is fighting his war. Moreover, it is not clear from what all this contamination resulted, nor exactly what these chemicals were, why they were in use, what kind of effect they might have, and how the situation is being addressed. “David versus Goliath” is a clean and affecting narrative but more attention to the wider issues—scientific, political, and ethical—would have been welcome.

Still, it is certainly a compelling tale and Ensminger is excellent and honourable company. The story meanders occasionally but builds to a satisfying conclusion with national news stations publicising the scandal and congressmen offering the campaign their backing. The Marine Corps destroyed the lives of many of those who lived on Camp Lejeune. *Semper Fi* further contends there are over 130 contaminated military sites in the USA, making the Department of Defence “the nation's largest polluter”. But there is a pleasing irony to the fact that the military also hardened their nemesis to the rigours that such a gruelling and long-running campaign would demand of him. Indeed, Ensminger seems to display a greater fealty to his former brothers-in-arms than their employer did. *Semper Fi* indeed.”

LITERATURE REVIEW OF THE ABOVE CITATIONS:

1. Epidemiology and risk factors for breast cancer. UpToDate, Dec 2012
2. Brinton LA. Etiologic factors for male breast cancer in the U.S. Veterans Affairs medical care system database. *Breast Cancer Res Treat* - 01-JAN-2010; 119(1): 185-92
3. Contractor KB. Male breast cancer: is the scenario changing. *World J Surg Oncol* - 01-JAN-2008; 6: 58
4. Villeneuve S. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. *Occup Environ Med* - 01-DEC-2010; 67(12): 837-44
5. Brinton LA. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* - 15-OCT-2008; 100(20): 1477-81
6. Ottini L. Male breast cancer. *Crit Rev Oncol Hematol* - 01-FEB-2010; 73(2): 141-55
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8. Sandhu NP. Male breast cancer. *Journal of Men's Health* - September, 2012; 9(3); 146-153
9. Satram-Hoang S. A pilot study of male breast cancer in the Veterans Affairs healthcare system. *J Environ Pathol Toxicol Oncol* - 01-JAN-2010; 29(3): 235-44
10. Lynn K. Rare male breast cancer has similarities to female disease. *MLO Med Lab Obs* -

- 01-DEC-2010; 42(12): 34, 36
11. Culell P. Male breast cancer: a multicentric study. *Breast J* - 01-MAR-2007; 13(2): 213-5
 12. White, Jonathan (2011). Male breast carcinoma: increased awareness needed. *Breast cancer research : BCR(1465-5411)*, 13(5), p.219
 13. Zygogianni AG. Male breast carcinoma: epidemiology, risk factors and current therapeutic approaches. *Asian Pac J Cancer Prev* - 01-JAN-2012; 13(1): 15-9
 14. Narula HS. Gynecomastia. *Endocrinol Metab Clin North Am* - 01-JUN-2007; 36(2): 497-519
 15. Burki TK. Semper Fi: Always Faithful; *Lancet Oncol* - April, 2012; 13(4); 344

I didn't cite one of the references above in the body of this document by Johansen Taber, Katherine A, in my report so I didn't list it above in the literature review.

MY CONCLUSIONS IN MY REPORT:

I performed a review of the literature in regards to male breast cancer (MBC). The following is a summary of that review.

MBC is rare, accounting for approximately 1% of all breast cancers. Its incidence is increasing. One report suggests that incidence has increased 26% over the past 25 years. The median age of onset of MBC is 65 to 67, approximately 5 to 10 years older than in women. Because it is so rare, relatively little is known about its cause and establishing precise risk factors for the disease has been challenging [1-15]. Randomized and prospective data are lacking and all studies have been based on a small series of patients. The exact cause of breast cancer is not known and it is believed that it occurs due to many factors. Men are at a higher risk of developing breast cancer if they have:

- a) Other family members who have had breast cancer.
- b) Changes in certain genes (such as BRCA1 or BRCA2).
- c) A history of radiation exposure, such as treatment for another type of cancer.
- d) Higher than normal levels of the hormone estrogen in their bodies. This may be due to: Unknown origins, treatment with estrogen-containing drugs, cirrhosis of the liver, being overweight (obese).
- e) Klinefelter's syndrome (chromosome abnormality).
- f) Large intake of alcohol.
- g) Abnormalities of the testicles: past history of mumps, undescended testicle, surgical removal of the testicles.
- h) Certain occupational exposures (not proven, but may be associated with male breast cancer). Such exposures may include: high temperatures, gasoline fumes.

A literature review current through Dec 2012 by UpToDate has documented that “although the majority of men with breast cancer have no identifiable risk factors, several have been identified, many related to hormone levels. Many of these risk factors are the same as in women, including family history, Jewish ancestry, obesity, low levels of physical activity, prior chest wall irradiation, and benign breast disease. Other risk factors that are modestly unique to men include never being married, gynecomastia, a history of testicular or liver pathology, a history of a bone fracture after age 45, and Klinefelter’s syndrome.” Studies have been conflicting on whether gynecomastia is a true risk factor for the development of breast cancer. In terms of environmental exposures, “organochlorines including polychlorinated biphenyls (PCB's), dioxins, and organochlorine pesticides such as DDT are compounds that are weak estrogens, highly lipophilic, and capable of persisting in body tissues for years, however, most large studies have failed to find an association between exposure to these compounds and MBC.” [UpToDate, 1].

Another study which evaluated environmental chemicals suspected of playing a role in breast cancer concluded that their findings suggested that some environmental chemicals were possible mammary carcinogens, including petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons due to a consistent elevated risk of MBC observed in motor vehicle mechanics. This study included 104 cases and 1901 controls [Villeneuve, 4]. Overall, the role of environmental exposures in MBC warrants further research [Sandhu, 8].

In summary, after research of the current literature, there is no definitive medical evidence to suggest that the contaminated water at Camp Lejeune was a causative factor in the development of breast cancer in the veteran. Although the veteran’s oncologist states that the contaminated water more likely than not led to Mr. breast cancer, there is no definitive medical evidence found in the literature, based on multiple studies and observations, to support this statement. More research is required at this time since there is no medical evidence which shows that trichloroethylene, tetrachloroethylene, benzene or vinyl chloride are associated with an elevated risk of male breast cancer.

Metabolic risk score and cancer risk: pooled analysis of seven cohorts.

[Stocks T](#)¹, [Bjørge T](#)², [Ulmer H](#)³, [Manjer J](#)³, [Häggström C](#)³, [Nagel G](#)², [Engeland A](#)², [Johansen D](#)³, [Hallmans G](#)³, [Selmer R](#)³, [Concin H](#)³, [Tretli S](#)³, [Jonsson H](#)³, [Stattin P](#)³.

Abstract

BACKGROUND:

There are few data on the joint influence of metabolic factors on risk of separate cancers.

METHODS:

We analysed data on body mass index, blood pressure and plasma levels of glucose, total cholesterol and triglycerides from seven European cohorts comprising 564 596 men and women with a mean age of 44 years. We weighted those factors equally into a standardized metabolic risk score [MRS, mean = 0, standard deviation (SD) = 1], with an individual's level indicated as SDs from the sex- and cohort-specific means. Cancer hazard ratios were calculated by Cox regression with age as timescale and with relevant adjustments including smoking status. All statistical tests were two-sided.

RESULTS:

During a mean follow-up of 12 years, 21 593 men and 14 348 women were diagnosed with cancer. MRS was linearly and positively associated with incident cancer in total and at sites ($P < 0.05$). In men, risk per SD MRS was increased by 43% (95% confidence interval: 27-61) for renal cell cancer, 43% (16-76) for liver cancer, 29% (20-38) for colon cancer, 27% (5-54) for oesophageal cancer, 20% (9-31) for rectal cancer, 19% (4-37) for leukaemias, 15% (1-30) for oral cancer and 10% (2-19) for bladder cancer. In women, risk increases per SD MRS were 56% (42-70) for endometrial cancer, 53% (29-81) for pancreatic cancer, 40% (16-67) for renal cell cancer, 27% (9-47) for cervical cancer and 17% (3-32) for rectal cancer.

CONCLUSION:

This largest study to date on the joint influence of metabolic factors on risk of separate cancers showed increased risks for several cancers, in particular renal cell and liver cancer in men and endometrial and pancreatic cancer in women.

KEYWORDS:

cohort studies; metabolic syndrome x; neoplasms

From: (b) (6)
To: (b) (6)
Subject: more
Date: Wednesday, January 22, 2014 3:05:14 PM
Attachments: [EAS](#)

Attachments:

ETOH and cancer.pdf (202577 Bytes)
thyroid cancer.pdf (205764 Bytes)

[Environ Health](#). 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.

Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

[Bove FJ¹](#), [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

Author information

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at Camp Lejeune during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 Camp Pendleton workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune and Camp Pendleton workers and assess the effects of estimated cumulative contaminant exposures within the Camp Lejeune cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at Camp Lejeune. The confidence interval (CI) indicated precision of effect estimates.

RESULTS:

Compared to Camp Pendleton, Camp Lejeune workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the Camp Lejeune cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION:

The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the Camp Lejeune cohort died by end of follow-up, producing small numbers of ca

Multiple Sclerosis

IOM 2003 Conclusions

At the time of the IOM (2003) report, four case-control studies of solvent exposure (in general) and multiple sclerosis (MS) had been conducted in Scandinavia. Two had negative results, and the other two, conducted in Sweden and based on overlapping populations, reported some positive associations between self-reported occupational and leisure-time solvent exposure and MS in men. The positive findings are tempered by the limited quality of exposure assessment, the lack of adjustment for potential confounders, and small sample and were thus short of "limited/suggestive" evidence of an association. No studies focused specifically on TCE or PCE were found. IOM concluded that there was inadequate/insufficient evidence to determine whether an association exists between exposure to TCE, PCE, or other solvents reviewed and MS.

2008 Evaluation

No additional studies of solvent exposure and MS were identified.

- There continues to be inadequate/insufficient evidence to determine whether an association exists between solvent exposure and MS.

Full text: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3502195/>
[J Natl Cancer Inst.](#) 2012 Nov 21;104(22):1724-37. doi: 10.1093/jnci/djs411. Epub 2012 Oct 30.

Myelodysplastic syndrome and benzene exposure among petroleum workers: an international pooled analysis.

[Schnatter AR](#), [Glass DC](#), [Tang G](#), [Irons RD](#), [Rushton L](#).

Source:Occupational and Public Health Division, ExxonMobil Biomedical Sciences, Inc, 1545 US Highway 22 East, Annandale, NJ 08801-3059, USA. a.r.schnatter@exxonmobil.com

BACKGROUND:

Benzene at high concentrations is known to cause acute myeloid leukemia (AML), but its relationship with other lymphohematopoietic (LH) cancers remains uncertain, particularly at low concentrations. In this pooled analysis, we examined the risk of five LH cancers relative to lower levels of benzene exposure in petroleum workers.

METHODS:

We updated three nested case-control studies from Australia, Canada, and the United Kingdom with new incident LH cancers among petroleum distribution workers through December 31, 2006, and pooled 370 potential case subjects and 1587 matched LH cancer-free control subjects. Quantitative benzene exposure in parts per million (ppm) was blindly reconstructed using historical monitoring data, and exposure certainty was scored as high, medium, or low. Two hematopathologists assigned diagnoses and scored the certainty of diagnosis as high, medium, or low. Dose-response relationships were examined for five LH cancers, including the three most common leukemia cell-types (AML, chronic myeloid leukemia [CML], and chronic lymphoid leukemia [CLL]) and two myeloid tumors (myelodysplastic syndrome [MDS] and myeloproliferative disease [MPD]). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression, controlling for age, sex, and time period.

RESULTS:

Cumulative benzene exposure showed a monotonic dose-response relationship with MDS (highest vs lowest tertile, >2.93 vs ≤ 0.348 ppm-years, OR = 4.33, 95% CI = 1.31 to 14.3). For peak benzene exposures (>3 ppm), the risk of MDS was increased in high and medium certainty diagnoses (peak exposure vs no peak exposure, OR = 6.32, 95% CI = 1.32 to 30.2) and in workers having the highest exposure certainty (peak exposure vs no peak exposure, OR = 5.74, 95% CI = 1.05 to 31.2). There was little evidence of dose-response relationships for AML, CLL, CML, or MPD.

CONCLUSIONS:

Relatively low-level exposure to benzene experienced by petroleum distribution workers was associated with an increased risk of MDS, but not AML, suggesting that MDS may be the more relevant health risk for lower exposures.

From: (b) (6)
To: (b) (6)
Subject: good 2015 article on prostate cancer risk from fam hx
Date: Tuesday, June 02, 2015 8:32:13 PM

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293302/pdf/pros0075-0390.pdf>

From: (b) (6)
To: (b) (6)
Subject: good article
Date: Tuesday, November 25, 2014 1:28:48 PM

World J Gastroenterol 2013 September 14; 19(34): 5598-5606

ISSN 1007-9327 (print) ISSN 2219-2840 . Epidemiology of esophageal cancer

Yuwei Zhang.

From: (b) (6)
To: (b) (6)
Subject: good one for the sharepoint
Date: Tuesday, March 25, 2014 6:28:35 PM
Attachments: [EAS](#)

Best Practice & Research Clinical Haematology
<<http://www.sciencedirect.com/science/journal/15216926>>

Volume 20, Issue 4 <<http://www.sciencedirect.com/science/journal/15216926/20/4>>, December 2007, Pages 637–664

New Insights into the Biology and Advances in the Management of Multiple Myeloma

Edited By Jean Luc Harousseau

<<http://www.sciencedirect.com/science/journal/15216926/20/4>>

5

Epidemiology of the plasma-cell disorders

· Robert A. Kyle
<<http://www.sciencedirect.com/science/article/pii/S152169260700062X?via=ihub>>, MD
<<http://www.sciencedirect.com/science/article/pii/S152169260700062X?via=ihub#cor1>> <<mailto:kyle.robert@mayo.edu>> (Professor of Medicine)

Attachments:

image001.gif (9368 Bytes)
image002.gif (269 Bytes)
image003.gif (386 Bytes)

Modifiable risk behaviors in patients with head and neck cancer.

[Sivasithamparam J](#), [Visk CA](#), [Cohen EE](#), [King AC](#). **Source** Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois.

Abstract

BACKGROUND:

Use of tobacco products, excessive alcohol consumption, and high-risk sexual behaviors increase the risk of developing head and neck cancer and impacts treatment effectiveness after diagnosis. This study examined smoking and engagement in other modifiable behavioral risk factors and human papillomavirus (HPV) status in patients with head and neck cancer in order to facilitate identification and foster development of targeted interventions in high-risk patients.

METHODS:

Participants were 102 patients with head and neck cancer at a large urban cancer center who completed a self-report background and health questionnaire and provided a saliva sample for determination of the long-acting nicotine metabolite cotinine.

RESULTS:

Compared with former and never-smokers, current smokers were less educated, less likely to be married or living with a partner, and consumed more alcohol. Cotinine analysis indicated that 4 of 16 (25%) patients who denied past-month cigarette use misrepresented their true smoking status. Of patients with oropharyngeal cancer, 74% were confirmed as HPV-positive, and compared with HPV-negative patients, they were younger, more likely to be married/partnered and of Caucasian race, and reported more past vaginal and oral sexual partners. Only one-third of HPV-positive patients were aware of their HPV disease status.

CONCLUSIONS:

Cigarette smoking is associated with engagement in other modifiable risk factors in patients with head and neck cancer. Self-report measures of smoking may not accurately depict true smoking status. HPV-positive cancer patients were more likely to endorse a history of multiple sexual partners. Regular screening and targeted interventions for these distinct risk factors are warranted. *Cancer* 2013;000:000-000. © 2013 American Cancer Society.

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PMID:

23575663

Human health effects of tetrachloroethylene: key findings and scientific issues.

[Guyton KZ](#)¹, [Hogan KA](#), [Scott CS](#), [Cooper GS](#), [Bale AS](#), [Kopylev L](#), [Barone S](#), [Makris SL](#), [Glenn B](#), [Subramaniam RP](#), [Gwinn MR](#), [Dzubow RC](#), [Chiu WA](#).

Abstract

BACKGROUND:

The U.S. Environmental Protection Agency (EPA) completed a toxicological review of tetrachloroethylene (perchloroethylene, PCE) in February 2012 in support of the Integrated Risk Information System (IRIS).

OBJECTIVES: We reviewed key findings and scientific issues regarding the human health effects of PCE described in the U.S. EPA's Toxicological Review of Tetrachloroethylene (Perchloroethylene).

METHODS:

The updated assessment of PCE synthesized and characterized a substantial database of epidemiological, experimental animal, and mechanistic studies. Key scientific issues were addressed through modeling of PCE toxicokinetics, synthesis of evidence from neurological studies, and analyses of toxicokinetic, mechanistic, and other factors (tumor latency, severity, and background rate) in interpreting experimental animal cancer findings. Considerations in evaluating epidemiological studies included the quality (e.g., specificity) of the exposure assessment methods and other essential design features, and the potential for alternative explanations for observed associations (e.g., bias or confounding).

DISCUSSION:

Toxicokinetic modeling aided in characterizing the complex metabolism and multiple metabolites that contribute to PCE toxicity. The exposure assessment approach—a key evaluation factor for epidemiological studies of bladder cancer, non-Hodgkin lymphoma, and multiple myeloma—provided suggestive evidence of carcinogenicity. Bioassay data provided conclusive evidence of carcinogenicity in experimental animals. Neurotoxicity was identified as a sensitive noncancer health effect, occurring at low exposures: a conclusion supported by multiple studies. Evidence was integrated from human, experimental animal, and mechanistic data sets in assessing adverse health effects of PCE.

CONCLUSIONS: PCE is likely to be carcinogenic to humans. Neurotoxicity is a sensitive adverse health effect of PCE.

From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL]
Date: Friday, February 20, 2015 2:08:01 PM
Attachments: [EAS](#)

Hi guys. I think there has been a presumption in the past that all SMEs remember or ever learned stats. I found this great summary that I think would help a lot with SMEs knowing how to interpret the literature, and especially the Bove studies. Should it be sent out to the group?

(b) (6)

Compensation & Pension
Environmental Health Clinician
DMA Subject Matter Expert Panel
VISN 11 Primary MRO
Ann Arbor VAMC
734-769-7100 x (b) (6) (office)
(b) (6) (cell)
(b) (6)

From: (b) (6)]
Sent: Friday, February 20, 2015 2:06 PM
To: (b) (6)
Subject: [EXTERNAL]

(b) (6)

(b) (6)

From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Date: Friday, September 12, 2014 12:52:17 PM
Attachments: [EAS](#)
Importance: High

Lets add these papers to the resource section

From: (b) (6)
Sent: Wednesday, August 27, 2014 8:29 AM
To: (b) (6)
Subject: FW: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Importance: High

(b) (6),

Per our discussion. See you next week if I'm here.

Thank you,

(b) (6)

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ICARE



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From: (b) (6)
Sent: Thursday, August 14, 2014 10:41 PM
To: (b) (6)

(b) (6)

Subject: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Importance: High

Attached are 2 Information Papers on the new ATSDR study of mortality in civilian employees who worked at Camp Lejeune and Camp Pendleton.

I wrote these at the request of staff of the US Marine Corps, and on behalf of the DoD/VA Deployment Health Work Group.

The 2-page version includes more background. The one-page version includes fewer results, but more on implications of the study.

I hope these critiques are useful to our colleagues in the VA and US Marine Corps.

Please tell me if you have any questions on this.

(b) (6)

From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] breast ca
Date: Wednesday, June 11, 2014 10:27:02 AM

I have not read the whole article yet but seems relevant.

From: (b) (6)
Sent: Tuesday, June 10, 2014 8:30 PM
To: (b) (6)
Subject: [EXTERNAL] breast ca

<http://cancerres.aacrjournals.org/content/74/11/3076.long>

(b) (6)

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: FW: [EXTERNAL] NEJM article smoking
Date: Tuesday, March 24, 2015 11:28:19 AM

Hey guys, I read this last nite; definitely pertinent to CLCW.

(b)
(6)

From: (b) (6)
Sent: Monday, March 23, 2015 9:32 AM
To: (b) (6)
Subject: [EXTERNAL] NEJM article smoking

<http://www.nejm.org/doi/pdf/10.1056/NEJMsa1407211>

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From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] smoking reports
Date: Monday, December 15, 2014 3:19:27 PM

Two recent reports (2014) on the adverse health effects of smoking which have incorporated recent medical literature: these would be useful for the Sharepoint

(b) (6)

From: (b) (6)
Sent: Monday, December 15, 2014 10:52 AM
To: (b) (6)
Subject: [EXTERNAL] smoking reports

<http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>

<http://www.ncbi.nlm.nih.gov/pubmed/25317719>

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FATTY LIVER DISEASE

Fatty liver disease is clearly recognized as a primary direct consequence of obesity and alcohol consumption. On a population base those two are the most common causes, around the world, achieving a prevalence of over 34% in the US NHANES (1988-1994) (Sirota 2012) and over 30% throughout the world (Durazzo 2012), and the proportion of overweight, obesity, and morbid obesity has only increased since then. In addition to alcohol and obesity, occupational exposure to organic solvent with known or imputed liver toxicity contribute to the risk (Hodgson 1991, Lundqvist 1999). The higher the dose of hepatotoxin, the greater the likelihood of hepatitis, a 4.5-fold risk in one study and a 7-fold risk in the other. Still, even in working populations with potential exposure to hepatotoxins obesity appears to be the primary risk factor. Environmental exposure, i.e., ground water pollution (Najem 1994), does not to be associated with liver disease in humans even through several animal studies demonstrated minimal changes in rat livers

The risk from obesity is so great

Hodgson M, van Thiel DH, Goodman-Klein B. Obesity and hepatotoxins as risk factors for fatty liver disease. *Br J Ind Med.* 1991 Oct;48(10):690-5.

Lundqvist G, Flodin U, Axelson O. A case-control study of fatty liver disease and organic solvent exposure. *Am J Ind Med.* 1999 Feb;35(2):132-6.

Sirota JC, McFann K, Targher G, Chonchol M, Jalal DI. Association between Nonalcoholic Liver Disease and Chronic Kidney Disease: An Ultrasound Analysis from NHANES 1988-1994. *Am J Nephrol.* 2012;36(5):466-71. doi: 10.1159/000343885. Epub 2012 Nov 2.

Durazzo M, Belci P, Collo A, Grisoglio E, Bo S. Focus on therapeutic strategies of nonalcoholic Fatty liver disease. *Int J Hepatol.* 2012;2012:464706. doi: 10.1155/2012/464706. Epub 2012 Nov 8.

Najem GR, Strunck T, Feuerman M. Health effects of a Superfund hazardous chemical waste disposal site. *Am J Prev Med.* 1994 May-Jun;10(3):151-5.

National academy of sciences. Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects. National Research Council, 2009.

From: (b) (6)
To: (b) (6)
Subject: for sharepoint
Date: Thursday, March 19, 2015 9:19:43 AM
Attachments: [EAS](#)

(b) (6)

Compensation & Pension

Environmental Health Clinician

DMA Clinical Advisory Board
Ann Arbor VAMC

Attachments:

Occ exposure rare cancers.pdf (2181007 Bytes)

From: (b) (6)
To: (b) (6)
Subject: for the website: 2015 article on TCE
Date: Tuesday, February 17, 2015 1:53:57 PM

Trichloroethylene: Mechanistic, Epidemiologic and Other Supporting Evidence of Carcinogenic Hazard

Ivan Rusyn¹, Weihsueh A.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3867557/pdf/nihms-518376.pdf>

Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

[Bove FJ](#)¹, [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

Author information

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at Camp Lejeune or Camp Pendleton, California during this period. Camp Pendleton's drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune (N = 154,932) and Camp Pendleton (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the Camp Lejeune cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS:

There were 8,964 and 9,365 deaths respectively, in the Camp Lejeune and Camp Pendleton cohorts. Compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the Camp Lejeune cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

CONCLUSION:

The study found elevated HRs at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposures

Environ Health Perspect. 2009 May; 117(5): 696–702.

Published online 2009 January 9. doi: [10.1289/ehp.11782](https://doi.org/10.1289/ehp.11782)

PMCID: PMC2685829

Review

Evidence of Autoimmune-Related Effects of Trichloroethylene Exposure from Studies in Mice and Humans

[Glinda S. Cooper](#),¹ [Susan L. Makris](#),¹ [Paul J. Nietert](#),² and [Jennifer Jinot](#)¹

<mailto:cooper.glinda@epa.gov>

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Abstract

Objective

Our objective was to examine experimental and epidemiologic studies pertaining to immune-related, and specifically autoimmune-related, effects of trichloroethylene (TCE).

Data sources and extraction

We performed a literature search of PubMed and reviewed bibliographies in identified articles. We then systematically reviewed immune-related data, focusing on clinical and immunologic features and mechanistic studies.

Data synthesis

Studies conducted in MRL^{+/+} lupus mice report an accelerated autoimmune response in relation to exposure to TCE or some metabolites. Effects have been reported after 4 weeks of exposure to TCE at doses as low as 0.1 mg/kg/day in drinking water and have included increased antinuclear antibodies and interferon- γ (IFN- γ) and decreased secretion of interleukin-4 (IL-4), consistent with an inflammatory response. Autoimmune hepatitis, inflammatory skin lesions, and alopecia have been found after exposures of 32–48 weeks. Recent mechanistic experiments in mice examined oxidative stress and, specifically, effects on lipid-peroxidation–derived aldehydes in TCE-induced autoimmune disease. Two studies in humans reported an increase in IL-2 or IFN- γ and a decrease in IL-4 in relation to occupational or environmental TCE exposure. Occupational exposure to TCE has also been associated with a severe, generalized hypersensitivity skin disorder accompanied by systemic effects, including hepatitis. In three case–control studies of scleroderma with a measure of occupational TCE exposure, the combined odds ratio was 2.5 [95% confidence interval (CI), 1.1–5.4] in men and 1.2 (95% CI, 0.58–2.6) in women.

Conclusion

The consistency among the studies and the concordance between the studies in mice and humans support an etiologic role of TCE in autoimmune disease. Multisite collaborations and studies of preclinical immune markers are needed to further develop this field of research.

Keywords: autoimmune liver disease, solvents, systemic sclerosis, trichloroethylene

Trichloroethylene (TCE) is an industrial solvent that has been used extensively in industrial operations involving metal cleaning and degreasing. Its metabolism through a cytochrome P450 (CYP) pathway involving the enzyme CYP2E1 results in numerous metabolites, including chloral, chloral hydrate, dichloroacetic acid, trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide (

The following popper user interface control may not be accessible. Tab to the next button to revert the control to an accessible version.

[Destroy user interface control](#) Lash et al. 2000). Many studies of immune-related effects of TCE have been conducted in the past decade, with much of this work focusing on autoimmune disease. We reviewed this recent research to determine the strength and consistency of data from experimental and epidemiologic studies, and the concordance between human and animal data, pertaining to these effects.

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[Urol Oncol.](#) 2012 Mar-Apr;30(2):220-4. doi:
10.1016/j.urolonc.2011.10.001.

Environmental and modifiable risk factors in renal cell carcinoma.

[Navai N](#), [Wood CG](#).

Author information

Abstract

OBJECTIVES:

Prevention of disease requires a firm understanding of the relevant environmental and modifiable risk factors. We present a comprehensive review of these factors in renal cell carcinoma.

MATERIALS AND METHODS:

A literature search of the PubMed database was performed to identify clinical studies examining the relationship between environmental and modifiable factors in the development of renal cell carcinoma (terms utilized: kidney cancer; renal cell carcinoma; risk factors; environment; obesity; hypertension; trichloroethylene). An emphasis was placed on more recent studies.

RESULTS:

Case control and large cohort studies have examined the relationship of numerous environmental and modifiable factors and the risk of renal cell carcinoma. Of particular note are dose-dependent increases in smokers, the obese, and hypertensive patients.

CONCLUSIONS:

Environmental and modifiable risk factors contribute significantly to the risk of sporadic renal cell carcinoma. Emphasis should be placed on smoking cessation and hypertension control. Emerging evidence would suggest that dietary intake and quality impact renal cell carcinoma risk.

[FULL TEXT LINK](#)

[Rev Environ Health](#). 2008 Jan-Mar;23(1):1-37.

Environmental and occupational causes of cancer: new evidence 2005-2007.

[Clapp RW](#), [Jacobs MM](#), [Loechler EL](#).

Source Boston University School of Public Health, Boston, MA 02118, USA.
richard.clapp@gmail.com

Abstract

What do we currently know about the occupational and environmental causes of cancer? As of 2007, the International Agency for Research on Cancer (IARC) identified 415 known or suspected carcinogens. Cancer arises through an extremely complicated web of multiple causes, and we will likely never know the full range of agents or combinations of agents. We do know that preventing exposure to individual carcinogens prevents the disease. Declines in cancer rates—such as the drop in male lung cancer cases from the reduction in tobacco smoking or the drop in bladder cancer among cohorts of dye workers from the elimination of exposure to specific aromatic amines—provides evidence that preventing cancer is possible when we act on what we know. Although the overall age-adjusted cancer incidence rates in the United States among both men and women have declined in the last decade, the rates of several types of cancers are on the rise; some of which are linked to environmental and occupational exposures. This report chronicles the most recent epidemiologic evidence linking occupational and environmental exposures with cancer. Peer-reviewed scientific studies published from January 2005 to June 2007 were reviewed, supplementing our state-of-the-evidence report published in September 2005. Despite weaknesses in certain individual studies, we consider the evidence linking the increased risk of several types of cancer with specific exposures somewhat strengthened by recent publications, among them brain cancer from exposure to non-ionizing radiation, particularly radiofrequency fields emitted by mobile telephones; breast cancer from exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) before puberty; leukemia from exposure to 1,3-butadiene; lung cancer from exposure to air pollution; non-Hodgkin's lymphoma (NHL) from exposure to pesticides and solvents; and prostate cancer from exposure to pesticides, polycyclic aromatic hydrocarbons (PAHs), and metal working fluids or mineral oils. In addition to NHL and prostate cancer, early findings from the National Institutes of Health Agricultural Health Study suggest that several additional cancers may be linked to a variety of pesticides. Our report also briefly describes the toxicological evidence related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans, namely exposures to bisphenol A and epigenetic, trans-generational effects. To underscore the multi-factorial, multi-stage nature of cancer, we also present a technical description of cancer causation summarizing current knowledge in molecular biology. We argue for a new cancer prevention paradigm, one based on an understanding that cancer is ultimately caused by multiple interacting factors rather than a paradigm based on dubious attributable fractions. This new cancer prevention paradigm demands that we limit exposure to avoidable environmental and occupational carcinogens, in combination with additional important risk factors like diet and lifestyle. The research literature related to environmental and occupational causes of cancer is constantly growing, and future

updates will be carried out in light of new biological understanding of the mechanisms and new methods for studying exposures in human populations. The current state of knowledge is sufficient to compel us to act on what we know. We repeat the call of ecologist Sandra Steingraber: "From the right to know and the duty to inquire flows the obligation to act."

Kamangar F, Chow W-H, Abnet C, Dawsey S. Environmental Causes of Esophageal Cancer. *Gastroenterol Clin North Am*. 38(1): 27-vii.

Gastroenterol Clin North Am. Author manuscript; available in PMC 2010 March 1.

Published in final edited form as:

[Gastroenterol Clin North Am. 2009 March; 38\(1\): 27–vii.](#)

doi: [10.1016/j.gtc.2009.01.004](https://doi.org/10.1016/j.gtc.2009.01.004)

PMCID: PMC2685172

NIHMSID: NIHMS111277

Environmental Causes of Esophageal Cancer

[Farin Kamangar](#), MD, PhD, [Wong-Ho Chow](#), PhD, [Christian Abnet](#), PhD, MPH, and [Sanford Dawsey](#), MD

Synopsis

This article reviews the environmental risk factors and predisposing conditions for the two main histological types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). Tobacco smoking, excessive alcohol consumption, drinking maté, low intake of fresh fruits and vegetables, achalasia, and low socioeconomic status increase the risk of ESCC. Results of investigations on several other potential risk factors, including opium consumption, intake of hot drinks, eating pickled vegetables, poor oral health, and exposure to human papillomavirus, polycyclic aromatic hydrocarbons, *N*-nitroso compounds, acetaldehyde, and fumonisins are also discussed. Gastroesophageal reflux, obesity, tobacco smoking, hiatal hernia, achalasia, and probably absence of *H. pylori* in the stomach increase the risk of EA. Results of studies investigating other factors, including low intake of fresh fruits and vegetables, consumption of carbonated soft drink, use of H₂ blockers, non-steroidal anti-inflammatory drugs, and drugs that relax the lower esophageal sphincter are also discussed.

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J Cancer Epidemiol. 2012; 2012: 978930.

Published online 2012 September 12. doi: [10.1155/2012/978930](https://doi.org/10.1155/2012/978930)

PMCID: PMC3447374

Current Understanding of Lifestyle and Environmental Factors and Risk of Non-Hodgkin Lymphoma: An Epidemiological Update

[Bryan A. Bassig](#),¹ [Qing Lan](#),² [Nathaniel Rothman](#),² [Yawei Zhang](#),¹ and [Tongzhang Zheng](#)^{1,*}

¹Division of Environmental Health Sciences, Yale School of Public Health, New Haven, CT 06510, USA

²Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD 20892, USA

*Tongzhang Zheng: Email: tongzhang.zheng/at/yale.edu

Academic Editor: P. Vineis

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Received May 24, 2012; Revised July 20, 2012; Accepted August 4, 2012.

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Abstract

The incidence rates of non-Hodgkin lymphoma (NHL) have steadily increased over the last several decades in the United States, and the temporal trends in incidence can only be partially explained by the HIV epidemic. In 1992, an international workshop sponsored by the United States National Cancer Institute concluded that there was an “emerging epidemic” of NHL and emphasized the need to investigate the factors responsible for the increasing incidence of this disease. Over the past two decades, numerous epidemiological studies have examined the risk factors for NHL, particularly for putative environmental and lifestyle risk factors, and international consortia have been established in order to investigate rare exposures and NHL subtype-specific associations. While few consistent risk factors for NHL aside from immunosuppression and certain infectious agents have emerged, suggestive associations with several lifestyle and environmental factors have been reported in epidemiologic studies. Further, increasing evidence has suggested that the effects of these and other exposures may be limited to or stronger for particular NHL subtypes. This paper examines the progress that has been made over the last twenty years in elucidating the etiology of NHL, with a primary emphasis on lifestyle factors and environmental exposures.

Environmental risk factors in systemic sclerosis.

[Dospinescu P](#), [Jones GT](#), [Basu N](#).

Source

Department of Rheumatology, Aberdeen Royal Infirmary, Aberdeen, UK.

Abstract

PURPOSE OF REVIEW:

Environmental risk factors have been implicated in the pathogenesis of systemic sclerosis (SSc). Recent evidence further supports this relationship and constitutes the focus of this review article.

RECENT FINDINGS:

Exposure to silica through various occupations remains one of the main environmental risk factors for SSc. Emerging evidence has also implicated organic solvents in the development of this difficult-to-manage condition. The individual role of these toxins is, however, difficult to ascertain due to methodological limitations in study design. Other occupational agents, such as epoxy resins, welding fumes and hand-arm vibration, have been investigated, but no definitive associations may be made due to small sample sizes. The controversial association between silicone breast surgery and SSc has not been proven and, amongst other non-occupational factors, smoking does not increase the risk of development but does appear to impact upon the severity of disease.

SUMMARY:

A number of environmental exposures are likely to play an important role in the development of the disease; however, current evidence consists mainly of heterogeneous studies with relatively small sample sizes. In the future, multicentre collaborations may help inform preventive strategies.

<http://www.ncbi.nlm.nih.gov/pubmed/23287382>

[FULL TEXT](#)

Clin Colon Rectal Surg. 2009 November; 22(4): 191–197.

PMCID: PMC2796096

Colorectal Cancer

Guest Editor Robin P. Boushey M.D., Ph.D.

Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors

[Fatima A. Hagggar](#), M.P.H.^{1,2} and [Robin P. Boushey](#), M.D., Ph.D.¹

ABSTRACT

In this article, the incidence, mortality, and survival rates for colorectal cancer are reviewed, with attention paid to regional variations and changes over time. A concise overview of known risk factors associated with colorectal cancer is provided, including familial and hereditary factors, as well as environmental lifestyle-related risk factors such as physical inactivity, obesity, smoking, and alcohol consumption.

[Morgan JW, Cassady RE](#). Community cancer assessment in response to long-time exposure to perchlorate and trichloroethylene in drinking water. [J Occup Environ Med](#). 2002 Jul;44(7):616-21.

Full text: http://ovidsp.tx.ovid.com/sp-3.8.0b/ovidweb.cgi?&S=GDPOFPHOJCDDGOMANCOKEALBFFLHAA00&Link+Set=S.sh.18.19.23.27%7c5%7csl_10

AB Objective: To analyze if the combination of organizational climate and work commitment can predict return to work (RTW). Methods: This prospective Swedish study was based on 2285 participants, 19 to 64 years old, consecutively selected from the employed population, newly sick-listed for more than 14 days. Data were collected in 2008 through postal questionnaire and from register data. Results: Among women, the combination of good organizational climate and fair work commitment predicted an early RTW with an adjusted relative risk of 2.05 (1.32 to 3.18). Among men, none of the adjusted variables or combinations of variables was found significantly to predict RTW. Conclusions: This study demonstrated the importance of integrative effects of organizational climate and individual work commitment on RTW among women. These factors did not predict RTW in men. More research is needed to understand the RTW process among men. (C)2013The American College of Occupational and Environmental Medicine

Supported by sanofi-aventis



What are confidence intervals and p-values?

Huw TO Davies PhD
Professor of Health
Care Policy and
Management,
University of St
Andrews

Iain K Crombie PhD
FFPHM Professor of
Public Health,
University of Dundee

- A confidence interval calculated for a **measure of treatment effect** shows the range within which the true treatment effect is likely to lie (subject to a number of assumptions).
- A p-value is calculated to assess whether trial results are likely to have occurred simply through chance (assuming that there is no real difference between new treatment and old, and assuming, of course, that the study was well conducted).
- Confidence intervals are preferable to p-values, as they tell us the **range of possible effect sizes** compatible with the data.
- p-values simply provide a cut-off beyond which we assert that the findings are 'statistically significant' (by convention, this is $p < 0.05$).
- A confidence interval that **embraces the value of no difference between treatments** indicates that the treatment under investigation is not significantly different from the control.
- Confidence intervals **aid interpretation of clinical trial data** by putting upper and lower bounds on the likely size of any true effect.
- **Bias must be assessed** before confidence intervals can be interpreted. Even very large samples and very narrow confidence intervals can mislead if they come from biased studies.
- **Non-significance does not mean 'no effect'**. Small studies will often report non-significance even when there are important, real effects which a large study would have detected.
- Statistical significance does not necessarily mean that the effect is real: by chance alone about **one in 20 significant findings will be spurious**.
- Statistically significant does not necessarily mean clinically important. It is the **size of the effect** that determines the importance, not the presence of statistical significance.

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What are confidence intervals and p-values?

Measuring effect size

Clinical trials aim to generate new knowledge on the effectiveness (or otherwise) of healthcare interventions. Like all clinical research, this involves estimating a key parameter of interest, in this case the effect size. The effect size can be measured in a variety of ways, such as the relative risk reduction, the absolute risk reduction or the number needed to treat (NNT; Table 1).

Relative measures tend to emphasise potential benefits, whereas **absolute measures** provide an across-the-board

summary.¹ Either may be appropriate, subject to correct interpretation.

Whatever the measure used, some assessment must be made of the trustworthiness or **robustness** of the findings. The findings of the study provide a point estimate of effect, and this raises a dilemma: are the findings from this sample also likely to be true about other similar groups of patients? Before we can answer such a question, two issues need to be addressed. Does any apparent treatment benefit arise because of the way the study has been

Box 1. Hypothesis testing and the generation of p-values

The logic of hypothesis testing and p-values is convoluted. Suppose a new treatment appears to outperform the standard therapy in a research study. We are interested in assessing whether this apparent effect is likely to be real or could just be a chance finding: p-values help us to do this.

In calculating the p-value, we first assume that there really is no true difference between the two treatments (this is called the **null hypothesis**). We then calculate how likely we are to see the difference that we have observed just by chance if our supposition is true (that is, if there is really no true difference). This is the p-value.

So the p-value is the probability that we would observe effects as big as those seen in the study if there was really no difference between the treatments. If p is small, the findings are unlikely to have arisen by chance and we reject the idea that there is no difference between the two treatments (we reject the null hypothesis). If p is large, the observed difference is plausibly a chance finding and we do not reject the idea that there is no difference between the treatments. Note that we do not reject the idea, but we do not accept it either: we are simply unable to say one way or another until other factors have been considered.

But what do we mean by a 'small' p-value (one small enough to cause us to reject the idea that there was really no difference)? By convention, p-values of less than 0.05 are considered 'small'. That is, if p is less than 0.05 there is a less than one in 20 chance that a difference as big as that seen in the study could have arisen by chance if there was really no true difference. With p-values this small (or smaller) we say that the results from the trial are statistically significant (unlikely to have arisen by chance). Smaller p-values (say $p < 0.01$) are sometimes called 'highly significant' because they indicate that the observed difference would happen less than once in a hundred times if there was really no true difference.

Table 1. Summary of effect measures

| Measure of effect | Abbreviation | Description | No effect | Total success |
|-------------------------|--------------|---|-----------------|--------------------|
| Absolute risk reduction | ARR | Absolute change in risk: the risk of an event in the control group minus the risk of an event in the treated group; usually expressed as a percentage | ARR=0% | ARR=initial risk |
| Relative risk reduction | RRR | Proportion of the risk removed by treatment: the absolute risk reduction divided by the initial risk in the control group; usually expressed as a percentage | RRR=0% | RRR=100% |
| Relative risk | RR | The risk of an event in the treated group divided by the risk of an event in the control group; usually expressed as a decimal proportion, sometimes as a percentage | RR=1 or RR=100% | RR=0 |
| Odds ratio | OR | Odds of an event in the treated group divided by the odds of an event in the control group; usually expressed as a decimal proportion | OR=1 | OR=0 |
| Number needed to treat | NNT | Number of patients who need to be treated to prevent one event; this is the reciprocal of the absolute risk reduction (when expressed as a decimal fraction); it is usually rounded to a whole number | NNT= ∞ | NNT=1/initial risk |

conducted (**bias**), or could it arise simply because of **chance**? The short note below briefly covers the importance of assessing bias but focuses more on assessing the role of chance.

Bias

Bias is a term that covers any **systematic errors** that result from the way the study was designed, executed or interpreted. Common flaws in treatment trials are:

- Lack of (or failure in) randomisation, leading to unbalanced groups
- Poor blinding, leading to unfair treatment and biased assessments
- Large numbers of patients lost to follow-up.

Assessment in these areas is crucial before the results from any trial can be assessed, and many useful guides exist to assist this process, such as an article by Guyatt *et al* and books by Sackett *et al* and by Crombie.²⁻⁵ Interpretation of the effects of chance is only meaningful once bias has been excluded as an explanation for any observed differences.^{6,7}

Chance variability

The results from any particular study will vary just by chance. Studies differ in terms of the

people who are included, and the ways in which these specific individuals react to therapeutic interventions. Even when everything possible is held constant, there will still be some random variations. Hence we need some tools to help us to assess whether differences that we see between new treatment and old in any particular study are real and important, or just manifestations of chance variability. Confidence intervals and p-values help us to do this.

What are p-values?

Until comparatively recently, assessments of the role of chance were routinely made using **hypothesis testing**, which produces a 'p-value' (Box 1). The p-value allows assessment of whether or not the findings are 'significantly different' or 'not significantly different' from some reference value (in trials, this is usually the value reflecting 'no effect'; Table 1). A different and potentially more useful approach to assessing the role of chance has come to the fore: confidence intervals.⁸ Although these might appear rather dissimilar to p-values, the theory and calculations underlying these two approaches are largely the same.

What are confidence intervals?

Confidence intervals provide different information from that arising from hypothesis tests. Hypothesis testing produces a decision about any observed difference: either that the difference is 'statistically significant' or that it is 'statistically non-significant'. In contrast, confidence intervals provide a **range** about the observed effect size. This range is constructed in such a way that we know how likely it is to capture the true – but unknown – effect size.

Thus, the formal definition of a confidence interval is: 'a range of values for a variable of interest [in our case, the measure of treatment effect] constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits'.⁹

It is conventional to create confidence intervals at the 95% level – so this means that 95% of the time properly constructed confidence intervals should contain the true value of the variable of interest. This corresponds to hypothesis testing with p-values, with a conventional cut-off for p of less than 0.05.

More colloquially, the confidence interval provides a range for our best guess of the size of the true treatment effect that is plausible given the size of the difference actually observed.

Assessing significance from a confidence interval

One useful feature of confidence intervals is that one can easily tell whether or not statistical significance has been reached, just as in a hypothesis test.

- If the confidence interval **captures** the value reflecting 'no effect', this represents a difference that is statistically non-significant (for a 95% confidence interval, this is non-significance at the 5% level).
- If the confidence interval **does not enclose** the value reflecting 'no effect', this represents a difference that is statistically significant (again, for a 95% confidence interval, this is significance at the 5% level).

Thus, 'statistical significance'

(corresponding to $p < 0.05$) can be inferred from confidence intervals – but, in addition, these intervals show the largest and smallest effects that are likely, given the observed data. This is useful extra information.

An example of the use of confidence intervals is shown in Box 2.¹⁰

Examining the width of a confidence interval

One of the advantages of confidence intervals over traditional hypothesis testing is the additional information that they convey. The upper and lower bounds of the interval give us information on how big or small the true effect might plausibly be, and the width of the confidence interval also conveys some useful information.

If the confidence interval is narrow, capturing only a small range of effect sizes, we can be quite confident that any effects far from this range have been ruled out by the study. This situation usually arises when the size of the study is quite large and, hence, the estimate of the true effect is quite precise. Another way of saying this is to note that the study has reasonable 'power' to detect an effect.

However, if the confidence interval is quite wide, capturing a diverse range of effect sizes, we can infer that the study was probably quite small. Thus, any estimates of effect size will be quite imprecise. Such a study is 'low-powered' and provides us with less information.

Errors in interpretation

Confidence intervals, like p-values, provide us with a guide to help with the interpretation of research findings in the light of the effects of chance. There are, however, three important pitfalls in interpretation.

Getting it wrong: seeing effects that are not real

First of all, we may examine the confidence interval and/or the p-value and observe that the difference is 'statistically significant'. From this we will usually conclude that there is a difference between the two treatments. However, just because we are unlikely to observe such a large difference simply by chance, this does not mean that it will not happen. By definition, about one in 20

Box 2. An example of the use of confidence intervals¹⁰

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor which has been tested for use in patients at high risk of cardiovascular events. In one study published in the *New England Journal of Medicine*,¹⁰ a total of 9,297 patients were recruited into a randomised, double-blind, controlled trial. The key findings presented on the primary outcome and deaths are shown below.

Incidence of primary outcome and deaths from any cause

| Outcome | Ramipril group (n=4,645) number (%) | Placebo group (n=4,652) number (%) | Relative risk (95% CI) |
|--|---|--|---------------------------|
| Cardiovascular event (including death) | 651 (14.0) | 826 (17.8) | 0.78 (0.70–0.86) |
| Death from non-cardiovascular cause | 200 (4.3) | 192 (4.1) | 1.03 (0.85–1.26) |
| Death from any cause | 482 (10.4) | 569 (12.2) | 0.84 (0.75–0.95) |

These data indicate that fewer people treated with ramipril suffered a cardiovascular event (14.0%) compared with those in the placebo group (17.8%). This gives a relative risk of 0.78, or a reduction in (relative) risk of 22%. The 95% confidence interval for this estimate of the relative risk runs from 0.70 to 0.86. Two observations can then be made from this confidence interval.

- First, the observed difference is statistically significant at the 5% level, because the interval does not embrace a relative risk of one.
- Second, the observed data are consistent with as much as a 30% reduction in relative risk or as little as a 14% reduction in risk.

Similarly, the last row of the table shows that statistically significant reductions in the overall death rate were recorded: a relative risk of 0.84 with a confidence interval running from 0.75 to 0.95. Thus, the true reduction in deaths may be as much as a quarter or it could be only as little as 5%; however, we are 95% certain that the overall death rate is reduced in the ramipril group.

Finally, exploring the data presented in the middle row shows an example of how a confidence interval can demonstrate non-significance. There were a few more deaths from non-cardiovascular causes in the ramipril group (200) compared with the placebo group (192). Because of this, the relative risk is calculated to be 1.03 – showing a slight increase in risk in the ramipril group. However, the confidence interval is seen to capture the value of no effect (relative risk = 1), running as it does from 0.85 to 1.26. The observed difference is thus non-significant; the true value could be anything from a 15% reduction in non-cardiovascular deaths for ramipril to a 26% increase in these deaths. Not only do we know that the result is not significant, but we can also see how large or small a true difference might plausibly be, given these data.

significant findings will be spurious – arising simply from chance. Thus, we may be misled by chance into believing in something that is not real – technically, this is called a ‘**type I error**’.

It is a frustrating but unavoidable feature of statistical significance (whether assessed using confidence intervals or p-values) that around

one in 20 will mislead. Yet we cannot know which of any given set of comparisons is doing the misleading. This observation cautions against generating too many statistical comparisons: the more comparisons made in any given study, the greater the chance that at least some of them will be spurious findings. Thus, clinical trials which

show significance in only one or two subgroups are unconvincing – such significance may be deceptive. Unless particular subgroup analyses have been specified in advance, differences other than for the primary endpoint for the whole group should be viewed with suspicion.

Statistical significance and clinical significance

Statistical significance is also sometimes misinterpreted as signifying an important result: this is a second important pitfall in interpretation. Significance testing simply asks whether the data produced in a study are compatible with the notion of no difference between the new and control interventions. Rejecting equivalence of the two interventions does not necessarily mean that we accept that there is an important difference between them. A large study may identify as statistically significant a fairly small difference. It is then quite a separate judgement to assess the clinical significance of this difference. In assessing the importance of significant results, it is the size of the effect – not just the size of the significance – that matters.

Getting it wrong again: failing to find real effects

A further error that we may make is to conclude from a non-significant finding that there is no effect, when in fact there is a real effect – this is called a **'type II error'**. Equating non-significance with 'no effect' is a common misconception. A non-significant confidence interval simply tells us that the observed difference is consistent with there being no true difference between the two groups. Thus, we are unable to reject this possibility. This is where confidence intervals are much more helpful than simple p-values: the observed difference will also be compatible with a range of other effect sizes as described by the confidence interval.⁸ We are unable to reject these possibilities and must then assess whether some of them (usually the upper and lower limits of the confidence interval) might be important. Just because we have not found a significant treatment effect, it does not mean that there is no treatment effect to be found.¹¹ The

crucial question is: how carefully have we interpreted the findings?

Extrapolating beyond the trial

For all the complexity of understanding bias and chance in the interpretation of the findings from clinical trials, another important consideration should not be forgotten. The findings from any given study relate to the patients included in that study. Even if an effect is assessed as probably real and large enough to be clinically important, a further question remains: how well are the findings applicable to other groups of patients, and do they particularise to a given individual?¹² Neither confidence intervals nor p-values are much help with this judgement. Assessment of this **external validity** is made based on the patients' characteristics and on the setting and the conduct of the trial.

Summary

Confidence intervals and p-values take as their starting point the results observed in a study. Crucially, we must check first that this is an unbiased study. The question that confidence intervals then answer is: what is the range of real effects that is compatible with these data? The confidence interval is just such a range, which 95% of the time will contain the true value of the main measure of effect (relative risk reduction, absolute risk reduction, NNT or whatever; Table 1).

This allows us to do two things. First, if the confidence interval embraces the value of no effect (for example, no difference between two treatments as shown by a relative risk equal to one or an absolute difference equal to zero), then the findings are non-significant. If the confidence interval does not embrace the value of no difference, then the findings are statistically significant. Thus, confidence intervals provide the same information as a p-value. But more than this: the upper and lower extremities of the confidence interval also tell us how large or small the real effect might be and yet still give us the observed findings by chance. This additional information is very helpful in allowing us to interpret both borderline significance and non-significance. Confidence intervals from large studies tend to be quite narrow in width, showing the precision with which the study is

able to estimate the size of any real effect. In contrast, confidence intervals from smaller studies are usually wide, showing that the findings are compatible with a wide range of effect sizes.

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What are

confidence intervals and p-values?

First edition published 2003

Author: Huw TO Davies

This publication, along with the others in the series, is available on the internet at www.whatisseries.co.uk

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Supported by *sanofi-aventis*

Cigar and pipe smoking and cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC).

[McCormack VA](#), [Agudo A](#), [Dahm CC](#), [Overvad K](#), [Olsen A](#), [Tjønneland A](#), [Kaaks R](#), [Boeing H](#), [Manjer J](#), [Almquist M](#), [Hallmans G](#), [Johansson I](#), [Chirlaque MD](#), [Barricarte A](#), [Dorransoro M](#), [Rodriguez L](#), [Redondo ML](#), [Khaw KT](#), [Wareham N](#), [Allen N](#), [Key T](#), [Riboli E](#), [Boffetta P](#).

Source

International Agency for Research on Cancer, Lyon, France.

Abstract

The carcinogenicity of cigar and pipe smoking is established but the effect of detailed smoking characteristics is less well defined. We examined the effects on cancer incidence of exclusive cigar and pipe smoking, and in combination with cigarettes, among 102,395 men from Denmark, Germany, Spain, Sweden and the United Kingdom in the EPIC cohort. Hazard ratios (HR) and their 95% confidence intervals (CI) for cancer during a median 9-year follow-up from ages 35 to 70 years were estimated using proportional hazards models. Compared to never smokers, HR of cancers of lung, upper aerodigestive tract and bladder combined was 2.2 (95% CI: 1.3, 3.8) for exclusive cigar smokers (16 cases), 3.0 (2.1, 4.5) for exclusive pipe smokers (33 cases) and 5.3 (4.4, 6.4) for exclusive cigarette smokers (1,069 cases). For each smoking type, effects were stronger in current smokers than in ex-smokers and in inhalers than in non-inhalers. Ever smokers of both cigarettes and cigars [HR 5.7 (4.4, 7.3), 120 cases] and cigarettes and pipes [5.1 (4.1, 6.4), 247 cases] had as high a raised risk as had exclusive cigarette smokers. In these smokers, the magnitude of the raised risk was smaller if they had switched to cigars or pipes only (i.e., quit cigarettes) and had not compensated with greater smoking intensity. Cigar and pipe smoking is not a safe alternative to cigarette smoking. The lower cancer risk of cigar and pipe smokers as compared to cigarette smokers is explained by lesser degree of inhalation and lower smoking intensity.

Cigar, pipe, and cigarette smoking and bladder cancer risk in European men

A. Pitard¹, P. Brennan¹, J. Clavel², E. Greiser³, G. Lopez-Abente⁴, J. Chang-Claude⁵, J. Wahrendorf⁵, C. Serra⁶, M. Kogevinas⁷ & P. Boffetta^{1,*}

¹Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69008 Lyon, France; Ph.: +33-4-72738441; Fax: +33-4-72738342; E-mail: boffetta@iarc.fr; ²Unit 170, National Institute of Health and Medical Research (INSERM), Villejuif, France; ³Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany; ⁴Unit of Cancer Epidemiology, National Centre for Epidemiology, Madrid, Spain; ⁵German Cancer Research Centre, Heidelberg, Germany; ⁶Center for Studies, Medical Programs and Services, Parc Tauli Foundation, Sadabell, Spain; ⁷Municipal Institute of Medical Investigation, Barcelona, Spain (*Author for correspondence)

Received 7 August 2000; accepted in revised form 14 February 2001

Key words: bladder neoplasms, cigar, cigarettes, epidemiology, pipe.

Abstract

Objective: Estimating the risk of bladder cancer from cigar and pipe smoking is complicated by a small number of non-cigarette smokers included in most relevant studies.

Methods: We undertook a pooled analysis of the data on men from six published case-control studies from Denmark, France, Germany, and Spain, to assess the association between pipe and cigar smoking and bladder cancer, and to compare it with the risk from cigarette smoking. Complete history of tobacco smoking was ascertained separately for cigarettes, cigars, and pipe. Odds ratios (ORs) were estimated after adjusting for age, study, and employment in high-risk occupations.

Results: The pooled data set comprised 2279 cases and 5268 controls, of whom 88 cases and 253 controls smoked only cigars or pipe. The OR for pure cigarette smoking was 3.5 (95% confidence interval [CI] 2.9–4.2), that for pure pipe smoking was 1.9 (95% CI 1.2–3.1) and that for pure cigar smoking was 2.3 (95% CI 1.6–3.5). The increase in the OR of bladder cancer that was observed with duration of smoking was non-significantly lower for cigars than for cigarettes.

Conclusion: Our results suggest that smoking of cigars and pipe is carcinogenic to the urinary bladder, although the potency might be lower than for cigarettes.

Introduction

The causal association between cigarette smoking and bladder cancer risk is well established [1, 2]. However, information on a carcinogenic effect of other tobacco products on the bladder is limited and conflicting. Indeed, most relevant epidemiological studies include relatively small numbers of persons who are exclusively pipe or cigar smokers, and only a few studies include a sufficiently large number of pure cigar and pipe smokers to allow for quantitative analysis [3–9].

In a large study from the United States, pure pipe smokers were estimated to have an odds ratio (OR) of 1.2 (95% confidence interval [CI] 0.75–2.0) and

pure cigar smokers were estimated to have an OR of 1.3 (95% CI 0.92–1.9) [5]. A higher relative risk was observed for those who inhaled pipe smoke deeply (OR 3.1, 95% CI 1.3–7.5). In a further analysis of a subset of data from the same study, an increased risk of bladder cancer (OR 2.5, CI 1.0–6.0) was seen for pure cigar smokers, but no elevated risk was observed for pipe smokers [6]. Morrison et al. [4] conducted a large international case-control study in Boston (USA), Manchester (UK), and Nagoya (Japan). They found that, among men from Manchester who had never smoked cigarettes, the relative risk of bladder cancer associated with ever smoking a pipe was 3.9 (95% CI 1.3–11.8). In the remaining studies [3, 7–9], cigar and

[Free Article](#)

Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium

[Michael B. Cook](#), [Farin Kamangar](#), [David C. Whiteman](#), [Neal D. Freedman](#), [Marilie D. Gammon](#), [Leslie Bernstein](#), [Linda M. Brown](#), [Harvey A. Risch](#), [Weimin Ye](#), [Linda Sharp](#), [Nirmala Pandeya](#), [Penelope M. Webb](#), [Anna H. Wu](#), [Mary H. Ward](#), [Carol Giffen](#), [Alan G. Casson](#), [Christian C. Abnet](#), [Liam J. Murray](#), [Douglas A. Corley](#), [Olof Nyrén](#), [Thomas L. Vaughan](#), and [Wong-Ho Chow](#)

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This article has been [cited by](#) other articles in PMC.

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Abstract

Background

Previous studies that showed an association between smoking and adenocarcinomas of the esophagus and esophagogastric junction were limited in their ability to assess differences by tumor site, sex, dose–response, and duration of cigarette smoking cessation.

Methods

We used primary data from 10 population-based case–control studies and two cohort studies from the Barrett’s Esophagus and Esophageal Adenocarcinoma Consortium. Analyses were restricted to white non-Hispanic men and women. Patients were classified as having esophageal adenocarcinoma (n = 1540), esophagogastric junctional adenocarcinoma (n = 1450), or a combination of both (all adenocarcinoma; n = 2990). Control subjects (n = 9453) were population based. Associations between pack-years of cigarette smoking and risks of adenocarcinomas were assessed, as well as their potential modification by sex and duration of smoking cessation. Study-specific odds ratios (ORs) estimated using multivariable logistic regression models, adjusted for age, sex, body mass index, education, and gastroesophageal reflux, were pooled using a meta-analytic methodology to generate summary odds ratios. All statistical tests were two-sided.

Results

The summary odds ratios demonstrated strong associations between cigarette smoking and esophageal adenocarcinoma (OR = 1.96, 95% confidence interval [CI] = 1.64 to 2.34), esophagogastric junctional adenocarcinoma (OR = 2.18, 95% CI = 1.84 to 2.58), and all adenocarcinoma (OR = 2.08, 95% CI = 1.83 to 2.37). In addition, there was a strong dose–response association between pack-years of cigarette smoking and each outcome ($P < .001$). Compared with current smokers, longer smoking cessation was associated with a decreased risk of all adenocarcinoma after adjusting for pack-years (<10 years of smoking cessation: OR = 0.82, 95% CI = 0.60 to 1.13; and ≥ 10 years of smoking cessation: OR = 0.71, 95% CI = 0.56 to 0.89). Sex-specific summary odds ratios were similar.

Conclusions

Cigarette smoking is associated with increased risks of adenocarcinomas of the esophagus and esophagogastric junction in white men and women; compared with current smoking, smoking cessation was associated with reduced risks.

From: (b) (6)
To: [VHA CO CLCW SME](#)
Subject: CLCW: Article on the temporality of post benzene leukemia
Date: Thursday, October 15, 2015 12:38:27 PM
Attachments: [Time and benzene and leukemia.pdf](#)

From: (b) (6)
Sent: Friday, September 11, 2015 3:15 AM
To: (b) (6)
Cc: (b) (6)
Subject: [EXTERNAL] Article on the temporality of post benzene leukemia

Hi (b) (6),

I don't know if everyone already has this article, but I searched for something regarding this topic and finally found exactly what I was looking for. The case I was working on was at CL for < 2 years and smoked for 17 years after leaving the service. He was then diagnosed with AML 57 years after leaving CL. I was determined to find something that talked about latency, but really had to search. I thought I would offer it to the others.

(b) (6)

(b) (6)

From: (b) (6)
To: [VHA CO CLCW SME](#)
Subject: CLCW: TCE and RCC re CLCW
Date: Tuesday, February 17, 2015 12:31:22 PM
Attachments: [EAS](#)

Submitted by (b) (6) :

Please find attached a copy of the pages from the text book: Occupational Cancers, published in 2014 for RCC and TCE reviewing 20 studies between 1988-2010. The large size of the text book did not lend itself well to copying/scanning.

[J Occup Environ Med](#). 2011 Sep;53(9):992-1007. doi: 10.1097/JOM.0b013e31822e0940.

Cancer mortality among aircraft manufacturing workers: an extended follow-up.

[Lipworth L](#), [Sonderman JS](#), [Mumma MT](#), [Tarone RE](#), [Marano DE](#), [Boice JD Jr](#), [McLaughlin JK](#).

Source: International Epidemiology Institute, Rockville, MD 20850, USA. loren@iei.us

Abstract

OBJECTIVE:

Extended cancer follow-up among 77,943 aircraft workers.

METHODS:

Comprehensive exposure information enabled detailed classification of trichloroethylene (TCE), perchloroethylene (PCE), mixed solvents, and chromates exposure among these workers.

RESULTS:

Exposure to TCE, PCE, mixed solvents or chromates was not associated with increased cancer risk overall or for most cancer sites. Elevated rates compared with the general population were seen for non-Hodgkin lymphoma for PCE exposure, and colon and testicular cancers and multiple myeloma for mixed solvents exposure. Internal cohort analyses, however, showed no significant trends of increasing risk for these cancers with increasing years of exposure to TCE, PCE or mixed solvents.

CONCLUSION:

This large, long-term cohort study with comprehensive exposure assessment found no consistent evidence of increased cancer risk overall or by site among aircraft workers, including those with long-term exposure to TCE, PCE, and mixed solvents.

(C)2011The American College of Occupational and Environmental Medicine

Article link: [http://ovidsp.tx.ovid.com/sp-](http://ovidsp.tx.ovid.com/sp-3.8.0b/ovidweb.cgi?&S=FHGHPKOOMDDGOBDNCOKIDIBDNMHAA00&Link+Set=S.sh.18.19.23.27%7c8%7csl_10)

[3.8.0b/ovidweb.cgi?&S=FHGHPKOOMDDGOBDNCOKIDIBDNMHAA00&Link+Set=S.sh.18.19.23.27%7c8%7csl_10](http://ovidsp.tx.ovid.com/sp-3.8.0b/ovidweb.cgi?&S=FHGHPKOOMDDGOBDNCOKIDIBDNMHAA00&Link+Set=S.sh.18.19.23.27%7c8%7csl_10)



Dear Registrant,

On March 15, 2013 the Agency for Toxic Substances and Disease Registry (ATSDR) released its "Chapter A: Summary and Findings" water modeling report for the Hadnot Point and Holcomb Boulevard Water Treatment Plants and Vicinities for Marine Corps Base Camp Lejeune, N.C.

(<http://www.atsdr.cdc.gov/sites/lejeune/hadnotpoint.html>). You will receive a hard copy of the ATSDR fact sheet and other information in the mail in the coming weeks.

This report provides ATSDR's assessment of past exposures to a class of chemicals known as "volatile organic compounds" (VOCs) in the drinking water distributed by these two Camp Lejeune water treatment systems. These VOCs were commonly used as solvents for cleaning machinery and weapons, for dry cleaning, and some are found in fuels.

ATSDR's water modeling estimates that the first month any VOC exceeded the current Environmental Protection Agency (EPA) regulatory standards in drinking water in the Hadnot Point system was August 1953, and at least one VOC exceeded the current standard in Hadnot Point drinking water from August 1953 through January 1985.

This release marks a major milestone towards the completion of scientific efforts pertaining to this issue and another step in ongoing efforts to provide comprehensive science-based answers to the health questions that have been raised. ATSDR will use these results and the results of a similar water model developed for the Tarawa Terrace area in 2007 to estimate chemical exposures for several of their on-going health studies.

Since 1991, the Marine Corps has supported scientific and public health organizations that are studying these issues. We continue to support these initiatives and are working diligently to identify and notify individuals who, in the past, may have been exposed to the chemicals in drinking water. For more information about these efforts, or to update your contact information, please see: <http://www.marines.mil/clwater/>, call (877) 261-9782 or e-mail at clwater@usmc.mil.

For the complete report and for information about studies being conducted by

ATSDR, visit <http://www.atsdr.cdc.gov/sites/lejeune/> or call (800) 232-4636.

To contact Veterans Affairs to learn more about the health care benefits, please visit <http://www.publichealth.va.gov/exposures/camp-lejeune/> or call (877) 222-8387 (Healthcare) or (800) 827-1000 (Benefits).

Sincerely,
The Camp Lejeune Historic Drinking Water Program



Copyright 2012. U.S. Marine Corps. All Rights Reserved.

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: Camp Lejeune studies and updates
Date: Saturday, December 07, 2013 12:17:37 PM

Hi, All

updates about Camp Lejeune Studies were posted on Dec 5, 2013 re: adverse pregnancy outcomes (birth defects and childhood cancers) and male breast cancer

<http://www.atsdr.cdc.gov/sites/lejeune/activities.html>

Also from the Associated Press is the following:

“RALEIGH, N.C. (AP) — A long-awaited study by the U.S. Centers for Disease Control and Prevention confirms a link between tainted tap water at a U.S. Marine Corps base in North Carolina and increased risk of serious birth defects and childhood cancers.

The study released late Thursday by the CDC's Agency for Toxic Substances & Disease Registry surveyed the parents of 12,598 children born at Camp Lejeune between 1968 and 1985, the year drinking-water wells contaminated with chemicals from a leaky fuel depot and a dry cleaner were closed.

The study concludes that babies born to mothers who drank the tap water while pregnant were four times more likely than normal to have such serious birth defects as spinal bifida. Babies whose mothers were exposed also had an elevated risk of such childhood cancers as leukemia”

Keep in contact and Best to all during the Holiday season!

(b) (6)

(b) (6), Syracuse VAMC)

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#), [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Source

University of Montreal Hospital Research Center, Montreal, Quebec, Canada.

Abstract

OBJECTIVE:

To evaluate the association between exposure to chlorinated solvents and cancer.

METHODS:

We conducted a case-control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer.

RESULTS:

The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS:

There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma

From: (b) (6)
To: (b) (6)
Subject: brain cancer article
Date: Thursday, February 19, 2015 3:46:13 PM
Attachments: [EAS](#)

Looks like we need a brain cancer category.

(b) (6)

*Compensation & Pension
Environmental Health Clinician
DMA Clinical Advisory Board
Ann Arbor VAMC*

Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors.

[Salehi F](#), [Turner MC](#), [Phillips KP](#), [Wigle DT](#), [Krewski D](#), [Aronson KJ](#).

Source

McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Canada.

Abstract

Breast cancer is the most frequently diagnosed cancer among Canadian women, accounting for about 30% of all new cancer cases each year. Although the incidence of breast cancer has increased over the past 50 years, the cause of this rise is unknown. Risk factors for breast cancer may be classified into four broad categories: (1) genetic/familial, (2) reproductive/hormonal, (3) lifestyle, and (4) environmental. Established risk factors for breast cancer include older age, later age at first full-term pregnancy, no full-term pregnancies, postmenopausal obesity, and genetic factors. However, these known risk factors cannot account for the majority of cases. In the early 1990s, it was suggested that exposure to some environmental chemicals such as organochlorine compounds may play a causal role in the etiology of breast cancer through estrogen-related pathways. The relationship between organochlorines and breast cancer risk has been studied extensively in the past decade and more, and at this point there is no clear evidence to support a causal role of most organochlorine pesticides in the etiology of human breast cancer, but more evidence is needed to assess risk associated with polychlorinated biphenyls (PCBs). Future studies need to consider the combined effects of exposures, concentrate on vulnerable groups such as those with higher levels of exposure, only consider exposures occurring during the most etiologically relevant time periods, and more thoroughly consider gene-environment interactions.

Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors.

[Salehi F](#), [Turner MC](#), [Phillips KP](#), [Wigle DT](#), [Krewski D](#), [Aronson KJ](#).

Source

McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Canada.

Abstract

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[CA Cancer J Clin](#). 2002 Sep-Oct;52(5):301-9.

Organochlorines and breast cancer risk.

[Calle EE](#), [Frumkin H](#), [Henley SJ](#), [Savitz DA](#), [Thun MJ](#).

Source

American Cancer Society, Atlanta, GA, USA.

Abstract

Organochlorines are a diverse group of synthetic chemicals that include polychlorinated biphenyls (PCBs), dioxins, and organochlorine pesticides such as dichlorodiphenyl-

trichloroethane (DDT), lindane, and hexachlorobenzene. Although use of DDT and PCBs has been banned in the United States since the 1970s, some organochlorine compounds have accumulated and persisted within the environment. As a result, measurable amounts can still be found in human tissue. Because some organochlorine compounds act as estrogen agonists or antagonists within in vitro and experimental animal systems, a possible association of breast cancer risk with organochlorine exposure has been hypothesized and investigated. Although a few studies support this hypothesis, the vast majority of epidemiological studies do not. While some of these compounds may have other adverse environmental or health effects, organochlorine exposure is not believed to be causally related to breast cancer. Women concerned about possible organochlorine exposure can be reassured that available evidence does not suggest an association between these chemicals and breast cancer.

[Occup Environ Med.](#) 2010 Dec;67(12):837-44. doi: 10.1136/oem.2009.052175. Epub 2010 Aug 25.

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.

[Villeneuve S](#), [Cyr D](#), [Lynge E](#), [Orsi L](#), [Sabroe S](#), [Merletti F](#), [Gorini G](#), [Morales-Suarez-Varela M](#), [Ahrens W](#), [Baumgardt-Elms C](#), [Kaerlev L](#), [Eriksson M](#), [Hardell L](#), [Févotte J](#), [Guénel P](#).

Source

CESP-INSERM (National Institute of Health and Medical Research), Villejuif, France.

Abstract

OBJECTIVES:

Male breast cancer is a rare disease of largely unknown aetiology. In addition to genetic and hormone-related risk factors, a large number of environmental chemicals are suspected of playing a role in breast cancer. The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men may help to identify mammary carcinogens in the environment.

METHODS:

Occupational risk factors for male breast cancer were investigated in a multi-centre case-control study conducted in eight European countries which included 104 cases and 1901 controls. Lifetime work history was obtained during in-person interviews. Occupational exposures to endocrine disrupting chemicals (alkylphenolic compounds, phthalates, polychlorinated biphenyls and dioxins) were assessed on a case-by-case basis using expert judgement.

RESULTS:

Male breast cancer incidence was particularly increased in motor vehicle mechanics (OR 2.1, 95% CI 1.0 to 4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers, and furniture manufacture workers. The OR for exposure to alkylphenolic compounds above the median was 3.8 (95% CI 1.5 to 9.5). This association persisted after adjustment for occupational exposures to other environmental oestrogens.

CONCLUSION:

These findings suggest that some environmental chemicals are possible mammary carcinogens. Petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer.

[Am J Ind Med.](#) 2011 Jul;54(7):499-509. doi: 10.1002/ajim.20952. Epub 2011 Apr 6.

Breast cancer risk by occupation and industry: analysis of the CECILE study, a population-based case-control study in France.

[Villeneuve S](#), [Févotte J](#), [Anger A](#), [Truong T](#), [Lamkarkach F](#), [Gaye O](#), [Kerbrat P](#), [Arveux P](#), [Miglianico L](#), [Imbernon E](#), [Guénel P](#).

Source

National Institute of Health and Medical Research, Center for Research in Epidemiology and Population Health, Environmental Epidemiology of Cancer, Villejuif, France.

Abstract

BACKGROUND:

It has been suggested that certain occupational exposures may play a role in breast cancer etiology. The recognition of high-risk occupations may give clues about potential mammary carcinogens in the work place.

METHODS:

We conducted a population-based case-control study in France including 1,230 breast cancer cases and 1,315 population controls with detailed information on lifetime work history. Odds ratios for women ever employed in an occupation or industry were adjusted for well-established risk factors for breast cancer.

RESULTS:

Adjusted odds ratios were marginally increased in some white-collar occupations, as well as in textile workers (2.4; 95% CI [0.9-6.0]), rubber and plastics product makers (1.8; 95% CI [0.9-3.5]), and in women employed for more than 10 years as nurses (1.4; 95% CI [0.9-2.1]) and as tailors/dressmakers (1.5; 95% CI [0.9-2.6]). The incidence of breast cancer was increased among women employed in the manufacture of chemicals, of non-metallic mineral products, and decreased among women in agriculture.

CONCLUSIONS:

These findings suggest a possible role of occupational exposures in breast cancer, including night-shift work, solvents and endocrine disrupting chemicals and require further studies with detailed assessment of occupational exposures.

[Rev Environ Health](#). 2008 Jan-Mar;23(1):1-37.

Environmental and occupational causes of cancer: new evidence 2005-2007.

[Clapp RW](#), [Jacobs MM](#), [Loechler EL](#).

Source

Boston University School of Public Health, Boston, MA 02118, USA. richard.clapp@gmail.com

Abstract

What do we currently know about the occupational and environmental causes of cancer? As of 2007, the International Agency for Research on Cancer (IARC) identified 415 known or suspected carcinogens. Cancer arises through an extremely complicated web of multiple causes, and we will likely never know the full range of agents or combinations of agents. We do know that preventing exposure to individual carcinogens prevents the disease. Declines in cancer rates—such as the drop in male lung cancer cases from the reduction in tobacco smoking or the drop in bladder cancer among cohorts of dye workers from the elimination of exposure to specific aromatic amines—provides evidence that preventing cancer is possible when we act on what we know. Although the overall age-adjusted cancer incidence rates in the United States among both men and women have declined in the last decade, the rates of several types of cancers are on the rise; some of which are linked to environmental and occupational exposures. This report chronicles the most recent epidemiologic evidence linking occupational and environmental exposures with cancer. Peer-reviewed scientific studies published from January 2005 to June 2007 were reviewed, supplementing our state-of-the-evidence report published in September 2005. Despite weaknesses in certain individual studies, we consider the evidence linking the increased risk of several types of cancer with specific exposures somewhat strengthened by recent publications, among them brain cancer from exposure to non-ionizing radiation, particularly radiofrequency fields emitted by mobile telephones; breast cancer from exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) before puberty; leukemia from exposure to 1,3-butadiene; lung cancer from exposure to air pollution; non-Hodgkin's lymphoma (NHL) from exposure to pesticides and solvents; and prostate cancer from exposure to pesticides, polyaromatic hydrocarbons (PAHs), and metal working fluids or mineral oils. In addition to NHL and prostate cancer, early findings from the National Institutes of Health Agricultural Health Study suggest that several additional cancers may be linked to a variety of pesticides. Our report also briefly describes the toxicological evidence related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans, namely exposures to bis-phenol A and epigenetic, trans-generational effects. To underscore the multi-factorial, multi-stage nature of cancer, we also present a technical description of cancer causation summarizing current knowledge in molecular biology. We argue for a new cancer prevention paradigm, one based on an understanding that cancer is ultimately caused by multiple interacting factors rather than a paradigm based on dubious attributable fractions. This new cancer prevention paradigm demands that we limit exposure to avoidable environmental and occupational carcinogens, in combination with additional important risk factors like diet and lifestyle. The research literature related to environmental and occupational causes of cancer is constantly growing, and future updates will be carried out in light of new biological understanding of the mechanisms and new methods for studying exposures in human populations. The current state of knowledge is sufficient to compel us to act on what we know. We repeat the call of ecologist Sandra Steingraber: "From the right to know and the duty to inquire flows the obligation to act."

[Environ Health Perspect.](#) 1998 Aug;106 Suppl 4:947-53.

Tetrachloroethylene-contaminated drinking water and the risk of breast cancer.

[Aschengrau A](#), [Paulu C](#), [Ozonoff D](#).

Source

Department of Epidemiology, University School of Public Health, Boston, Massachusetts, USA.
aaschen@bu.edu

Abstract

We conducted a population-based case-control study to evaluate the relationship between cases of breast cancer and exposure to tetrachloroethylene (PCE) from public drinking water (n = 258 cases and 686 controls). Women were exposed to PCE when it leached from the vinyl lining of water distribution pipes. The relative delivered dose was estimated using an algorithm that accounted for residential history, water flow, and pipe characteristics. Only small increases in breast cancer risk were seen among ever-exposed women either when latency was ignored or when 5 to 15 years of latency was considered. No or small increases were seen among highly exposed women either when latency was ignored or when 5 years of latency was considered. However, the adjusted odds ratios (ORs) were more increased for highly exposed women when 7 and 9 years of latency, respectively, were considered (OR 1.5 95% CI 0.5-4.7 and OR 2.3, 95% CI 0.6-8.8 for the 75th percentile, and OR 2.7, 95% CI 0.4-15.8 and OR 7.6, 95% CI 0.9-161.3 for the 90th percentile). The number of highly exposed women was too small for meaningful analysis when more years of latency were considered. Because firm conclusions from these data are limited, we recently undertook a new study with a large number of more recently diagnosed cases

Link to full article: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1533339>

Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: reanalysis of a case-control study using a modified exposure assessment

Lisa G Gallagher¹, Veronica M Vieira¹, David Ozonoff¹, Thomas F Webster¹ and Ann Aschengrau^{2*}

Abstract

Background: Tetrachloroethylene (PCE) is an important occupational chemical used in metal degreasing and drycleaning and a prevalent drinking water contaminant. Exposure often occurs with other chemicals but it occurred alone in a pattern that reduced the likelihood of confounding in a unique scenario on Cape Cod, Massachusetts. We previously found a small to moderate increased risk of breast cancer among women with the highest exposures using a simple exposure model. We have taken advantage of technical improvements in publically available software to incorporate a more sophisticated determination of water flow and direction to see if previous results were robust to more accurate exposure assessment.

Methods: The current analysis used PCE exposure estimates generated with the addition of water distribution modeling software (EPANET 2.0) to test model assumptions, compare exposure distributions to prior methods, and re-examine the risk of breast cancer. In addition, we applied data smoothing to examine nonlinear relationships between breast cancer and exposure. We also compared a set of measured PCE concentrations in water samples collected in 1980 to modeled estimates.

Results: Thirty-nine percent of individuals considered unexposed in prior epidemiological analyses were considered exposed using the current method, but mostly at low exposure levels. As a result, the exposure distribution was shifted downward resulting in a lower value for the 90th percentile, the definition of "high exposure" in prior analyses. The current analyses confirmed a modest increase in the risk of breast cancer for women with high PCE exposure levels defined by either the 90th percentile (adjusted ORs 1.0-1.5 for 0-19 year latency assumptions) or smoothing analysis cut point (adjusted ORs 1.3-2.0 for 0-15 year latency assumptions). Current exposure estimates had a higher correlation with PCE concentrations in water samples (Spearman correlation coefficient = 0.65, $p < 0.0001$) than estimates generated using the prior method (0.54, $p < 0.0001$).

Conclusions: The incorporation of sophisticated flow estimates in the exposure assessment method shifted the PCE exposure distribution downward, but did not meaningfully affect the exposure ranking of subjects or the strength of the association with the risk of breast cancer found in earlier analyses. Thus, the current analyses show a slightly elevated breast cancer risk for highly exposed women, with strengthened exposure assessment and minimization of misclassification by using the latest technology.

* Correspondence: aascheng@bu.edu

²Department of Epidemiology Boston University School of Public Health 715 Albany Street, Talbot 3 East, Boston, MA 021, USA

Full list of author information is available at the end of the article



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PCE in Water

Dose Model Appendix

The personal delivered dose model (PDD) sums the contribution of dose from inhalation, ingestion, and dermal absorption for each subject over all their residences. The subject interviews provided information on duration, frequency, temperature of baths and showers, water consumption, and residency time for all residences over a forty-year period. Inhalation doses from baths or showers were calculated as the product of concentration of PCE in the air, inhalation rate, duration, frequency, and residence time, and then summed for an overall inhalation dose. The PCE concentration in air was calculated using the two-resistance theory modeled by Little [11]. The Henry's law constant was calculated using the temperature-dependent values of vapor pressure, modeled using Antoine's equation. The overall mass transfer coefficient was calculated as the sum of two resistances in series, from the air film and water film. Similar to models used by McKone [10] and Little [17], the liquid and gas-phase mass transfer coefficients were modeled to be proportional to diffusivity, but the PDD model incorporated temperature-dependent diffusivity and viscosity.

Dose from ingestion was calculated as the product of PCE concentration in the water, the volume of water consumed, and the duration of tap water consumption. No ingestion dose was calculated for years that subjects reported bottled water use. Dose from dermal absorption was calculated using a nonsteady-state application of Fick's Law developed by the Environmental Protection Agency [12] and based on theoretical work by Cleek and Bunge [18]. The traditional steady-state approach for estimating the dermally absorbed dose of organic chemicals from water was revised by EPA because PCE does not reach steady state during the relatively short contact time of water on a subject's skin during bathing. The permeability coefficient for PCE was calculated using

the equations developed by Potts and Guy [19]. The personal delivered dose model was also developed for trichloroethylene (TCE) and validated using a series of shower experiments by Giardino and Andelman [20]. Sensitivity analyses revealed that the PDD model was most influenced by the initial PCE concentration and residency time and least influenced by temperature [21].

The surgeon general report on smoking and health 50 years later: breast cancer and the cost of increasing caution.

[Glantz SA](#), [Johnson KC](#).

Author information

Abstract

Despite the Surgeon General's strong track record and the rapidly expanding body of solid scientific work demonstrating that smoking caused a wide range of diseases, the decision making process for concluding "causality" in Surgeon General reports has become increasingly cautious and defensive. Whereas, the 1964 report did not conclude that smoking caused heart disease, it recommended that "from the public health viewpoint [one should] assume that the established association has causative meaning rather than to suspend judgment until no uncertainty remains," the de facto practice has become to do just the opposite. In particular, the 2004 report reached an affirmative negative conclusion that active smoking did not cause breast cancer and the 2006 report on passive smoking only found the link "suggestive." In contrast, in 2005 the California EPA found both active and passive smoking caused breast cancer in younger women. The evidence has continued to strengthen since 2005: there are now 12 large cohort studies that consistently demonstrate a dose-response relationship with smoking before first birth and increased breast cancer risk. The Surgeon General's increasing caution is preventing young women around the world from appreciating the risks that smoking and secondhand smoke pose for developing breast cancer. *Cancer Epidemiol Biomarkers Prev*; 23(1); 37-46. ©2014 AACR.

PMID:

24420985

[PubMed - in process]

Breast cancer risk after occupational solvent exposure: the influence of timing and setting.

[Ekenga CC](#)¹, [Parks CG](#)², [D'Aloisio AA](#)², [DeRoo LA](#)³, [Sandler DP](#)².

Author information

Abstract

Organic solvents are ubiquitous in occupational settings where they may contribute to risks for carcinogenesis. However, there is limited information on organic solvents as human breast carcinogens. We examined the relationship between occupational exposure to solvents and breast cancer in a prospective study of 47,661 women with an occupational history in the Sister Study cohort. Occupational solvent exposure was categorized using self-reported job-specific solvent use collected at baseline. Multivariable Cox regression analyses were used to assess breast cancer risk, adjusting for established breast cancer risk factors. A total of 1,798 women were diagnosed with breast cancer during follow-up, including 1,255 invasive cases. Overall the risk of invasive breast cancer was not associated with lifetime exposure to solvents [HR, 1.04; 95% confidence interval (CI), 0.88-1.24]. Parous women who worked with solvents before their first full-term birth had an increased risk of estrogen receptor-positive invasive breast cancer compared with women who never worked with solvents (HR, 1.39; 95% CI, 1.03-1.86). A significantly elevated risk for estrogen receptor-positive invasive breast cancer was associated with solvent exposure among clinical laboratory technologists and technicians (HR, 2.00; 95% CI, 1.07-3.73). Occupational exposure to solvents before first birth, a critical period of breast tissue differentiation, may result in increased vulnerability for breast cancer. Our findings suggest a need for future studies in this area to focus on exposure time windows and solvent types in different occupational settings.

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Male bladder cancer risk and occupational exposure according to a job-exposure matrix-a case-control study in British Columbia, Canada.

[Richardson K](#), [Band PR](#), [Astrakianakis G](#), [Le ND](#).

Source: Cancer Control Research, BC Cancer Research Centre, Vancouver, British Columbia, Canada.

Abstract

OBJECTIVES:

The authors investigated the risk of bladder cancer in association with exposure to over 12 000 occupational chemical agents, complex mixtures, and other substances (hereafter referred to as chemical agents).

METHODS: Adult males diagnosed with cancer between 1983 and 1990 in British Columbia, Canada, were surveyed. Detailed occupational histories and confounding information was provided by a self-administered questionnaire. Cancer controls were matched to bladder cancer cases, resulting in 1062 cases and 8057 controls for the analysis. An extensive United-States-based job-exposure matrix was applied to estimate cumulative exposure to occupational chemical agents. Odds ratios for bladder cancer due to exposure to chemical agents were estimated via conditional logistic regression analyses, adjusted for important confounders.

RESULTS: A significantly ($P < 0.05$) increased risk was detected for ever exposure to 635 chemical agents, and 341 chemical agents exhibited a significantly increasing dose-response relationship. Adjustment for multiple comparisons resulted in a subset of 29 chemical agents that continued to show significant results. A principal components analysis classified these 29 chemical agents into five independent groups, distinguished mainly by job. Exposures to these chemical agents were largely due to employment in the logging and construction industries and occupations involving motor vehicles. Consistent results were observed for bladder carcinogens reported in the literature.

CONCLUSIONS: This study suggests that several specific chemical agents were significantly associated with the risk of bladder cancer. The chemical agents were mainly derivatives or combustion products of fossil fuels. The results corroborate important findings from the literature and document a risk for specific chemical agents not previously reported.

Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies.

[Brennan P](#), [Bogillot O](#), [Cordier S](#), [Greiser E](#), [Schill W](#), [Vineis P](#), [Lopez-Abente G](#), [Tzonou A](#), [Chang-Claude J](#), [Bolm-Audorff U](#), [Jöckel KH](#), [Donato F](#), [Serra C](#), [Wahrendorf J](#), [Hours M](#), [T'Mannetje A](#), [Kogevinas M](#), [Boffetta P](#).

Source

International Agency for Research on Cancer, Lyon, France. Brennan@iarc.fr

Abstract

The primary risk factor for bladder cancer is cigarette smoking. Using a combined analysis of 11 case-control studies, we have accurately measured the relationship between cigarette smoking and bladder cancer in men. Available smoking information on 2,600 male bladder cancer cases and 5,524 male controls included duration of smoking habit, number of cigarettes smoked per day and time since cessation of smoking habit for ex-smokers. There was a linear increasing risk of bladder cancer with increasing duration of smoking, ranging from an odds ratio (OR) of 1.96 after 20 years of smoking (95% confidence interval [CI] 1.48-2.61) to 5.57 after 60 years (CI 4.18-7.44). A dose relationship was observed between number of cigarettes smoked per day and bladder cancer up to a threshold limit of 15-20 cigarettes per day, OR = 4.50 (CI 3.81-5.33), after which no increased risk was observed. An immediate decrease in risk of bladder cancer was observed for those who gave up smoking. This decrease was over 30% after 1-4 years, OR = 0.65 (0.53-0.79), and was over 60% after 25 years of cessation, OR = 0.37 (0.30-0.45). However, even after 25 years, the decrease in risk did not reach the level of the never-smokers, OR = 0.20 (0.17-0.24). The proportion of bladder cancer cases attributable to ever-smoking was 0.66 (0.61-0.70) for all men and 0.73 (0.66-0.79) for men younger than 60. These estimates are higher than previously calculated.

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Bladder cancer risk and pipes, cigars, and smokeless tobacco.

[Hartge P](#), [Hoover R](#), [Kantor A](#).

Abstract

Interview data from 2982 patients with bladder cancer and 5782 controls selected from the general population were used to assess the effects of non-cigarette tobacco use on bladder cancer risk. Compared to men who had never smoked, those who had smoked pipes but not cigars or cigarettes had a relative risk estimated at 1.23 (95% confidence interval [CI] = 0.75-2.00). Those who smoked cigars but not pipes or cigarettes were estimated to have a relative risk of 1.33 (95% CI = 0.92-1.94). Little evidence of dose response was observed. The excess relative risk to pipe smokers was limited to those who inhaled deeply.

Bladder cancer, a review of the environmental risk factors.

[Letašiová S¹](#), [Medve'ová A](#), [Šovčíková A](#), [Dušínská M](#), [Volkovová K](#), [Mosoiu C](#), [Bartonová A](#).

Author information

- ¹Institute of Biochemistry, Nutrition and Health Protection, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovak Republic. silvia.letasiova@gmail.com

Abstract

BACKGROUND:

Many epidemiological studies and reviews have been performed to identify the causes of bladder cancer. The aim of this review is to investigate the links between various environmental risk factors and cancer of the bladder.

METHODS:

A systematic literature search was performed using PubMed, Science Direct, Scopus, Scholar Google and Russian Google databases to identify reviews and epidemiological studies on bladder cancer risk factors associated with the environment published between 1998 and 2010. Only literature discussing human studies was considered.

RESULTS:

Smoking, mainly cigarette smoking, is a well known risk factor for various diseases, including bladder cancer. Another factor strongly associated with bladder cancer is exposure to arsenic in drinking water at concentrations higher than 300 µg/l. The most notable risk factor for development of bladder cancer is occupational exposure to aromatic amines (2-naphthylamine, 4-aminobiphenyl and benzidine) and 4,4'-methylenebis(2-chloroaniline), which can be found in the products of the chemical, dye and rubber industries as well as in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust. There are also data suggesting an effect from other types of smoking besides cigarettes (cigar, pipe, Egyptian waterpipe, smokeless tobacco and environmental tobacco smoking), and other sources of arsenic exposure such as air, food, occupational hazards, and tobacco. Other studies show that hairdressers and barbers with occupational exposure to hair dyes experience enhanced risk of bladder cancer. For example, a study related to personal use of hair dyes demonstrates an elevated bladder cancer risk for people who used permanent hair dyes at least once a month, for one year or longer.

CONCLUSION:

Smoking, in particular from cigarettes, exposure to arsenic in drinking water, and occupational exposure to aromatic amines and 4,4'-methylenebis(2-chloroaniline) are well known risk factors for various diseases including bladder cancer. Although the number of chemicals related to occupational exposure is still growing, it is worth noting that it may take several years or decades between exposure and the subsequent cancer.

Body mass index, height, and risk of lymphoid neoplasms in a large US cohort.

[Patel AV](#), [Diver WR](#), [Teras LR](#), [Birmann BM](#), [Gapstur SM](#).

Abstract

ABSTRACT Results from epidemiologic studies examining associations between body size and risk of non-Hodgkin lymphoma (NHL) are inconsistent and etiology may vary by histologic subtypes of disease. Using Cox proportional hazards regression, multivariable relative risks (RR) and 95% confidence intervals (CI) were computed for associations of body mass index (BMI) and height with NHL in the prospective American Cancer Society Cancer Prevention Study-II Nutrition Cohort. From 1992-2007, 2,074 incident NHL cases were identified among 152,423 men and women. Obese individuals (BMI $\geq 30\text{kg/m}^2$) had 23% higher incidence of NHL (95% CI 1.08-1.40) compared to normal weight (BMI 18.5- $<25\text{kg/m}^2$). Height was positively associated with NHL (RR=1.25, 95% CI 1.10-1.43, sex-specific quintile 5 vs. 1). BMI associations were strongest for diffuse large B-cell lymphoma; height was most strongly associated with chronic lymphocytic leukemia/small lymphocytic lymphoma and to a lesser extent with multiple myeloma. These findings provide further evidence that body size may play a role in the etiology of NHL, which is of public health importance given the rapid rise in obesity worldwide.

[Lancet](#). 2014 Aug 30;384(9945):755-65. doi: 10.1016/S0140-6736(14)60892-8. Epub 2014 Aug 13

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults.

[Bhaskaran K](#)¹, [Douglas I](#)², [Forbes H](#)², [dos-Santos-Silva I](#)², [Leon DA](#)², [Smeeth L](#)³.

Abstract

BACKGROUND: High body-mass index (BMI) predisposes to several site-specific cancers, but a large-scale systematic and detailed characterisation of patterns of risk across all common cancers adjusted for potential confounders has not previously been undertaken. We aimed to investigate the links between BMI and the most common site-specific cancers.

METHODS: With primary care data from individuals in the Clinical Practice Research Datalink with BMI data, we fitted Cox models to investigate associations between BMI and 22 of the most common cancers, adjusting for potential confounders. We fitted linear then non-linear (spline) models; investigated effect modification by sex, menopausal status, smoking, and age; and calculated population effects.

FINDINGS: 5·24 million individuals were included; 166,955 developed cancers of interest. BMI was associated with 17 of 22 cancers, but effects varied substantially by site. Each 5 kg/m² increase in BMI was roughly linearly associated with cancers of the uterus (hazard ratio [HR] 1·62, 99% CI 1·56-1·69; p<0·0001), gallbladder (1·31, 1·12-1·52; p<0·0001), kidney (1·25, 1·17-1·33; p<0·0001), cervix (1·10, 1·03-1·17; p=0·00035), thyroid (1·09, 1·00-1·19; p=0·0088), and leukaemia (1·09, 1·05-1·13; p≤0·0001). BMI was positively associated with liver (1·19, 1·12-1·27), colon (1·10, 1·07-1·13), ovarian (1·09, 1·04-1·14), and postmenopausal breast cancers (1·05, 1·03-1·07) overall (all p<0·0001), but these effects varied by underlying BMI or individual-level characteristics. We estimated inverse associations with prostate and premenopausal breast cancer risk, both overall (prostate 0·98, 0·95-1·00; premenopausal breast cancer 0·89, 0·86-0·92) and in never-smokers (prostate 0·96, 0·93-0·99; premenopausal breast cancer 0·89, 0·85-0·94). By contrast, for lung and oral cavity cancer, we observed no association in never smokers (lung 0·99, 0·93-1·05; oral cavity 1·07, 0·91-1·26): inverse associations overall were driven by current smokers and ex-smokers, probably because of residual confounding by smoking amount. Assuming causality, 41% of uterine and 10% or more of gallbladder, kidney, liver, and colon cancers could be attributable to excess weight. We estimated that a 1 kg/m² population-wide increase in BMI would result in 3790 additional annual UK patients developing one of the ten cancers positively associated with BMI.

INTERPRETATION:

BMI is associated with cancer risk, with substantial population-level effects. The heterogeneity in the effects suggests that different mechanisms are associated with different cancer sites and different patient subgroups.

Full Text

Benzene and multiple myeloma: appraisal of the scientific evidence

1. [Daniel E. Bergsagel](#),
2. [Otto Wong](#),
3. [P. Leif Bergsagel](#),
4. [Raymond Alexanian](#),
5. [Kenneth Anderson](#),
6. [Robert A. Kyle](#), and
7. [Gerhard K. Raabe](#)

Blood August 15, 1999 vol. 94 no. 4 1174-1182

The recent paper by Bergsagel et al raised questions of scope, content, and provenance.^{[1](#)} Goldstein and Shalat have addressed many of the issues of scope and content in their review, and a response to their letter has been received from the authors of the paper.^{[2](#)} We will not address those issues again. However, the issue of the article's provenance has not been addressed, and it is to that provenance we now turn.

When the Bergsagel review was published, one of us wrote to the editor to ask what the source of funding for this paper might have been. The editor responded at that time that since *Blood* did not have a policy that required financial disclosure, he had no information on the source or sources of funding for the paper. He recommended that we write the authors to obtain this information. Two letters to the authors went unanswered. Further inquiry to the editor provided welcome assurance that *Blood's* editorial policy had been changed [New policy follows the response to this letter—Ed]. *Blood* will require financial disclosure in the future. However, the policy could not fairly be applied retroactively. Because the provenance of the Bergsagel paper remained at issue, the editor invited a letter to encourage the authors to provide the financial support information.

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

[Abdul Khalade](#),¹ [Maritta S Jaakkola](#),² [Eero Pukkala](#),^{3,4} and [Jouni JK Jaakkola](#)^{1,5}

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Abstract

Background

A substantial number of epidemiologic studies have provided estimates of the relation between exposure to benzene at work and the risk of leukemia, but the results have been heterogeneous. To bridge this gap in knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of leukemia, including all types combined and the four main subgroups acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

Methods

A systematic literature review was carried out using two databases 'Medline' and 'Embase' from 1950 through to July 2009. We selected articles which provided information that can be used to estimate the relation between benzene exposure and cancer risk (effect size).

Results

In total 15 studies were identified in the search, providing 16 effect estimates for the main analysis. The summary effect size for any leukemia from the fixed-effects model was 1.40 (95% CI, 1.23-1.57), but the study-specific estimates were strongly heterogeneous ($I^2 = 56.5\%$, Q stat = 34.47, $p = 0.003$). The random-effects model yielded a summary- effect size estimate of 1.72 (95% CI, 1.37-2.17). Effect estimates from 9 studies were based on cumulative exposures. In these studies the risk of leukemia increased with a dose-response pattern with a summary-effect estimate of 1.64 (95% CI, 1.13-2.39) for low (< 40 ppm-years), 1.90 (95% CI, 1.26-2.89) for medium (40-99.9 ppm-years), and 2.62 (95% CI, 1.57-4.39) for high exposure category (> 100

ppm-years). In a meta-regression, the trend was statistically significant ($P = 0.015$). Use of cumulative exposure eliminated heterogeneity. The risk of AML also increased from low (1.94, 95% CI, 0.95-3.95), medium (2.32, 95% CI, 0.91-5.94) to high exposure category (3.20, 95% CI, 1.09-9.45), but the trend was not statistically significant.

Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

[Abdul Khalade](#),¹ [Maritta S Jaakkola](#),² [Eero Pukkala](#),^{3,4} and [Jouni JK Jaakkola](#)^{1,5}

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Abstract

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Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

[Go to:](#)

Background

Le Noire and Claude published in 1897 the first report on the possible role of occupational exposure to benzene in the development of leukemia [1]. Since then a substantial number of epidemiologic studies in different occupational groups have assessed benzene exposure and made attempts to quantify the magnitude of risk related to such exposure. In 2005, Schnatter and colleagues published a systematic review of the available 22 epidemiologic studies of the relation between benzene exposure and leukemia subtypes [2]. They concluded that there was consistent evidence that the risk of acute myeloid leukemia (AML) is related to benzene exposure with an indication of a dose-response pattern, and a suggestion for chronic lymphoid leukemia (CLL), whereas the data for chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL) are sparse. They did not present any quantitative assessment of these relations. To our knowledge there are no previous meta-analyses that have estimated the effect of exposure to benzene on the risk of leukemia taking into account the cumulative exposure from individual studies. To bridge this gap in current knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of any leukemia and the risks of main subtypes of leukemia in adults, including AML, ALL, CLL, and CML.

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Methods

Search strategy and inclusion criteria

We conducted a systematic literature review using Medline and Embase databases from 1950 through July 2009. The following search terms were applied: benzene [Benzene derivatives, Polycyclic aromatic hydrocarbons]; occupational exposure, [Inhalation exposure, Maximum allowable concentration, Threshold limit values] and cancer [Neoplasms]. The search command was further refined to include any leukemia combined [leukemia, lymphoid] and the subgroups of leukemia, including AML, CML, and CLL. The Newcastle-Ottawa-Scale (NOS) was used to

assess the quality of papers. The articles from the search were then screened according to the following *a priori* inclusion criteria:

- (1) Provides information that can be used to estimate the relation between benzene exposure and cancer risk (effect size) in terms of odds ratio (OR), relative risk (RR), standardized mortality ratio (SMR), standardized relative risk (SRR), cumulative incidence ratio (CIR), or standardized incidence rate ratio (SIR);
- (2) Original study;
- (3) Provides comparable measures of effect estimates and/or cumulative exposure to benzene
- (4) Is a cohort, case-control or cross-sectional study in design; and
- (5) Includes occupationally active adults as a study population.

The selection of studies was based on a clearly defined search strategy. In addition to the primary Medline and Embase searches, we identified references that were cited by the articles identified in the primary database searches. Many of these secondary references directly investigated the relation between benzene exposure and cancer risk with leukemia being the main cancer. Two observers independently checked the eligibility of the studies according to *a priori* set inclusion and exclusion criteria, and identified the most appropriate effect or prevalence estimates. There was little disagreement between the two observers and these were settled by discussion. Incompatibility of the exposure or outcome criteria with our preset criteria was the main reason for exclusion.

Duplicate reports of studies were rejected and the study with the longest follow-up period or the most recent study of the cohort were chosen. All studies providing sufficient information on the relation between work exposure to benzene and leukemia were included, irrespective of whether this question was their primary or secondary objective, as measuring benzene alone was very unlikely due to fact that other chemicals were often present in the workplace alongside. The references of all included and excluded studies were further screened to identify any relevant papers. The definitions of the outcomes were based on the codes of the International Classification of Diseases (ICD) Revision 10 as follows any leukemia (C91-95), acute lymphocytic leukemia (C91.0), chronic lymphocytic leukemia (C91.1), acute myeloid leukemia (C92.0) and chronic myeloid leukemia (C92.1). A total of 15 papers which provided 16 effect estimates for the risk of leukemia in relation to benzene exposure were selected. Of these three studies applied codes of ICD revision 8, ten studies used revision 9, one revision 8 onwards, and one revision 6-9. There were no studies reporting classifications based on ICD-10 although it was available for use from 1992.

Data extraction

Two co-authors (AK, JJ) independently examined the papers and identified and recorded the main characteristics of the study including: (1) author(s) with the year of publication; (2) study design; (3) size of study population; (4) study group; (5) geographical location; (6) time window

of exposure; (7) exposure assessment; (8) study outcome; (9) effect estimate for given exposure category; (10) study selection criteria; (11) comparability in terms of confounders accounted for in the studies, for example smoking, age, socio-economic status; (12) the outcome for cohort studies and the exposure ascertained for case-control studies; and (13) the overall quality of the based on (10), (11) and (12). We defined the categories for cumulative exposure on as low from > 0 to < 40 , medium from 40 to < 100 and high 100+ parts per million (ppm)-years. The two sets of data were then grouped together to identify any discrepancy in recording of the findings, and such discrepancies were then reviewed and re-assessed for the final recording.

Assessment of study quality

We applied the Newcastle-Ottawa Scale (NOS) to assess the quality of the specific studies. The NOS for cohort and case-control studies includes the following items: 1) representativeness of the exposed cohort/adequacy of case definition; 2) selection of the non-exposed cohort/representativeness of the cases; 3) ascertainment of exposure/selection of controls; 4) demonstration that outcome of interest was not present at start of study/definition of controls; 5) comparability of cohorts on the basis of the design or analysis/comparability of cases and controls on the basis of the design or analysis; 6) assessment of outcome/ascertainment of exposure; 7) sufficiency of follow-up for outcomes to occur/similarity of method of ascertainment for cases and controls; and 8) adequacy of follow-up of cohorts/non-response rate. A star can be awarded for good quality for each item (except 1-2 stars for item 5) resulting in a range of 0-9 stars, more stars indicating higher quality.

Statistical methods

We first calculated summary effect estimates for the four outcomes (Leuk, AML, CLL, CML) by using both the fixed-effects and random-effects models. The fixed-effects model applied the general variance-based method with inverse variances of individual study effect estimates as weights [3]. The random-effects model applied the method of DerSimonian and Laird [3]. The natural log of the effect estimates and its standard error were calculated from the effect estimates and confidence intervals (CI) presented in the articles. We ran the Stata version 10 for the fixed- and random-effects models by using the "meta" command. The Q statistics and subgroup analysis were then applied to address potential heterogeneity between study-specific effect estimates. Finally, we conducted a dose-response analysis in a meta-regression model of $\ln(\text{effect estimate})$ by average cumulative exposure in the exposure category.

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Results

Studies

The Medline and Embase search identified a total of 466 articles. We screened the abstracts, and excluded 287 as being clearly irrelevant or duplicates of the same study. The remaining 179 abstracts were then evaluated using *a priori* inclusion criteria (see Methods). A total of 14

articles met the selection criteria for inclusion and 165 were excluded. The reasons for exclusion were: no information on the relation of interest (n = 121) and/or no quantitative effect estimate or sufficient figures to calculate an effect estimate (n = 29) and/or duplicate publication of the same data (n = 7). Some studies provided no information on cumulative exposure to benzene (n = 8). The included articles cited additional 23 seemingly relevant articles of which one was included. The meta-analysis was based on 15 articles with 16 effect estimates summarized in Additional File [1](#): Table S1. Similar review produced 8 articles with 9 effect estimates for AML, 10 for CLL, 6 for CML and no articles for ALL. These fifteen studies were grouped according to the weighted average of the cumulative exposure. Additional file [2](#) lists the studies cited in the narrative systematic review by Schnatter et al. [[2](#)] but not included in the present meta-analysis.

Design characteristics

From the 15 included studies, 10 were published in 1996-2004, [[4-14](#)] and the remaining five were published more recently in 2005-2008 (Additional File [1](#):Table S1) [[15-19](#)]. A total of 12 studies were cohort studies, and the remaining three were case-control studies. Seven studies were carried out in Europe (United Kingdom, Netherlands Sweden, Norway, Italy), one in Canada, five in the United States of America, one in China, and one in Australia. Additional File [1](#): Table S1 shows the workplace settings where the benzene exposure took place.

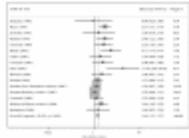
Exposure assessment and effect estimates

The exposure assessment of 9 studies was based on workplace exposure measurements and/or job exposure matrix. Three studies used work histories and/or benzene air concentrations. The remaining three studies defined exposure on the basis of employment in a given industry, and compared cancer mortality between the industry and general population. A total of 9 studies presented cumulative exposure.

Ten studies provided effect estimates in relative risks and odds ratios and five studies presented SMRs. SMRs were converted into relative risks to provide uniform estimates of the effect size (ES) for the meta-analysis. The effect estimates from the studies varied considerably from ES of 0.96 (95% CI, 0.20-4.67) to ES of 11.3 (95% CI, 2.85-45.1). Most studies presented effect estimates for several different cancer types, however only effect estimates for "any leukemia", AML, CLL and CML were extracted for this analysis.

Benzene exposure and the risk of any of leukemia

Additional File [1](#): Table S1 illustrates the study-specific effect estimates for any leukemia, as well as for the three leukemia subgroups used in the meta-analysis. Nine studies provided effect estimates based on cumulative exposure to benzene, which were categorized in to low, medium, and high exposure. The remaining five studies presented SMRs comparing mortality rates between exposed cohorts and general population. Figure [Figure11](#) shows a forest plot of all the study-specific effect estimates, the weights of the studies, and the summary effect estimate with the 95% confidence interval. Additional File [3](#): Table S3 presents the summary-effect estimates based on all 15 available studies (16 estimates), 9 studies with cumulative exposure categories, and 5 studies without quantitative exposure information.



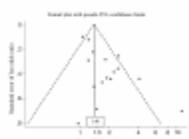
[Figure 1](#)

Forest plot showing the studies providing an estimate of the relation between exposure to benzene and the risk of any leukemia. The overall effect estimate is from the fixed-effects model.

In the fixed-effects model the summary effect size for benzene exposure was 1.40 (95% CI, 1.23-1.57), indicating a significantly increased risk of leukemia. However, both the I^2 index (56.5%) and Q statistics (34.47) revealed strong heterogeneity between the study-specific estimates (Additional File 3: Table S3). The random-effects model that allowed for heterogeneity yielded a summary ES of 1.72 (95% CI, 1.37-2.17). Additional File 3: Table S3 shows also summary-effect estimates for three levels of exposure, low (based on 8 studies), medium (6 studies), and high exposure (7 studies). Taking into account the average level of cumulative exposure in each study practically eliminated heterogeneity, so the variable exposure levels seemed to explain the heterogeneity observed in the overall estimate. The summary-effect estimates for low (1.64, 95% CI 1.13-2.39), medium (1.90, 95% CI 1.26-2.89), and high exposure (2.62, 95% CI 1.57-4.39) showed a clear dose-response pattern. The summary-effect estimate based on studies providing no dose information was slightly lower, 1.25 (95% CI 1.09-1.44).

To further elaborate the dose-response pattern we fitted a meta-regression model for $\ln(\text{effect estimate})$ by average cumulative exposure to benzene. There were several effect estimates for different contrasts: eight estimates for low vs. reference, six for medium vs. reference and seven for high vs. reference category. The meta-regression model showed a moderate, statistically significant association with the R-squared value of 37% and P value of < 0.05 .

The potential for publication bias was assessed by producing a funnel plot shown in Figure [Figure22](#). The vertical line indicates the summary-effect estimate from the fixed-effects model (1.40), and the corresponding pseudo 95% confidence limits converging as a function of the standard error (SE) of the effect estimate. The smaller studies with large SEs of $\ln \text{OR}$ seem to be scattered symmetrically around the summary-effect estimate, whereas the funnel plot shows substantial heterogeneity among the large studies with small SEs, with an imbalance toward large positive effect estimate. The pattern differs from a typical publication bias, in which the effect estimate from the small studies would be biased towards large positive values.



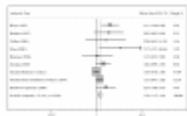
[Figure 2](#)

Funnel plot showing the effect estimates ($\ln \text{OR}$) by their standard errors ($\text{SE of } \ln \text{OR}$).

The vertical line indicates the summary effect estimate (1.40) from the fixed-effects model, and the dashed lines show pseudo 95% confidence limits for the summary ...

Benzene exposure and the risk of acute myeloid leukemia (AML)

The study-specific effect estimates for the relation between benzene exposure and the risk of AML appear in Additional File [1](#):Table S1. Additional File [3](#): Table S3 summarizes the results of the meta-analysis on AML. In the main analysis based on 9 articles, the fixed-effects model yielded a summary-effect estimate of 1.38 (95% CI, 1.15-1.64), and the study-specific effect estimates were homogeneous (I^2 index 51.4%, Q statistic of 16.46, P 0.036) (Figure [\(Figure3\).3](#)). Four studies provided information on dose, and the dose-specific effect estimates were homogeneous and presented a clear dose-response pattern (low: 1.94, 95% CI 0.95-3.95; medium 2.32, 95% CI 0.90-5.94; high: 3.20, 95% CI 1.09-9.45).



[Figure 3](#)

Forest plot showing the studies providing an estimate of the relation between exposure to benzene and the risk of acute myeloid leukemia. The summary effect estimate is from the fixed-effects model.

The meta-regression model for AML was based on four effect estimates for low vs. reference category, two for medium vs. reference and two for high vs. reference category. The model for the relation between cumulative exposure to benzene and the risk of AML showed no association (R-squared value of 3% and P value 0.813).

Benzene exposure and the risk of chronic myeloid leukemia (CML)

The summary-effect estimate for CML was 1.05 (95% CI, 0.83-1.34), and the study-specific estimates were homogeneous. There were no studies applying cumulative exposure. The Egger's statistics did not indicate any publication bias (P value 0.57).

Benzene exposure and the risk of chronic lymphocytic leukemia (CLL)

A total of 10 study-specific effect estimates yielded a summary-effect estimate of 1.31 (95% CI, 1.09-1.57). There was no indication of heterogeneity, and the random-effects model produced similar results (Additional File [3](#): Table S3). Six studies provided effect estimates based on cumulative exposure (dose). The summary-effect estimate for low exposure was 1.83 (95% CI 0.75-4.48), for medium exposure 1.67 (0.86-3.24), and for high exposure 3.50 (0.90-13.2), the latter was based on only one study available. There was no indication of publication bias (Egger's statistics: P value 0.06).

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Discussion

This systematic review and meta-analysis based on 15 available epidemiologic studies provides evidence of an association between benzene exposure at work and leukemia risk. The summary estimate from the fixed-effects model was 1.40 (95% CI 1.23-1.57), but the study-specific estimates were heterogeneous. Focusing on 9 studies that provided information on cumulative exposures and stratifying the effect estimates according to the magnitude of cumulative exposure eliminated the heterogeneity. The summary-effect estimate was 1.64 (1.13-2.39) for low, 1.90 (1.26-2.89) for medium, and 2.62 (1.57-4.39) for high exposure, showing evidence of a dose-response relation. The summary effect estimate for the studies which did not have dose information was lower 1.25 (1.09-1.44). Also the meta-regression model was consistent with a dose-response pattern. The results provided some evidence of an increased risk for AML and CLL. The meta-analysis indicated consistently a lack of association between benzene exposure and the risk of CML. There was not sufficient information on ALL.

The outcome assessment in all the specific studies was based on an ICD-diagnosis. Although there was a significant association between exposure to benzene and the broad category of any leukemia (ICD C91-95), there was substantial heterogeneity in the effects on specific leukemia ranging from a strong summary effect for AML to no effect for CML. Our results indicate that the use of the broad category of any leukemia underestimates the magnitude of the effect on AML. Although the summary-effect estimates for any leukemia, as well as for AML and CLL indicated an increased risk, the study-specific effect estimates presented strong heterogeneity.

We were able to retrieve some type of quantitative estimate for cumulative exposure to benzene from 9 studies. Additional File 1: Table S1 displays estimates of cumulative exposure for different exposure categories. Although exposure assessment varied between the studies, each study applied similar approaches to different levels of exposure. Use of exposure categories based on cumulative exposure reduced or practically eliminated this heterogeneity, suggesting that different amounts of benzene exposure in different studies explained the heterogeneity observed in the overall risk estimates. For example, for any leukemia the effect estimate for better quality studies (NOS 6-9) was 1.32 (95% CI 1.15-1.51), and for others (NOS 0-5) 1.79 (1.34-2.38). The summary-effect estimates for studies without dose information were presented mainly as standardized mortality ratios using external cancer mortality rates as the reference group. Their estimates were systematically lower than those from the studies providing data for dose-response analyses. A funnel plot analysis of studies on benzene exposure and leukemia risk did not show any suggestion of publication bias [20].

Several studies have been published since the most recent systematic reviews [2,21,22] on benzene and leukemia, and ours is to our knowledge the first meta-analysis on this topic.

In 1989, Lamm and colleagues published a risk assessment based on a large cohort study conducted by NIOSH (including 9 cases of leukemia), and compared their results with those of the other available large studies [21]. They concluded that AML can be caused by excessive benzene exposure, meaning a peak benzene exposure greater than 20 ppm or an estimated cumulative benzene exposure greater than 250 ppm-years. This finding was consistent across the reviewed studies except a Chinese study by Wong. This early review reported no consistent evidence for ALL, CML, or CLL in relation to benzene exposure. In 1997, Savitz and Andrews reviewed epidemiologic research on lymphatic and hematopoietic cancers. They identified 14

studies, three community-based and 11 industry-based, on benzene and total leukemia and 16 studies, nine community-based and seven industry-based, on benzene and specific histologic types of leukemia [22]. However, they did not conduct any meta-analyses. They concluded that the "epidemiologic evidence linking benzene to leukemia in the aggregate, as well as acute and chronic lymphocytic and myeloid leukemia, is no less persuasive than that for AML alone", but did not suggest any quantitative estimates.

In the most recent systematic review published in 2005, Schnatter and colleagues assessed 22 industry-based cohort and case-control studies. A high and significant AML risk was reported across study designs, especially in more highly exposed workers of rubber, shoe, and paint industry. Results on CLL were controversial with an increased risk in nested case-control studies, but with no increase in cohort studies. Data for ALL and CML were deemed sparse and inconclusive [2].

The results of our systematic review both strengthen the evidence of the effect of benzene exposure on leukemia risk, and provide quantitative estimates of effect size. We detected substantial heterogeneity between the different types of leukemia, which reduces the relevance of the overall estimate. Thus we also assessed the leukemia-specific effect sizes. The risk of AML was estimated to be two-fold for cumulative exposure below 40 ppm-years, 2.3-fold for exposures from 40 ppm-years to below 100 ppm-years, and over 3-fold for exposures 100 ppm-years and above. These estimates indicated an increased risk related to substantially lower dose than that suggested by Lamm and colleagues [21]. As a new contribution, our results also show that the available evidence is consistent with no effect on CML. Our results strengthen the evidence that benzene exposure also increases the risk of CLL, suggesting a dose-response pattern, although the effect estimate for the highest exposure category is based on a single study. Consistently with the previous reports, we found that there is no sufficient evidence to make any inference on the effects of benzene exposure to ALL.

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Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. The results showed some evidence of an increased risk for AML and CLL. The meta-analysis indicated consistently a lack of association between benzene exposure and the risk of CML. The evidence was insufficient to make any inference on the effects on ALL. For the purposes of clinical, occupational health, and policy implications, it is important to note that a significantly increased risk of any leukemia and AML was observed already in relation to the low benzene exposure and that the risk varied according to the type of leukemia.

In 1946, The American Conference of Governmental Industrial Hygienists set the first occupational exposure limit for benzene to 325 mg/m³ (100 ppm), and in 1963 the limit was reduced to 35 ppm. Currently most European and North American countries have harmonised the limit to 1.63-3.25 mg/m³ (0.5-1 ppm) This recent figure was agreed within the European Union in 1997 and was adopted within standard setting committee [23].

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Abbreviations

ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; CIR: Cumulative incidence ratio; ICD: International Classification of Diseases; OR: Odds ratio; NOS: Newcastle-Ottawa Scale; RR: Relative risk; SIR: Standardized incidence rate ratio; SRR: Standardized relative rate; SMR: Standardized mortality ratio.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AK conducted the literature search, reviewed the articles, conducted the statistical analyses, and drafted the manuscript. MSJ and EP made substantial contributions to interpretation of data, and were involved in drafting the manuscript or revising it critically for important intellectual content. JJKJ conceived and designed the study, reviewed the articles, and supervised the work in all phases. All authors read and approved the final manuscript.

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Supplementary Material

Additional file 1:

Table S1. Design characteristics of studies included in the meta-analysis

[Click here for file](#) ^(162K, DOC)

Additional file 2:

Table S2. Studies not included and the reasons for exclusion

[Click here for file](#) ^(43K, DOC)

Additional file 3:

Table S3. Summary of effect size for the relation between benzene exposure and risk of leukaemia and dose-response analysis

[Click here for file](#) ^(102K, DOC)

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Acknowledgements

The first author was funded by a PhD scholarship and travel award from the Medical & Public Health School of the University of Birmingham, UK. Many thanks also go out to the Center for Environmental and Respiratory Health Research, Institute of Health Sciences University of Oulu Finland for use of their facilities while there.

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Annals of Oncology
Volume 24, Issue 2
Pp. 301-308.
Light alcohol drinking and cancer: a meta-analysis

V. Bagnardi
University of Milan-Bicocca,

Abstract

Background There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day).

Patients and methods We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010.

Results We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (CI) 1.06–1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09–1.56) and female breast cancer (RR = 1.05; 95% CI 1.02–1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

Conclusions Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast.

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J Periodontol. 2005 Mar;76(3):406-10.

Is periodontitis associated with oral neoplasms?

Tezal M1, Grossi SG, Genco RJ.

Author information

Abstract

BACKGROUND:

Infections have been suggested in the etiology of oral cancer. This study was carried out to evaluate the effect of periodontal disease on oral soft tissue lesions.

METHODS:

A total of 13,798 subjects aged 20 years and older with at least six natural teeth and who participated in the Third National Health and Nutrition Examination Survey (NHANES III) constituted the study population. Severity of periodontal disease was represented by clinical attachment loss (CAL) and was dichotomized as $<$ or $=1.5$ mm versus >1.5 mm according to its distributions in the NHANES III population. Three separate dependent variables were employed: 1) tumor (non-specific); 2) precancerous lesions; and 3) any oral soft tissue lesion. The independent effect of CAL on those three dependent variables was assessed by weighted multiple logistic regression analyses adjusting for the effects of number of filled teeth, number of decayed teeth, presence of prosthesis, age, gender, race/ethnicity, education, tobacco, alcohol, occupational hazard, and interaction term "tobacco*occupational hazard." Odds ratios (OR) and their 95% confidence intervals (CI) were calculated.

RESULTS:

CAL was not related to the presence of any soft tissue lesion (OR = 1.09, 95% CI: 0.91 to 1.31), but was specifically related to the presence of tumor (OR = 4.57, 95% CI: 2.25 to 9.30) and precancerous lesions (OR = 1.55, 95% CI: 1.06 to 2.27).

CONCLUSION:

This study suggests associations between periodontal disease and the risk for precancerous lesions and tumors generating a hypothesis about a possible relationship between periodontal disease and oral neoplasms. Prospective or well-designed case-control studies with histologically confirmed incident oral cancer cases are necessary to confirm this relationship.

PMID: 15857075 [PubMed - indexed for MEDLINE]

(b) (6)

Compensation & Pension

Environmental Health Clinician

DMA Clinical Advisory Board
Ann Arbor VAMC

From: (b) (6)
To: (b) (6)
Subject: article
Date: Thursday, May 29, 2014 1:57:55 PM
Attachments: [EAS](#)

This is a good one

(b) (6)

*Compensation & Pension
Environmental Health Clinician
DMA Clinical Advisory Board
Ann Arbor VAMC*

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: Articles for CLCW library
Date: Tuesday, September 16, 2014 12:45:13 PM
Attachments: [EAS](#)

FYI

From: (b) (6)
Sent: Tuesday, September 16, 2014 12:43 PM
To: VHA CO CLCW SME
Subject: CLCW: Bove Article Abstracts

Good Afternoon,

Per the monthly call, I have included the abstracts for the two controversial Bove et al articles on Camp Lejeune. We will discuss these at the monthly call next week.

(b)

[Environ Health](#). 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.

Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

[Bove FJ](#)¹, [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

[Author information](#)

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at Camp Lejeune during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 Camp Pendleton workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune and Camp Pendleton workers and assess the effects of estimated cumulative contaminant exposures within the Camp Lejeune cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at Camp Lejeune. The confidence interval (CI) indicated precision of effect estimates.

RESULTS:

Compared to Camp Pendleton, Camp Lejeune workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the Camp Lejeune cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION:

The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the Camp Lejeune cohort died by end of follow-up, producing small numbers of ca

[Environ Health](#). 2014 Feb 19;13(1):10. doi: 10.1186/1476-069X-13-10.

Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

[Bove FJ¹](#), [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

[Author information](#)

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at Camp Lejeune or Camp Pendleton, California during this period. Camp Pendleton's drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune (N = 154,932) and Camp Pendleton (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the Camp Lejeune cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS:

There were 8,964 and 9,365 deaths respectively, in the Camp Lejeune and Camp Pendleton cohorts. Compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios

(HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the Camp Lejeune cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

CONCLUSION:

The study found elevated HRs at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposu

Attachments:

jama_259_15_037.pdf (687315 Bytes)

Good pasture syndrome & Solvent Exp.pdf (809930 Bytes)

Occupational Exposures in rare cancer.pdf (2181007 Bytes)

From: (b) (6)
To: (b) (6)
Subject: add to share point
Date: Wednesday, February 05, 2014 5:06:18 PM

Occup Environ Med. <<http://www.ncbi.nlm.nih.gov/pubmed/23723297>> 2013 Aug;70(8):591-9. doi: 10.1136/oemed-2012-101212. Epub 2013 May 30.

Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis.

Karami S <http://www.ncbi.nlm.nih.gov/pubmed?term=Karami%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Bassig B <http://www.ncbi.nlm.nih.gov/pubmed?term=Bassig%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Stewart PA <http://www.ncbi.nlm.nih.gov/pubmed?term=Stewart%20PA%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Lee KM <http://www.ncbi.nlm.nih.gov/pubmed?term=Lee%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Rothman N <http://www.ncbi.nlm.nih.gov/pubmed?term=Rothman%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Moore LE <http://www.ncbi.nlm.nih.gov/pubmed?term=Moore%20LE%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>, Lan Q <http://www.ncbi.nlm.nih.gov/pubmed?term=Lan%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=23723297>.

Author information <<http://www.ncbi.nlm.nih.gov/pubmed/23723297>>

- Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20852, USA.

Abstract

The carcinogenic potential of trichloroethylene (TCE) continues to generate much controversy, even after the US Environmental Protection Agency raised its classification to 'carcinogenic to humans'. We conducted a meta-analysis of published cohort and case-control studies exploring occupational TCE exposure in relation to five different lymphatic and haematopoietic cancers: non-Hodgkin's lymphoma (NHL, N=24), Hodgkin's lymphoma (HL, N=13), multiple myeloma (MM, N=11), leukaemia (N=12) and chronic/small lymphocytic leukaemia (CLL/SLL, N=7). Studies published between 1950 and 2011 were identified through a PubMed Medline search. All studies included in analyses were classified as those that assessed either occupational TCE exposure specifically ('TCE-exposure' studies) or a broader classification of all chlorinated solvents ('chlorinated solvent-exposure' studies). A significantly raised summary estimate for NHL was seen for all cohort and case-control 'TCE-exposure' studies combined (N=19; relative risk (RR)=1.32, 95% CI 1.14

to 1.54; I(2)=25.20; p-heterogeneity=0.12) and for cohort 'TCE-exposure' studies (N=10; RR=1.52, 95% CI 1.29 to 1.79; I(2)=7.09; p-heterogeneity=0.63). A non-significant but raised summary estimate was seen for NHL case-control 'TCE-exposure' studies. No significant association with NHL risk was detected overall for any 'chlorinated solvent-exposure' studies. Summary estimates for occupational TCE exposure were not associated with risk of HL, MM, leukaemia or CLL/SLL. Our updated meta-analysis of NHL, which incorporates new analytical results from three cohort and four case-control studies, supports an association between occupational TCE exposure and NHL.

PMID:

23723297

[PubMed - indexed for MEDLINE]

(b) (6)

(b) (6), *Primary and Specialty Medicine Service Line*

VA Midwest Health Care Network VISN 23

2805 Dodd Ave, Suite 250

Eagan, MN 55121

Main Office

Office Phone: 651.405.5670

Black Berry: (b) (6)

*“The best reason for having dreams is that in dreams no reasons are necessary.”
Ashleigh Brilliant*

FULL TEXT

[Ann Oncol](#). 2013 Mar;24(3):807-16. doi: 10.1093/annonc/mds508. Epub 2012 Oct 26.

Alcohol drinking and all cancer mortality: a meta-analysis.

[Jin M¹](#), [Cai S](#), [Guo J](#), [Zhu Y](#), [Li M](#), [Yu Y](#), [Zhang S](#), [Chen K](#).

Author information

Abstract

BACKGROUND:

Epidemiological studies have suggested an inconsistent relationship between alcohol drinking and risk of all cancer mortality. As far as we know, no meta-analysis has been conducted to explore this issue.

PATIENTS AND METHODS:

We carried out a PubMed search to find relevant articles published before April 2012 in English. Categorical and dose-response meta-analyses were conducted to identify the impact of alcohol drinking on all cancer mortality. Potential sources of heterogeneity were detected by meta-regression and stratification analyses. Sensitivity and cumulative meta-analyses were also carried out.

RESULTS: <http://annonc.oxfordjournals.org/content/24/3/807.long>

Eighteen independent cohort studies met the inclusion criteria. Compared with non/occasional drinkers, the pooled relative risks (RRs) were 0.91 [95% confidence interval (CI) 0.89-0.94] for light, 1.02 (95% CI 0.99-1.06) for moderate, and 1.31 (95% CI 1.23-1.39) for heavy drinkers. Former drinkers presented a higher risk (RR = 1.32, 95% CI 1.15-1.50) than current drinkers (RR = 1.06, 95% CI 0.98-1.16). There was a J-shaped relationship between all cancer mortality and alcohol consumption in males but not in females.

CONCLUSIONS:

This meta-analysis confirms the health hazards of heavy drinking (≥ 50 g/day) and benefits of light drinking (≤ 12.5 g/day). Large-sample, well-designed, prospective epidemiological studies, especially on heavy drinking among women, should be developed in future.

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

[Abdul Khalade](#)¹, [Maritta S Jaakkola](#)², [Eero Pukkala](#)^{3,4} and [Jouni JK Jaakkola](#)^{1,5}✉

¹Institute of Occupational and Environmental Medicine, University of Birmingham, UK

²Center for Environmental and Respiratory Health Research, Respiratory Medicine Unit, Department of Internal Medicine, Institute of Clinical Medicine, University of Oulu, P.O. B. 5000, 90014 Oulu, Finland

³Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Pieni Roobertinkatu 9, Helsinki, Finland

⁴School of Public Health, University of Tampere, Tampere, Finland

⁵Center for Environmental and Respiratory Health Research, Institute of Health Sciences, University of Oulu, P.O. B. 5000, 90014 Oulu, Finland

✉Corresponding author.

Abdul Khalade: AXK042@bham.ac.uk ; Maritta S Jaakkola: maritta.jaakkola@oulu.fi ; Eero Pukkala: eero.pukkala@cancer.fi ; Jouni JK Jaakkola: jouni.jaakkola@oulu.fi

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Received August 19, 2009; Accepted June 28, 2010.

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This article has been [cited by](#) other articles in PMC.

[Go to:](#)

Abstract

Background

A substantial number of epidemiologic studies have provided estimates of the relation between exposure to benzene at work and the risk of leukemia, but the results have been heterogeneous. To bridge this gap in knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of leukemia, including all types combined and the four main subgroups acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

Methods

A systematic literature review was carried out using two databases 'Medline' and 'Embase' from 1950 through to July 2009. We selected articles which provided information that can be used to estimate the relation between benzene exposure and cancer risk (effect size).

Results

In total 15 studies were identified in the search, providing 16 effect estimates for the main analysis. The summary effect size for any leukemia from the fixed-effects model was 1.40 (95% CI, 1.23-1.57), but the study-specific estimates were strongly heterogeneous ($I^2 = 56.5\%$, Q stat = 34.47, $p = 0.003$). The random-effects model yielded a summary- effect size estimate of 1.72 (95% CI, 1.37-2.17). Effect estimates from 9 studies were based on cumulative exposures. In these studies the risk of leukemia increased with a dose-response pattern with a summary-effect estimate of 1.64 (95% CI, 1.13-2.39) for low (< 40 ppm-years), 1.90 (95% CI, 1.26-2.89) for medium (40-99.9 ppm-years), and 2.62 (95% CI, 1.57-4.39) for high exposure category (> 100 ppm-years). In a meta-regression, the trend was statistically significant ($P = 0.015$). Use of cumulative exposure eliminated heterogeneity. The risk of AML also increased from low (1.94, 95% CI, 0.95-3.95), medium (2.32, 95% CI, 0.91-5.94) to high exposure category (3.20, 95% CI, 1.09-9.45), but the trend was not statistically significant.

Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

From: (b) (6)
To: (b) (6)
Subject: an article to share
Date: Thursday, September 11, 2014 12:34:22 PM
Attachments: [EAS](#)

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From: (b) (6)
To: (b) (6)
Subject: another
Date: Tuesday, November 18, 2014 9:27:35 AM
Attachments: [EAS](#)

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Attachments:
global epidemic of oral cancer.pdf (650262 Bytes)

From: (b) (6)
To: (b) (6)
Subject: FYI October 2014 draft ATSDR TOXICOLIGIC PROFILES are available online fo PCE and TCE::
Date: Tuesday, May 05, 2015 3:36:57 PM

These are still in draft form, and not officially sanctioned, but check them out:

<http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf>

<http://www.atsdr.cdc.gov/toxprofiles/tp18.pdf>

From: (b) (6)
To: (b) (6)
Subject: good 2015 article on prostate cancer risk from fam hx
Date: Tuesday, June 02, 2015 8:32:13 PM

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293302/pdf/pros0075-0390.pdf>

From: (b) (6)
To: (b) (6)
Subject: good article
Date: Tuesday, November 25, 2014 1:28:48 PM

World J Gastroenterol 2013 September 14; 19(34): 5598-5606

ISSN 1007-9327 (print) ISSN 2219-2840 . Epidemiology of esophageal cancer

Yuwei Zhang.

From: (b) (6)
To: (b) (6)
Subject: good one for the sharepoint
Date: Tuesday, March 25, 2014 6:28:35 PM
Attachments: [EAS](#)

Best Practice & Research Clinical Haematology
<<http://www.sciencedirect.com/science/journal/15216926>>

Volume 20, Issue 4 <<http://www.sciencedirect.com/science/journal/15216926/20/4>>, December 2007, Pages 637–664

New Insights into the Biology and Advances in the Management of Multiple Myeloma

Edited By Jean Luc Harousseau

<<http://www.sciencedirect.com/science/journal/15216926/20/4>>

5

Epidemiology of the plasma-cell disorders

· Robert A. Kyle
<<http://www.sciencedirect.com/science/article/pii/S152169260700062X?via=ihub>>, MD
<<http://www.sciencedirect.com/science/article/pii/S152169260700062X?via=ihub#cor1>> <<mailto:kyle.robert@mayo.edu>> (Professor of Medicine)

Attachments:

image001.gif (9368 Bytes)
image002.gif (269 Bytes)
image003.gif (386 Bytes)

Modifiable risk behaviors in patients with head and neck cancer.

[Sivasithamparam J](#), [Visk CA](#), [Cohen EE](#), [King AC](#). **Source** Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois.

Abstract

BACKGROUND:

Use of tobacco products, excessive alcohol consumption, and high-risk sexual behaviors increase the risk of developing head and neck cancer and impacts treatment effectiveness after diagnosis. This study examined smoking and engagement in other modifiable behavioral risk factors and human papillomavirus (HPV) status in patients with head and neck cancer in order to facilitate identification and foster development of targeted interventions in high-risk patients.

METHODS:

Participants were 102 patients with head and neck cancer at a large urban cancer center who completed a self-report background and health questionnaire and provided a saliva sample for determination of the long-acting nicotine metabolite cotinine.

RESULTS:

Compared with former and never-smokers, current smokers were less educated, less likely to be married or living with a partner, and consumed more alcohol. Cotinine analysis indicated that 4 of 16 (25%) patients who denied past-month cigarette use misrepresented their true smoking status. Of patients with oropharyngeal cancer, 74% were confirmed as HPV-positive, and compared with HPV-negative patients, they were younger, more likely to be married/partnered and of Caucasian race, and reported more past vaginal and oral sexual partners. Only one-third of HPV-positive patients were aware of their HPV disease status.

CONCLUSIONS:

Cigarette smoking is associated with engagement in other modifiable risk factors in patients with head and neck cancer. Self-report measures of smoking may not accurately depict true smoking status. HPV-positive cancer patients were more likely to endorse a history of multiple sexual partners. Regular screening and targeted interventions for these distinct risk factors are warranted. *Cancer* 2013;000:000-000. © 2013 American Cancer Society.

Copyright © 2013 American Cancer Society.

PMID:

23575663

From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] smoking reports
Date: Monday, December 15, 2014 3:19:27 PM

Two recent reports (2014) on the adverse health effects of smoking which have incorporated recent medical literature: these would be useful for the Sharepoint

(b) (6)

From: (b) (6)
Sent: Monday, December 15, 2014 10:52 AM
To: (b) (6)
Subject: [EXTERNAL] smoking reports

<http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>

<http://www.ncbi.nlm.nih.gov/pubmed/25317719>

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From: (b) (6)
To: (b) (6)
Subject: FW: CLCW and RCC
Date: Monday, February 23, 2015 9:30:15 AM
Attachments: [EAS](#)

I could not find this on the SP site....can you please added if not already done so per (b) (6).

(b) (6)

From: (b) (6)
Sent: Thursday, February 19, 2015 11:43 AM
To: (b) (6)
Cc: (b) (6)
Subject: RE: CLCW and RCC

Thanks. I have been using that renal stone article. I thought I sent it to (b) (6) to put on the server. If it's not there, please forward it to her.

From: (b) (6)
Sent: Thursday, February 19, 2015 12:35 PM
To: (b) (6)
Cc: (b) (6)
Subject: CLCW and RCC

Might be of interest.

(b) (6)

<http://qjmed.oxfordjournals.org/content/early/2014/10/01/qjmed.hcu195>

[QJM](#). 2014 Sep 9. pii: hcu195. [Epub ahead of print]

The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis.

[Cheungpasitporn W](#)¹, [Thongprayoon C](#)², [O'Corragain OA](#)², [Edmonds PJ](#)², [Ungprasert P](#)², [Kittanamongkolchai W](#)², [Erickson SB](#)².

Author information

- ¹From the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA, University College Cork, Cork, Ireland, SUNY Upstate Medical University, Syracuse, NY, USA and Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA
cheungpasitporn.wisit@mayo.edu.
- ²From the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA, University College Cork, Cork, Ireland, SUNY Upstate Medical University, Syracuse, NY, USA and Division of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA.

Abstract

BACKGROUND:

The objective of this meta-analysis was to evaluate the association between a history of kidney stones and kidney cancer.

METHODS:

A literature search was performed from inception until June 2014. Studies that reported odds ratios or hazard ratios comparing the risk of renal cell carcinoma (RCC) and transitional cell carcinoma (TCC) of the upper urinary tract in patients with the history of kidney stones versus those without the history of kidney stones were included. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

RESULT:

Seven studies were included in our analysis to assess the association between a history of kidney stones and RCC. The pooled RR of RCC in patients with kidney stones was 1.76 (95% CI, 1.24-2.49). The subgroup analysis found that the history of kidney stones was associated with increased RCC risk only in males (RR, 1.41 [95% CI, 1.11-1.80]), but not in females (RR, 1.13 [95% CI, 0.86-1.49]). Five studies were selected to assess the association between a history of kidney stones and TCC. The pooled RR of TCC in patients with kidney stones was 2.14 (95% CI, 1.35-3.40).

CONCLUSION:

Our study demonstrates a significant increased risk of RCC and TCC in patients with prior kidney stones. However, the increased risk of RCC was noted only in male patients. This finding suggests that a history of kidney stones is associated with kidney cancer and may impact clinical management and cancer surveillance.

From: (b) (6)
To: (b) (6)
Subject: FW: Occupation and CaP
Date: Wednesday, October 29, 2014 3:58:29 PM

For SP?

From: (b) (6)
Sent: Wednesday, October 29, 2014 2:31 PM
To: (b) (6)
Subject: RE: Occupation and CaP

Thanks, (b) (6) This is a good article!

(b) (6)

From: (b) (6)
Sent: Wednesday, October 29, 2014 12:00 PM
To: (b) (6)
Cc: (b) (6)
Subject: Occupation and CaP

<http://epirev.oxfordjournals.org/content/23/1/138.long>

Occupation and CaP

(b) (6)

From: (b) (6)
To: (b) (6)
Subject: FW: requested article
Date: Friday, March 13, 2015 10:24:21 AM
Attachments: [EAS](#)

From: (b) (6) (b) (6)
Sent: Friday, March 13, 2015 10:18 AM
To: (b) (6)
Subject: FW: requested article

Here it is.

--(b) (6)

(b) (6)

(b) (6)

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Attachments:
oeh.2009.15.4.370.pdf (78899 Bytes)

From: (b) (6)
To: (b) (6)
Subject: FW: requested article
Date: Tuesday, November 18, 2014 12:41:35 PM
Attachments: [EAS](#)

New article (b) (6) found on renal stones and renal cancer.

From: (b) (6)
Sent: Tuesday, November 18, 2014 12:41 PM
To: (b) (6)
Subject: FW: requested article

--(b) (6)

(b) (6)

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Attachments:
36859795.pdf (310655 Bytes)

From: (b) (6)
To: (b) (6)
Subject: for the website: 2015 article on TCE
Date: Tuesday, February 17, 2015 1:53:57 PM

Trichloroethylene: Mechanistic, Epidemiologic and Other Supporting Evidence of Carcinogenic Hazard

Ivan Rusyn¹, Weihsueh A.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3867557/pdf/nihms-518376.pdf>

From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL]
Date: Friday, February 20, 2015 2:08:01 PM
Attachments: [EAS](#)

Hi guys. I think there has been a presumption in the past that all SMEs remember or ever learned stats. I found this great summary that I think would help a lot with SMEs knowing how to interpret the literature, and especially the Bove studies. Should it be sent out to the group?

(b) (6)

Compensation & Pension
Environmental Health Clinician
DMA Subject Matter Expert Panel
VISN 11 Primary MRO
Ann Arbor VAMC
734-769-7100 x (b) (6) (office)

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From: (b) (6)
Sent: Friday, February 20, 2015 2:06 PM
To: (b) (6)
Subject: [EXTERNAL]

(b) (6)

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From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Date: Friday, September 12, 2014 12:52:17 PM
Attachments: [EAS](#)
Importance: High

Lets add these papers to the resource section

From: (b) (6)
Sent: Wednesday, August 27, 2014 8:29 AM
To: (b) (6)
Subject: FW: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Importance: High

(b) (6)

Per our discussion. See you next week if I'm here.

Thank you,

(b) (6)

(b) (6)

ICARE



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Sent: Thursday, August 14, 2014 10:41 PM
To: (b) (6)

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(b) (6)

Subject: [EXTERNAL] 2 Info Papers on the new ATSDR study related to Camp Lejeune
Importance: High

Attached are 2 Information Papers on the new ATSDR study of mortality in civilian employees who worked at Camp Lejeune and Camp Pendleton.

I wrote these at the request of staff of the US Marine Corps, and on behalf of the DoD/VA Deployment Health Work Group.

The 2-page version includes more background. The one-page version includes fewer results, but more on implications of the study.

I hope these critiques are useful to our colleagues in the VA and US Marine Corps.

Please tell me if you have any questions on this.

(b) (6)

(b) (6)

Defense Medical Research and Development Program

Defense Health Headquarters

7700 Arlington Boulevard, Suite 5101 (Code: FHP&R)

Falls Church, VA 22042-5101

Phone: 703-681-8211

Fax: 703-681-9539

E-mail: (b) (6)

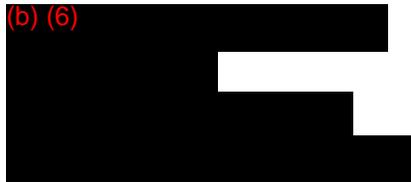
From: (b) (6)
To: (b) (6)
Subject: FW: [EXTERNAL] breast ca
Date: Wednesday, June 11, 2014 10:27:02 AM

I have not read the whole article yet but seems relevant.

From: (b) (6)]
Sent: Tuesday, June 10, 2014 8:30 PM
To: (b) (6)
Subject: [EXTERNAL] breast ca

<http://cancerres.aacrjournals.org/content/74/11/3076.long>

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A large black rectangular redaction box covers the majority of the text in this section. The only visible text is the redaction code "(b) (6)" at the top left of the box.

From: (b) (6)
To: (b) (6)
Cc: (b) (6)
Subject: FW: [EXTERNAL] NEJM article smoking
Date: Tuesday, March 24, 2015 11:28:19 AM

Hey guys, I read this last nite; definitely pertinent to CLCW.

(b)
(6)

From: (b) (6)
Sent: Monday, March 23, 2015 9:32 AM
To: (b) (6)
Subject: [EXTERNAL] NEJM article smoking

<http://www.nejm.org/doi/pdf/10.1056/NEJMsa1407211>

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Estimation of cigarette smoking-attributable morbidity in the United States.

[Rostron BL](#)¹, [Chang CM](#)¹, [Pechacek TF](#)².

Abstract

IMPORTANCE: Cigarette smoking has been found to harm nearly every bodily organ and is a leading cause of preventable disease, but current estimates of smoking-attributable morbidity by condition for the United States are generally unavailable.

OBJECTIVE: To estimate the burden of major medical conditions attributable to cigarette smoking in the United States.

DESIGN, SETTING, AND PARTICIPANTS: The disease burden of smoking was estimated using population-attributable risk calculations, taking into account the uncertainty of estimates. Population estimates came from 2009 US Census Bureau data and smoking prevalence, disease prevalence, and disease relative risk estimates came from National Health Interview Survey data for surveyed adults from 2006 through 2012. National Health and Nutrition Examination Survey spirometry data obtained from medical examination of surveyed adults from 2007 through 2010 was used to adjust for underreporting of chronic obstructive pulmonary disease.

EXPOSURES: Smoking status was assessed from self-reported National Health Interview Survey data.

MAIN OUTCOMES AND MEASURES:

The number of adults 35 years and older who had had a major smoking-attributable disease by sex and condition and the total number of these conditions were estimated for the United States in 2009.

RESULTS: Using National Health Interview Survey data, we estimated that 6.9 million (95% CI, 6.5-7.4 million) US adults had had a combined 10.9 million (95% CI, 10.3-11.5 million) self-reported smoking-attributable medical conditions. Using chronic obstructive pulmonary disease prevalence estimates obtained from National Health and Nutrition Examination Survey self-reported and spirometry data, we estimated that US adults had had a combined 14.0 million (95% CI, 12.9-15.1 million) smoking-attributable conditions in 2009.

CONCLUSIONS AND RELEVANCE:

We estimate that US adults have had approximately 14 million major medical conditions that were attributable to smoking. This figure is generally conservative owing to the existence of other diseases and medical events that were not included in these estimates. Cigarette smoking

remains a leading cause of preventable disease in the United States, underscoring the need for continuing and vigorous smoking-prevention efforts.

Comment in

- [Even more illness caused by smoking than previously estimated.](#) [JAMA Intern Med. 2014]

Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

[Bove FJ¹](#), [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

Author information

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at Camp Lejeune or Camp Pendleton, California during this period. Camp Pendleton's drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune (N = 154,932) and Camp Pendleton (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the Camp Lejeune cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS:

There were 8,964 and 9,365 deaths respectively, in the Camp Lejeune and Camp Pendleton cohorts. Compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the Camp Lejeune cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

CONCLUSION:

The study found elevated HRs at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposures

Environ Health Perspect. 2009 May; 117(5): 696–702.

Published online 2009 January 9. doi: [10.1289/ehp.11782](https://doi.org/10.1289/ehp.11782)

PMCID: PMC2685829

Review

Evidence of Autoimmune-Related Effects of Trichloroethylene Exposure from Studies in Mice and Humans

[Glinda S. Cooper](#),¹ [Susan L. Makris](#),¹ [Paul J. Nietert](#),² and [Jennifer Jinot](#)¹

<mailto:cooper.glinda@epa.gov>

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Abstract

Objective

Our objective was to examine experimental and epidemiologic studies pertaining to immune-related, and specifically autoimmune-related, effects of trichloroethylene (TCE).

Data sources and extraction

We performed a literature search of PubMed and reviewed bibliographies in identified articles. We then systematically reviewed immune-related data, focusing on clinical and immunologic features and mechanistic studies.

Data synthesis

Studies conducted in MRL^{+/+} lupus mice report an accelerated autoimmune response in relation to exposure to TCE or some metabolites. Effects have been reported after 4 weeks of exposure to TCE at doses as low as 0.1 mg/kg/day in drinking water and have included increased antinuclear antibodies and interferon- γ (IFN- γ) and decreased secretion of interleukin-4 (IL-4), consistent with an inflammatory response. Autoimmune hepatitis, inflammatory skin lesions, and alopecia have been found after exposures of 32–48 weeks. Recent mechanistic experiments in mice examined oxidative stress and, specifically, effects on lipid-peroxidation–derived aldehydes in TCE-induced autoimmune disease. Two studies in humans reported an increase in IL-2 or IFN- γ and a decrease in IL-4 in relation to occupational or environmental TCE exposure. Occupational exposure to TCE has also been associated with a severe, generalized hypersensitivity skin disorder accompanied by systemic effects, including hepatitis. In three case–control studies of scleroderma with a measure of occupational TCE exposure, the combined odds ratio was 2.5 [95% confidence interval (CI), 1.1–5.4] in men and 1.2 (95% CI, 0.58–2.6) in women.

Conclusion

The consistency among the studies and the concordance between the studies in mice and humans support an etiologic role of TCE in autoimmune disease. Multisite collaborations and studies of preclinical immune markers are needed to further develop this field of research.

Keywords: autoimmune liver disease, solvents, systemic sclerosis, trichloroethylene

Trichloroethylene (TCE) is an industrial solvent that has been used extensively in industrial operations involving metal cleaning and degreasing. Its metabolism through a cytochrome P450 (CYP) pathway involving the enzyme CYP2E1 results in numerous metabolites, including chloral, chloral hydrate, dichloroacetic acid, trichloroacetic acid, trichloroethanol, and trichloroethanol glucuronide (

The following popper user interface control may not be accessible. Tab to the next button to revert the control to an accessible version.

[Destroy user interface control](#) Lash et al. 2000). Many studies of immune-related effects of TCE have been conducted in the past decade, with much of this work focusing on autoimmune disease. We reviewed this recent research to determine the strength and consistency of data from experimental and epidemiologic studies, and the concordance between human and animal data, pertaining to these effects.

[Go to:](#)

FATTY LIVER DISEASE

Fatty liver disease is clearly recognized as a primary direct consequence of obesity and alcohol consumption. On a population base those two are the most common causes, around the world, achieving a prevalence of over 34% in the US NHANES (1988-1994) (Sirota 2012) and over 30% throughout the world (Durazzo 2012), and the proportion of overweight, obesity, and morbid obesity has only increased since then. In addition to alcohol and obesity, occupational exposure to organic solvent with known or imputed liver toxicity contribute to the risk (Hodgson 1991, Lundqvist 1999). The higher the dose of hepatotoxin, the greater the likelihood of hepatitis, a 4.5-fold risk in one study and a 7-fold risk in the other. Still, even in working populations with potential exposure to hepatotoxins obesity appears to be the primary risk factor. Environmental exposure, i.e., ground water pollution (Najem 1994), does not to be associated with liver disease in humans even through several animal studies demonstrated minimal changes in rat livers

The risk from obesity is so great

Hodgson M, van Thiel DH, Goodman-Klein B. Obesity and hepatotoxins as risk factors for fatty liver disease. *Br J Ind Med.* 1991 Oct;48(10):690-5.

Lundqvist G, Flodin U, Axelson O. A case-control study of fatty liver disease and organic solvent exposure. *Am J Ind Med.* 1999 Feb;35(2):132-6.

Sirota JC, McFann K, Targher G, Chonchol M, Jalal DI. Association between Nonalcoholic Liver Disease and Chronic Kidney Disease: An Ultrasound Analysis from NHANES 1988-1994. *Am J Nephrol.* 2012;36(5):466-71. doi: 10.1159/000343885. Epub 2012 Nov 2.

Durazzo M, Belci P, Collo A, Grisoglio E, Bo S. Focus on therapeutic strategies of nonalcoholic Fatty liver disease. *Int J Hepatol.* 2012;2012:464706. doi: 10.1155/2012/464706. Epub 2012 Nov 8.

Najem GR, Strunck T, Feuerman M. Health effects of a Superfund hazardous chemical waste disposal site. *Am J Prev Med.* 1994 May-Jun;10(3):151-5.

National academy of sciences. Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects. National Research Council, 2009.

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Subject: for sharepoint
Date: Thursday, March 19, 2015 9:19:43 AM
Attachments: [EAS](#)

(b) (6)

Compensation & Pension

Environmental Health Clinician

DMA Clinical Advisory Board
Ann Arbor VAMC

Attachments:

Occ exposure rare cancers.pdf (2181007 Bytes)

From: (b) (6)
To: (b) (6)
Subject: Environmental Factors and Risk of Non-Hodgkin Lymphoma.doc
Date: Monday, September 22, 2014 5:26:04 PM
Attachments: [EAS](#)

(b) (6) -

I have finished 4 cases today- and finishing #5.

Is it possible for someone to post the entire article of the abstract that I have attached.. I would like to see the whole article.

Thanks.

(b)
(6)

Attachments:

Environmental Factors and Risk of Non-Hodgkin Lymphoma.doc (43002 Bytes)

Current Understanding of Lifestyle and Environmental Factors and Risk of Non-Hodgkin Lymphoma: An Epidemiological Update

[Bryan A. Bassig](#),¹ [Qing Lan](#),² [Nathaniel Rothman](#),² [Yawei Zhang](#),¹ and [Tongzhang Zheng](#)^{1,*}

¹Division of Environmental Health Sciences, Yale School of Public Health, New Haven, CT 06510, USA

²Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD 20892, USA

*Tongzhang Zheng: Email: tongzhang.zheng/at/yale.edu

Academic Editor: P. Vineis

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Received May 24, 2012; Revised July 20, 2012; Accepted August 4, 2012.

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Abstract

The incidence rates of non-Hodgkin lymphoma (NHL) have steadily increased over the last several decades in the United States, and the temporal trends in incidence can only be partially explained by the HIV epidemic. In 1992, an international workshop sponsored by the United States National Cancer Institute concluded that there was an “emerging epidemic” of NHL and emphasized the need to investigate the factors responsible for the increasing incidence of this disease. Over the past two decades, numerous epidemiological studies have examined the risk factors for NHL, particularly for putative environmental and lifestyle risk factors, and international consortia have been established in order to investigate rare exposures and NHL subtype-specific associations. While few consistent risk factors for NHL aside from immunosuppression and certain infectious agents have emerged, suggestive associations with several lifestyle and environmental factors have been reported in epidemiologic studies. Further, increasing evidence has suggested that the effects of these and other exposures may be limited to or stronger for particular NHL subtypes. This paper examines the progress that has been made over the last twenty years in elucidating the etiology of NHL, with a primary emphasis on lifestyle factors and environmental exposures.

Environmental risk factors in systemic sclerosis.

[Dospinescu P](#), [Jones GT](#), [Basu N](#).

Source

Department of Rheumatology, Aberdeen Royal Infirmary, Aberdeen, UK.

Abstract

PURPOSE OF REVIEW:

Environmental risk factors have been implicated in the pathogenesis of systemic sclerosis (SSc). Recent evidence further supports this relationship and constitutes the focus of this review article.

RECENT FINDINGS:

Exposure to silica through various occupations remains one of the main environmental risk factors for SSc. Emerging evidence has also implicated organic solvents in the development of this difficult-to-manage condition. The individual role of these toxins is, however, difficult to ascertain due to methodological limitations in study design. Other occupational agents, such as epoxy resins, welding fumes and hand-arm vibration, have been investigated, but no definitive associations may be made due to small sample sizes. The controversial association between silicone breast surgery and SSc has not been proven and, amongst other non-occupational factors, smoking does not increase the risk of development but does appear to impact upon the severity of disease.

SUMMARY:

A number of environmental exposures are likely to play an important role in the development of the disease; however, current evidence consists mainly of heterogeneous studies with relatively small sample sizes. In the future, multicentre collaborations may help inform preventive strategies.

<http://www.ncbi.nlm.nih.gov/pubmed/23287382>

Epidemiology of esophageal cancer.

[Zhang Y](#)¹.

Author information

Abstract

Esophageal cancer (EsC) is one of the least studied and deadliest cancers worldwide because of its extremely aggressive nature and poor survival rate. It ranks sixth among all cancers in mortality. In retrospective studies of EsC, smoking, hot tea drinking, red meat consumption, poor oral health, low intake of fresh fruit and vegetables, and low socioeconomic status have been associated with a higher risk of esophageal squamous cell carcinoma. Barrett's esophagus is clearly recognized as a risk factor for EsC, and dysplasia remains the only factor useful for identifying patients at increased risk, for the development of esophageal adenocarcinoma in clinical practice. Here, we investigated the epidemiologic patterns and causes of EsC. Using population based cancer data from the Surveillance, Epidemiology and End Results Program of the United States; we generated the most up-to-date stage distribution and 5-year relative survival by stage at diagnosis for 1998-2009. Special note should be given to the fact that esophageal cancer, mainly adenocarcinoma, is one of the very few cancers that is contributing to increasing death rates (20%) among males in the United States. To further explore the mechanism of development of EsC will hopefully decrease the incidence of EsC and improve outcomes.

Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.

[Alberg AJ](#), [Brock MV](#), [Ford JG](#), [Samet JM](#), [Spivack SD](#).

Source

Hollings Cancer Center, Medical University of South Carolina, 68 President St, MSC 955, Charleston, SC 29425, USA. alberg@musc.edu

Abstract

BACKGROUND:

Ever since a lung cancer epidemic emerged in the mid-1900 s, the epidemiology of lung cancer has been intensively investigated to characterize its causes and patterns of occurrence. This report summarizes the key findings of this research.

METHODS:

A detailed literature search provided the basis for a narrative review, identifying and summarizing key reports on population patterns and factors that affect lung cancer risk.

RESULTS:

Established environmental risk factors for lung cancer include smoking cigarettes and other tobacco products and exposure to secondhand tobacco smoke, occupational lung carcinogens, radiation, and indoor and outdoor air pollution. Cigarette smoking is the predominant cause of lung cancer and the leading worldwide cause of cancer death. Smoking prevalence in developing nations has increased, starting new lung cancer epidemics in these nations. A positive family history and acquired lung disease are examples of host factors that are clinically useful risk indicators. Risk prediction models based on lung cancer risk factors have been developed, but further refinement is needed to provide clinically useful risk stratification. Promising biomarkers of lung cancer risk and early detection have been identified, but none are ready for broad clinical application.

CONCLUSIONS:

Almost all lung cancer deaths are caused by cigarette smoking, underscoring the need for ongoing efforts at tobacco control throughout the world. Further research is needed into the reasons underlying lung cancer disparities, the causes of lung cancer in never smokers, the potential role of HIV in lung carcinogenesis, and the development of biomarkers.

[Morgan JW, Cassady RE](#). Community cancer assessment in response to long-time exposure to perchlorate and trichloroethylene in drinking water. [J Occup Environ Med](#). 2002 Jul;44(7):616-21.

Full text: http://ovidsp.tx.ovid.com/sp-3.8.0b/ovidweb.cgi?&S=GDPOFPHOJCDDGOMANCOKEALBFFLHAA00&Link+Set=S.sh.18.19.23.27%7c5%7csl_10

AB Objective: To analyze if the combination of organizational climate and work commitment can predict return to work (RTW). Methods: This prospective Swedish study was based on 2285 participants, 19 to 64 years old, consecutively selected from the employed population, newly sick-listed for more than 14 days. Data were collected in 2008 through postal questionnaire and from register data. Results: Among women, the combination of good organizational climate and fair work commitment predicted an early RTW with an adjusted relative risk of 2.05 (1.32 to 3.18). Among men, none of the adjusted variables or combinations of variables was found significantly to predict RTW. Conclusions: This study demonstrated the importance of integrative effects of organizational climate and individual work commitment on RTW among women. These factors did not predict RTW in men. More research is needed to understand the RTW process among men. (C)2013The American College of Occupational and Environmental Medicine

Supported by sanofi-aventis



What are confidence intervals and p-values?

Huw TO Davies PhD
Professor of Health
Care Policy and
Management,
University of St
Andrews

Iain K Crombie PhD
FFPHM Professor of
Public Health,
University of Dundee

- A confidence interval calculated for a **measure of treatment effect** shows the range within which the true treatment effect is likely to lie (subject to a number of assumptions).
- A p-value is calculated to assess whether trial results are likely to have occurred simply through chance (assuming that there is no real difference between new treatment and old, and assuming, of course, that the study was well conducted).
- Confidence intervals are preferable to p-values, as they tell us the **range of possible effect sizes** compatible with the data.
- p-values simply provide a cut-off beyond which we assert that the findings are 'statistically significant' (by convention, this is $p < 0.05$).
- A confidence interval that **embraces the value of no difference between treatments** indicates that the treatment under investigation is not significantly different from the control.
- Confidence intervals **aid interpretation of clinical trial data** by putting upper and lower bounds on the likely size of any true effect.
- **Bias must be assessed** before confidence intervals can be interpreted. Even very large samples and very narrow confidence intervals can mislead if they come from biased studies.
- **Non-significance does not mean 'no effect'**. Small studies will often report non-significance even when there are important, real effects which a large study would have detected.
- Statistical significance does not necessarily mean that the effect is real: by chance alone about **one in 20 significant findings will be spurious**.
- Statistically significant does not necessarily mean clinically important. It is the **size of the effect** that determines the importance, not the presence of statistical significance.

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What are confidence intervals and p-values?

Measuring effect size

Clinical trials aim to generate new knowledge on the effectiveness (or otherwise) of healthcare interventions. Like all clinical research, this involves estimating a key parameter of interest, in this case the effect size. The effect size can be measured in a variety of ways, such as the relative risk reduction, the absolute risk reduction or the number needed to treat (NNT; Table 1).

Relative measures tend to emphasise potential benefits, whereas **absolute measures** provide an across-the-board

summary.¹ Either may be appropriate, subject to correct interpretation.

Whatever the measure used, some assessment must be made of the trustworthiness or **robustness** of the findings. The findings of the study provide a point estimate of effect, and this raises a dilemma: are the findings from this sample also likely to be true about other similar groups of patients? Before we can answer such a question, two issues need to be addressed. Does any apparent treatment benefit arise because of the way the study has been

Box 1. Hypothesis testing and the generation of p-values

The logic of hypothesis testing and p-values is convoluted. Suppose a new treatment appears to outperform the standard therapy in a research study. We are interested in assessing whether this apparent effect is likely to be real or could just be a chance finding: p-values help us to do this.

In calculating the p-value, we first assume that there really is no true difference between the two treatments (this is called the **null hypothesis**). We then calculate how likely we are to see the difference that we have observed just by chance if our supposition is true (that is, if there is really no true difference). This is the p-value.

So the p-value is the probability that we would observe effects as big as those seen in the study if there was really no difference between the treatments. If p is small, the findings are unlikely to have arisen by chance and we reject the idea that there is no difference between the two treatments (we reject the null hypothesis). If p is large, the observed difference is plausibly a chance finding and we do not reject the idea that there is no difference between the treatments. Note that we do not reject the idea, but we do not accept it either: we are simply unable to say one way or another until other factors have been considered.

But what do we mean by a 'small' p-value (one small enough to cause us to reject the idea that there was really no difference)? By convention, p-values of less than 0.05 are considered 'small'. That is, if p is less than 0.05 there is a less than one in 20 chance that a difference as big as that seen in the study could have arisen by chance if there was really no true difference. With p-values this small (or smaller) we say that the results from the trial are statistically significant (unlikely to have arisen by chance). Smaller p-values (say $p < 0.01$) are sometimes called 'highly significant' because they indicate that the observed difference would happen less than once in a hundred times if there was really no true difference.

Table 1. Summary of effect measures

| Measure of effect | Abbreviation | Description | No effect | Total success |
|-------------------------|--------------|---|-----------------|--------------------|
| Absolute risk reduction | ARR | Absolute change in risk: the risk of an event in the control group minus the risk of an event in the treated group; usually expressed as a percentage | ARR=0% | ARR=initial risk |
| Relative risk reduction | RRR | Proportion of the risk removed by treatment: the absolute risk reduction divided by the initial risk in the control group; usually expressed as a percentage | RRR=0% | RRR=100% |
| Relative risk | RR | The risk of an event in the treated group divided by the risk of an event in the control group; usually expressed as a decimal proportion, sometimes as a percentage | RR=1 or RR=100% | RR=0 |
| Odds ratio | OR | Odds of an event in the treated group divided by the odds of an event in the control group; usually expressed as a decimal proportion | OR=1 | OR=0 |
| Number needed to treat | NNT | Number of patients who need to be treated to prevent one event; this is the reciprocal of the absolute risk reduction (when expressed as a decimal fraction); it is usually rounded to a whole number | NNT= ∞ | NNT=1/initial risk |

conducted (**bias**), or could it arise simply because of **chance**? The short note below briefly covers the importance of assessing bias but focuses more on assessing the role of chance.

Bias

Bias is a term that covers any **systematic errors** that result from the way the study was designed, executed or interpreted. Common flaws in treatment trials are:

- Lack of (or failure in) randomisation, leading to unbalanced groups
- Poor blinding, leading to unfair treatment and biased assessments
- Large numbers of patients lost to follow-up.

Assessment in these areas is crucial before the results from any trial can be assessed, and many useful guides exist to assist this process, such as an article by Guyatt *et al* and books by Sackett *et al* and by Crombie.²⁻⁵ Interpretation of the effects of chance is only meaningful once bias has been excluded as an explanation for any observed differences.^{6,7}

Chance variability

The results from any particular study will vary just by chance. Studies differ in terms of the

people who are included, and the ways in which these specific individuals react to therapeutic interventions. Even when everything possible is held constant, there will still be some random variations. Hence we need some tools to help us to assess whether differences that we see between new treatment and old in any particular study are real and important, or just manifestations of chance variability. Confidence intervals and p-values help us to do this.

What are p-values?

Until comparatively recently, assessments of the role of chance were routinely made using **hypothesis testing**, which produces a 'p-value' (Box 1). The p-value allows assessment of whether or not the findings are 'significantly different' or 'not significantly different' from some reference value (in trials, this is usually the value reflecting 'no effect'; Table 1). A different and potentially more useful approach to assessing the role of chance has come to the fore: confidence intervals.⁸ Although these might appear rather dissimilar to p-values, the theory and calculations underlying these two approaches are largely the same.

What are confidence intervals?

Confidence intervals provide different information from that arising from hypothesis tests. Hypothesis testing produces a decision about any observed difference: either that the difference is 'statistically significant' or that it is 'statistically non-significant'. In contrast, confidence intervals provide a **range** about the observed effect size. This range is constructed in such a way that we know how likely it is to capture the true – but unknown – effect size.

Thus, the formal definition of a confidence interval is: 'a range of values for a variable of interest [in our case, the measure of treatment effect] constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits'.⁹

It is conventional to create confidence intervals at the 95% level – so this means that 95% of the time properly constructed confidence intervals should contain the true value of the variable of interest. This corresponds to hypothesis testing with p-values, with a conventional cut-off for p of less than 0.05.

More colloquially, the confidence interval provides a range for our best guess of the size of the true treatment effect that is plausible given the size of the difference actually observed.

Assessing significance from a confidence interval

One useful feature of confidence intervals is that one can easily tell whether or not statistical significance has been reached, just as in a hypothesis test.

- If the confidence interval **captures** the value reflecting 'no effect', this represents a difference that is statistically non-significant (for a 95% confidence interval, this is non-significance at the 5% level).
- If the confidence interval **does not enclose** the value reflecting 'no effect', this represents a difference that is statistically significant (again, for a 95% confidence interval, this is significance at the 5% level).

Thus, 'statistical significance'

(corresponding to $p < 0.05$) can be inferred from confidence intervals – but, in addition, these intervals show the largest and smallest effects that are likely, given the observed data. This is useful extra information.

An example of the use of confidence intervals is shown in Box 2.¹⁰

Examining the width of a confidence interval

One of the advantages of confidence intervals over traditional hypothesis testing is the additional information that they convey. The upper and lower bounds of the interval give us information on how big or small the true effect might plausibly be, and the width of the confidence interval also conveys some useful information.

If the confidence interval is narrow, capturing only a small range of effect sizes, we can be quite confident that any effects far from this range have been ruled out by the study. This situation usually arises when the size of the study is quite large and, hence, the estimate of the true effect is quite precise. Another way of saying this is to note that the study has reasonable 'power' to detect an effect.

However, if the confidence interval is quite wide, capturing a diverse range of effect sizes, we can infer that the study was probably quite small. Thus, any estimates of effect size will be quite imprecise. Such a study is 'low-powered' and provides us with less information.

Errors in interpretation

Confidence intervals, like p-values, provide us with a guide to help with the interpretation of research findings in the light of the effects of chance. There are, however, three important pitfalls in interpretation.

Getting it wrong: seeing effects that are not real

First of all, we may examine the confidence interval and/or the p-value and observe that the difference is 'statistically significant'. From this we will usually conclude that there is a difference between the two treatments. However, just because we are unlikely to observe such a large difference simply by chance, this does not mean that it will not happen. By definition, about one in 20

Box 2. An example of the use of confidence intervals¹⁰

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor which has been tested for use in patients at high risk of cardiovascular events. In one study published in the *New England Journal of Medicine*,¹⁰ a total of 9,297 patients were recruited into a randomised, double-blind, controlled trial. The key findings presented on the primary outcome and deaths are shown below.

Incidence of primary outcome and deaths from any cause

| Outcome | Ramipril group (n=4,645) number (%) | Placebo group (n=4,652) number (%) | Relative risk (95% CI) |
|--|---|--|---------------------------|
| Cardiovascular event (including death) | 651 (14.0) | 826 (17.8) | 0.78 (0.70–0.86) |
| Death from non-cardiovascular cause | 200 (4.3) | 192 (4.1) | 1.03 (0.85–1.26) |
| Death from any cause | 482 (10.4) | 569 (12.2) | 0.84 (0.75–0.95) |

These data indicate that fewer people treated with ramipril suffered a cardiovascular event (14.0%) compared with those in the placebo group (17.8%). This gives a relative risk of 0.78, or a reduction in (relative) risk of 22%. The 95% confidence interval for this estimate of the relative risk runs from 0.70 to 0.86. Two observations can then be made from this confidence interval.

- First, the observed difference is statistically significant at the 5% level, because the interval does not embrace a relative risk of one.
- Second, the observed data are consistent with as much as a 30% reduction in relative risk or as little as a 14% reduction in risk.

Similarly, the last row of the table shows that statistically significant reductions in the overall death rate were recorded: a relative risk of 0.84 with a confidence interval running from 0.75 to 0.95. Thus, the true reduction in deaths may be as much as a quarter or it could be only as little as 5%; however, we are 95% certain that the overall death rate is reduced in the ramipril group.

Finally, exploring the data presented in the middle row shows an example of how a confidence interval can demonstrate non-significance. There were a few more deaths from non-cardiovascular causes in the ramipril group (200) compared with the placebo group (192). Because of this, the relative risk is calculated to be 1.03 – showing a slight increase in risk in the ramipril group. However, the confidence interval is seen to capture the value of no effect (relative risk = 1), running as it does from 0.85 to 1.26. The observed difference is thus non-significant; the true value could be anything from a 15% reduction in non-cardiovascular deaths for ramipril to a 26% increase in these deaths. Not only do we know that the result is not significant, but we can also see how large or small a true difference might plausibly be, given these data.

significant findings will be spurious – arising simply from chance. Thus, we may be misled by chance into believing in something that is not real – technically, this is called a ‘**type I error**’.

It is a frustrating but unavoidable feature of statistical significance (whether assessed using confidence intervals or p-values) that around

one in 20 will mislead. Yet we cannot know which of any given set of comparisons is doing the misleading. This observation cautions against generating too many statistical comparisons: the more comparisons made in any given study, the greater the chance that at least some of them will be spurious findings. Thus, clinical trials which

show significance in only one or two subgroups are unconvincing – such significance may be deceptive. Unless particular subgroup analyses have been specified in advance, differences other than for the primary endpoint for the whole group should be viewed with suspicion.

Statistical significance and clinical significance

Statistical significance is also sometimes misinterpreted as signifying an important result: this is a second important pitfall in interpretation. Significance testing simply asks whether the data produced in a study are compatible with the notion of no difference between the new and control interventions. Rejecting equivalence of the two interventions does not necessarily mean that we accept that there is an important difference between them. A large study may identify as statistically significant a fairly small difference. It is then quite a separate judgement to assess the clinical significance of this difference. In assessing the importance of significant results, it is the size of the effect – not just the size of the significance – that matters.

Getting it wrong again: failing to find real effects

A further error that we may make is to conclude from a non-significant finding that there is no effect, when in fact there is a real effect – this is called a '**type II error**'. Equating non-significance with 'no effect' is a common misconception. A non-significant confidence interval simply tells us that the observed difference is consistent with there being no true difference between the two groups. Thus, we are unable to reject this possibility. This is where confidence intervals are much more helpful than simple p-values: the observed difference will also be compatible with a range of other effect sizes as described by the confidence interval.⁸ We are unable to reject these possibilities and must then assess whether some of them (usually the upper and lower limits of the confidence interval) might be important. Just because we have not found a significant treatment effect, it does not mean that there is no treatment effect to be found.¹¹ The

crucial question is: how carefully have we interpreted the findings?

Extrapolating beyond the trial

For all the complexity of understanding bias and chance in the interpretation of the findings from clinical trials, another important consideration should not be forgotten. The findings from any given study relate to the patients included in that study. Even if an effect is assessed as probably real and large enough to be clinically important, a further question remains: how well are the findings applicable to other groups of patients, and do they particularise to a given individual?¹² Neither confidence intervals nor p-values are much help with this judgement. Assessment of this **external validity** is made based on the patients' characteristics and on the setting and the conduct of the trial.

Summary

Confidence intervals and p-values take as their starting point the results observed in a study. Crucially, we must check first that this is an unbiased study. The question that confidence intervals then answer is: what is the range of real effects that is compatible with these data? The confidence interval is just such a range, which 95% of the time will contain the true value of the main measure of effect (relative risk reduction, absolute risk reduction, NNT or whatever; Table 1).

This allows us to do two things. First, if the confidence interval embraces the value of no effect (for example, no difference between two treatments as shown by a relative risk equal to one or an absolute difference equal to zero), then the findings are non-significant. If the confidence interval does not embrace the value of no difference, then the findings are statistically significant. Thus, confidence intervals provide the same information as a p-value. But more than this: the upper and lower extremities of the confidence interval also tell us how large or small the real effect might be and yet still give us the observed findings by chance. This additional information is very helpful in allowing us to interpret both borderline significance and non-significance. Confidence intervals from large studies tend to be quite narrow in width, showing the precision with which the study is

able to estimate the size of any real effect. In contrast, confidence intervals from smaller studies are usually wide, showing that the findings are compatible with a wide range of effect sizes.

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What are

confidence intervals and p-values?

First edition published 2003

Author: Huw TO Davies

This publication, along with the others in the series, is available on the internet at www.whatisseries.co.uk

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[Urol Oncol](#). 2012 Mar-Apr;30(2):220-4. doi:
10.1016/j.urolonc.2011.10.001.

Environmental and modifiable risk factors in renal cell carcinoma.

[Navai N](#), [Wood CG](#).

Author information

Abstract

OBJECTIVES:

Prevention of disease requires a firm understanding of the relevant environmental and modifiable risk factors. We present a comprehensive review of these factors in renal cell carcinoma.

MATERIALS AND METHODS:

A literature search of the PubMed database was performed to identify clinical studies examining the relationship between environmental and modifiable factors in the development of renal cell carcinoma (terms utilized: kidney cancer; renal cell carcinoma; risk factors; environment; obesity; hypertension; trichloroethylene). An emphasis was placed on more recent studies.

RESULTS:

Case control and large cohort studies have examined the relationship of numerous environmental and modifiable factors and the risk of renal cell carcinoma. Of particular note are dose-dependent increases in smokers, the obese, and hypertensive patients.

CONCLUSIONS:

Environmental and modifiable risk factors contribute significantly to the risk of sporadic renal cell carcinoma. Emphasis should be placed on smoking cessation and hypertension control. Emerging evidence would suggest that dietary intake and quality impact renal cell carcinoma risk.

[FULL TEXT LINK](#)

[Rev Environ Health](#). 2008 Jan-Mar;23(1):1-37.

Environmental and occupational causes of cancer: new evidence 2005-2007.

[Clapp RW](#), [Jacobs MM](#), [Loechler EL](#).

Source Boston University School of Public Health, Boston, MA 02118, USA.
richard.clapp@gmail.com

Abstract

What do we currently know about the occupational and environmental causes of cancer? As of 2007, the International Agency for Research on Cancer (IARC) identified 415 known or suspected carcinogens. Cancer arises through an extremely complicated web of multiple causes, and we will likely never know the full range of agents or combinations of agents. We do know that preventing exposure to individual carcinogens prevents the disease. Declines in cancer rates—such as the drop in male lung cancer cases from the reduction in tobacco smoking or the drop in bladder cancer among cohorts of dye workers from the elimination of exposure to specific aromatic amines—provides evidence that preventing cancer is possible when we act on what we know. Although the overall age-adjusted cancer incidence rates in the United States among both men and women have declined in the last decade, the rates of several types of cancers are on the rise; some of which are linked to environmental and occupational exposures. This report chronicles the most recent epidemiologic evidence linking occupational and environmental exposures with cancer. Peer-reviewed scientific studies published from January 2005 to June 2007 were reviewed, supplementing our state-of-the-evidence report published in September 2005. Despite weaknesses in certain individual studies, we consider the evidence linking the increased risk of several types of cancer with specific exposures somewhat strengthened by recent publications, among them brain cancer from exposure to non-ionizing radiation, particularly radiofrequency fields emitted by mobile telephones; breast cancer from exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) before puberty; leukemia from exposure to 1,3-butadiene; lung cancer from exposure to air pollution; non-Hodgkin's lymphoma (NHL) from exposure to pesticides and solvents; and prostate cancer from exposure to pesticides, polyaromatic hydrocarbons (PAHs), and metal working fluids or mineral oils. In addition to NHL and prostate cancer, early findings from the National Institutes of Health Agricultural Health Study suggest that several additional cancers may be linked to a variety of pesticides. Our report also briefly describes the toxicological evidence related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans, namely exposures to bis-phenol A and epigenetic, trans-generational effects. To underscore the multi-factorial, multi-stage nature of cancer, we also present a technical description of cancer causation summarizing current knowledge in molecular biology. We argue for a new cancer prevention paradigm, one based on an understanding that cancer is ultimately caused by multiple interacting factors rather than a paradigm based on dubious attributable fractions. This new cancer prevention paradigm demands that we limit exposure to avoidable environmental and occupational carcinogens, in combination with additional important risk factors like diet and lifestyle. The research literature related to environmental and occupational causes of cancer is constantly growing, and future

updates will be carried out in light of new biological understanding of the mechanisms and new methods for studying exposures in human populations. The current state of knowledge is sufficient to compel us to act on what we know. We repeat the call of ecologist Sandra Steingraber: "From the right to know and the duty to inquire flows the obligation to act."

Kamangar F, Chow W-H, Abnet C, Dawsey S. Environmental Causes of Esophageal Cancer. *Gastroenterol Clin North Am.* 38(1): 27-vii.

Gastroenterol Clin North Am. Author manuscript; available in PMC 2010 March 1.

Published in final edited form as:

[Gastroenterol Clin North Am. 2009 March; 38\(1\): 27–vii.](#)

doi: [10.1016/j.gtc.2009.01.004](https://doi.org/10.1016/j.gtc.2009.01.004)

PMCID: PMC2685172

NIHMSID: NIHMS111277

Environmental Causes of Esophageal Cancer

[Farin Kamangar](#), MD, PhD, [Wong-Ho Chow](#), PhD, [Christian Abnet](#), PhD, MPH, and [Sanford Dawsey](#), MD

Synopsis

This article reviews the environmental risk factors and predisposing conditions for the two main histological types of esophageal cancer, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). Tobacco smoking, excessive alcohol consumption, drinking maté, low intake of fresh fruits and vegetables, achalasia, and low socioeconomic status increase the risk of ESCC. Results of investigations on several other potential risk factors, including opium consumption, intake of hot drinks, eating pickled vegetables, poor oral health, and exposure to human papillomavirus, polycyclic aromatic hydrocarbons, *N*-nitroso compounds, acetaldehyde, and fumonisins are also discussed. Gastroesophageal reflux, obesity, tobacco smoking, hiatal hernia, achalasia, and probably absence of *H. pylori* in the stomach increase the risk of EA. Results of studies investigating other factors, including low intake of fresh fruits and vegetables, consumption of carbonated soft drink, use of H₂ blockers, non-steroidal anti-inflammatory drugs, and drugs that relax the lower esophageal sphincter are also discussed.

Cigar, pipe, and cigarette smoking and bladder cancer risk in European men

A. Pitard¹, P. Brennan¹, J. Clavel², E. Greiser³, G. Lopez-Abente⁴, J. Chang-Claude⁵, J. Wahrendorf⁵, C. Serra⁶, M. Kogevinas⁷ & P. Boffetta^{1,*}

¹Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69008 Lyon, France; Ph.: +33-4-72738441; Fax: +33-4-72738342; E-mail: boffetta@iarc.fr; ²Unit 170, National Institute of Health and Medical Research (INSERM), Villejuif, France; ³Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany; ⁴Unit of Cancer Epidemiology, National Centre for Epidemiology, Madrid, Spain; ⁵German Cancer Research Centre, Heidelberg, Germany; ⁶Center for Studies, Medical Programs and Services, Parc Tauli Foundation, Sadabell, Spain; ⁷Municipal Institute of Medical Investigation, Barcelona, Spain (*Author for correspondence)

Received 7 August 2000; accepted in revised form 14 February 2001

Key words: bladder neoplasms, cigar, cigarettes, epidemiology, pipe.

Abstract

Objective: Estimating the risk of bladder cancer from cigar and pipe smoking is complicated by a small number of non-cigarette smokers included in most relevant studies.

Methods: We undertook a pooled analysis of the data on men from six published case-control studies from Denmark, France, Germany, and Spain, to assess the association between pipe and cigar smoking and bladder cancer, and to compare it with the risk from cigarette smoking. Complete history of tobacco smoking was ascertained separately for cigarettes, cigars, and pipe. Odds ratios (ORs) were estimated after adjusting for age, study, and employment in high-risk occupations.

Results: The pooled data set comprised 2279 cases and 5268 controls, of whom 88 cases and 253 controls smoked only cigars or pipe. The OR for pure cigarette smoking was 3.5 (95% confidence interval [CI] 2.9–4.2), that for pure pipe smoking was 1.9 (95% CI 1.2–3.1) and that for pure cigar smoking was 2.3 (95% CI 1.6–3.5). The increase in the OR of bladder cancer that was observed with duration of smoking was non-significantly lower for cigars than for cigarettes.

Conclusion: Our results suggest that smoking of cigars and pipe is carcinogenic to the urinary bladder, although the potency might be lower than for cigarettes.

Introduction

The causal association between cigarette smoking and bladder cancer risk is well established [1, 2]. However, information on a carcinogenic effect of other tobacco products on the bladder is limited and conflicting. Indeed, most relevant epidemiological studies include relatively small numbers of persons who are exclusively pipe or cigar smokers, and only a few studies include a sufficiently large number of pure cigar and pipe smokers to allow for quantitative analysis [3–9].

In a large study from the United States, pure pipe smokers were estimated to have an odds ratio (OR) of 1.2 (95% confidence interval [CI] 0.75–2.0) and

pure cigar smokers were estimated to have an OR of 1.3 (95% CI 0.92–1.9) [5]. A higher relative risk was observed for those who inhaled pipe smoke deeply (OR 3.1, 95% CI 1.3–7.5). In a further analysis of a subset of data from the same study, an increased risk of bladder cancer (OR 2.5, CI 1.0–6.0) was seen for pure cigar smokers, but no elevated risk was observed for pipe smokers [6]. Morrison et al. [4] conducted a large international case-control study in Boston (USA), Manchester (UK), and Nagoya (Japan). They found that, among men from Manchester who had never smoked cigarettes, the relative risk of bladder cancer associated with ever smoking a pipe was 3.9 (95% CI 1.3–11.8). In the remaining studies [3, 7–9], cigar and

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Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium

[Michael B. Cook](#), [Farin Kamangar](#), [David C. Whiteman](#), [Neal D. Freedman](#), [Marilie D. Gammon](#), [Leslie Bernstein](#), [Linda M. Brown](#), [Harvey A. Risch](#), [Weimin Ye](#), [Linda Sharp](#), [Nirmala Pandeya](#), [Penelope M. Webb](#), [Anna H. Wu](#), [Mary H. Ward](#), [Carol Giffen](#), [Alan G. Casson](#), [Christian C. Abnet](#), [Liam J. Murray](#), [Douglas A. Corley](#), [Olof Nyrén](#), [Thomas L. Vaughan](#), and [Wong-Ho Chow](#)

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Abstract

Background

Previous studies that showed an association between smoking and adenocarcinomas of the esophagus and esophagogastric junction were limited in their ability to assess differences by tumor site, sex, dose–response, and duration of cigarette smoking cessation.

Methods

We used primary data from 10 population-based case–control studies and two cohort studies from the Barrett’s Esophagus and Esophageal Adenocarcinoma Consortium. Analyses were restricted to white non-Hispanic men and women. Patients were classified as having esophageal adenocarcinoma (n = 1540), esophagogastric junctional adenocarcinoma (n = 1450), or a combination of both (all adenocarcinoma; n = 2990). Control subjects (n = 9453) were population based. Associations between pack-years of cigarette smoking and risks of adenocarcinomas were assessed, as well as their potential modification by sex and duration of smoking cessation. Study-specific odds ratios (ORs) estimated using multivariable logistic regression models, adjusted for age, sex, body mass index, education, and gastroesophageal reflux, were pooled using a meta-analytic methodology to generate summary odds ratios. All statistical tests were two-sided.

Results

The summary odds ratios demonstrated strong associations between cigarette smoking and esophageal adenocarcinoma (OR = 1.96, 95% confidence interval [CI] = 1.64 to 2.34), esophagogastric junctional adenocarcinoma (OR = 2.18, 95% CI = 1.84 to 2.58), and all adenocarcinoma (OR = 2.08, 95% CI = 1.83 to 2.37). In addition, there was a strong dose–response association between pack-years of cigarette smoking and each outcome ($P < .001$). Compared with current smokers, longer smoking cessation was associated with a decreased risk of all adenocarcinoma after adjusting for pack-years (<10 years of smoking cessation: OR = 0.82, 95% CI = 0.60 to 1.13; and ≥ 10 years of smoking cessation: OR = 0.71, 95% CI = 0.56 to 0.89). Sex-specific summary odds ratios were similar.

Conclusions

Cigarette smoking is associated with increased risks of adenocarcinomas of the esophagus and esophagogastric junction in white men and women; compared with current smoking, smoking cessation was associated with reduced risks.

From: (b) (6)
To: [VHA CO CLCW SME](#)
Subject: CLCW: Article on the temporality of post benzene leukemia
Date: Thursday, October 15, 2015 12:38:27 PM
Attachments: [Time and benzene and leukemia.pdf](#)

From: (b) (6)
Sent: Friday, September 11, 2015 3:15 AM
To: (b) (6)
Cc: (b) (6)
Subject: [EXTERNAL] Article on the temporality of post benzene leukemia

Hi (b) (6)

I don't know if everyone already has this article, but I searched for something regarding this topic and finally found exactly what I was looking for. The case I was working on was at CL for < 2 years and smoked for 17 years after leaving the service. He was then diagnosed with AML 57 years after leaving CL. I was determined to find something that talked about latency, but really had to search. I thought I would offer it to the others.

(b)
(6)

(b) (6)

From: (b) (6)
To: [VHA CO CLCW SME](#)
Subject: CLCW: TCE and RCC re CLCW
Date: Tuesday, February 17, 2015 12:31:22 PM
Attachments: [EAS](#)

Submitted by (b) (6) :

Please find attached a copy of the pages from the text book: Occupational Cancers, published in 2014 for RCC and TCE reviewing 20 studies between 1988-2010. The large size of the text book did not lend itself well to copying/scanning.

[FULL TEXT](#)

Clin Colon Rectal Surg. 2009 November; 22(4): 191–197.

PMCID: PMC2796096

Colorectal Cancer

Guest Editor Robin P. Boushey M.D., Ph.D.

Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors

[Fatima A. Hagggar](#), M.P.H.^{1,2} and [Robin P. Boushey](#), M.D., Ph.D.¹

ABSTRACT

In this article, the incidence, mortality, and survival rates for colorectal cancer are reviewed, with attention paid to regional variations and changes over time. A concise overview of known risk factors associated with colorectal cancer is provided, including familial and hereditary factors, as well as environmental lifestyle-related risk factors such as physical inactivity, obesity, smoking, and alcohol consumption.

[J Occup Environ Med](#). 2011 Sep;53(9):992-1007. doi: 10.1097/JOM.0b013e31822e0940.

Cancer mortality among aircraft manufacturing workers: an extended follow-up.

[Lipworth L](#), [Sonderman JS](#), [Mumma MT](#), [Tarone RE](#), [Marano DE](#), [Boice JD Jr](#), [McLaughlin JK](#).

Source: International Epidemiology Institute, Rockville, MD 20850, USA. loren@iei.us

Abstract

OBJECTIVE:

Extended cancer follow-up among 77,943 aircraft workers.

METHODS:

Comprehensive exposure information enabled detailed classification of trichloroethylene (TCE), perchloroethylene (PCE), mixed solvents, and chromates exposure among these workers.

RESULTS:

Exposure to TCE, PCE, mixed solvents or chromates was not associated with increased cancer risk overall or for most cancer sites. Elevated rates compared with the general population were seen for non-Hodgkin lymphoma for PCE exposure, and colon and testicular cancers and multiple myeloma for mixed solvents exposure. Internal cohort analyses, however, showed no significant trends of increasing risk for these cancers with increasing years of exposure to TCE, PCE or mixed solvents.

CONCLUSION:

This large, long-term cohort study with comprehensive exposure assessment found no consistent evidence of increased cancer risk overall or by site among aircraft workers, including those with long-term exposure to TCE, PCE, and mixed solvents.

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Dear Registrant,

On March 15, 2013 the Agency for Toxic Substances and Disease Registry (ATSDR) released its "Chapter A: Summary and Findings" water modeling report for the Hadnot Point and Holcomb Boulevard Water Treatment Plants and Vicinities for Marine Corps Base Camp Lejeune, N.C.

(<http://www.atsdr.cdc.gov/sites/lejeune/hadnotpoint.html>). You will receive a hard copy of the ATSDR fact sheet and other information in the mail in the coming weeks.

This report provides ATSDR's assessment of past exposures to a class of chemicals known as "volatile organic compounds" (VOCs) in the drinking water distributed by these two Camp Lejeune water treatment systems. These VOCs were commonly used as solvents for cleaning machinery and weapons, for dry cleaning, and some are found in fuels.

ATSDR's water modeling estimates that the first month any VOC exceeded the current Environmental Protection Agency (EPA) regulatory standards in drinking water in the Hadnot Point system was August 1953, and at least one VOC exceeded the current standard in Hadnot Point drinking water from August 1953 through January 1985.

This release marks a major milestone towards the completion of scientific efforts pertaining to this issue and another step in ongoing efforts to provide comprehensive science-based answers to the health questions that have been raised. ATSDR will use these results and the results of a similar water model developed for the Tarawa Terrace area in 2007 to estimate chemical exposures for several of their on-going health studies.

Since 1991, the Marine Corps has supported scientific and public health organizations that are studying these issues. We continue to support these initiatives and are working diligently to identify and notify individuals who, in the past, may have been exposed to the chemicals in drinking water. For more information about these efforts, or to update your contact information, please see: <http://www.marines.mil/clwater/>, call (877) 261-9782 or e-mail at clwater@usmc.mil.

For the complete report and for information about studies being conducted by

ATSDR, visit <http://www.atsdr.cdc.gov/sites/lejeune/> or call (800) 232-4636.

To contact Veterans Affairs to learn more about the health care benefits, please visit <http://www.publichealth.va.gov/exposures/camp-lejeune/> or call (877) 222-8387 (Healthcare) or (800) 827-1000 (Benefits).

Sincerely,
The Camp Lejeune Historic Drinking Water Program



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Cc: (b) (6)
Subject: Camp Lejeune studies and updates
Date: Saturday, December 07, 2013 12:17:37 PM

Hi, All

updates about Camp Lejeune Studies were posted on Dec 5, 2013 re: adverse pregnancy outcomes (birth defects and childhood cancers) and male breast cancer

<http://www.atsdr.cdc.gov/sites/lejeune/activities.html>

Also from the Associated Press is the following:

“RALEIGH, N.C. (AP) — A long-awaited study by the U.S. Centers for Disease Control and Prevention confirms a link between tainted tap water at a U.S. Marine Corps base in North Carolina and increased risk of serious birth defects and childhood cancers.

The study released late Thursday by the CDC's Agency for Toxic Substances & Disease Registry surveyed the parents of 12,598 children born at Camp Lejeune between 1968 and 1985, the year drinking-water wells contaminated with chemicals from a leaky fuel depot and a dry cleaner were closed.

The study concludes that babies born to mothers who drank the tap water while pregnant were four times more likely than normal to have such serious birth defects as spinal bifida. Babies whose mothers were exposed also had an elevated risk of such childhood cancers as leukemia”

Keep in contact and Best to all during the Holiday season!

(b) (6)

(b) (6) Syracuse VAMC)

Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal.

[Christensen KY](#), [Vizcaya D](#), [Richardson H](#), [Lavoué J](#), [Aronson K](#), [Siemiatycki J](#).

Source

University of Montreal Hospital Research Center, Montreal, Quebec, Canada.

Abstract

OBJECTIVE:

To evaluate the association between exposure to chlorinated solvents and cancer.

METHODS:

We conducted a case-control study of occupational exposures and cancer in Montreal, Quebec, Canada, including 3730 cancer cases and 533 population controls. Occupational exposures were derived using a combination of subject-reported job history and expert assessment. We examined the associations between two chemical families and six chlorinated solvents with 11 sites of cancer.

RESULTS:

The majority of the associations examined were null, although many were based on small numbers. We found two significantly elevated odds ratios (ORs), one between perchloroethylene and prostate cancer (OR = 4.3; 95% CI: 1.4 to 13) and another between trichloroethylene and melanoma (OR = 3.2; 95% CI: 1.0 to 9.9).

CONCLUSIONS:

There was little evidence of associations between chlorinated solvents and cancer. Limited power precludes strong inferences about absence of risk. We raise hypotheses about two possible associations: perchloroethylene with prostate cancer and trichloroethylene with melanoma

Cigar and pipe smoking and cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC).

[McCormack VA](#), [Agudo A](#), [Dahm CC](#), [Overvad K](#), [Olsen A](#), [Tjønneland A](#), [Kaaks R](#), [Boeing H](#), [Manjer J](#), [Almquist M](#), [Hallmans G](#), [Johansson I](#), [Chirlaque MD](#), [Barricarte A](#), [Dorransoro M](#), [Rodriguez L](#), [Redondo ML](#), [Khaw KT](#), [Wareham N](#), [Allen N](#), [Key T](#), [Riboli E](#), [Boffetta P](#).

Source

International Agency for Research on Cancer, Lyon, France.

Abstract

The carcinogenicity of cigar and pipe smoking is established but the effect of detailed smoking characteristics is less well defined. We examined the effects on cancer incidence of exclusive cigar and pipe smoking, and in combination with cigarettes, among 102,395 men from Denmark, Germany, Spain, Sweden and the United Kingdom in the EPIC cohort. Hazard ratios (HR) and their 95% confidence intervals (CI) for cancer during a median 9-year follow-up from ages 35 to 70 years were estimated using proportional hazards models. Compared to never smokers, HR of cancers of lung, upper aerodigestive tract and bladder combined was 2.2 (95% CI: 1.3, 3.8) for exclusive cigar smokers (16 cases), 3.0 (2.1, 4.5) for exclusive pipe smokers (33 cases) and 5.3 (4.4, 6.4) for exclusive cigarette smokers (1,069 cases). For each smoking type, effects were stronger in current smokers than in ex-smokers and in inhalers than in non-inhalers. Ever smokers of both cigarettes and cigars [HR 5.7 (4.4, 7.3), 120 cases] and cigarettes and pipes [5.1 (4.1, 6.4), 247 cases] had as high a raised risk as had exclusive cigarette smokers. In these smokers, the magnitude of the raised risk was smaller if they had switched to cigars or pipes only (i.e., quit cigarettes) and had not compensated with greater smoking intensity. Cigar and pipe smoking is not a safe alternative to cigarette smoking. The lower cancer risk of cigar and pipe smokers as compared to cigarette smokers is explained by lesser degree of inhalation and lower smoking intensity.

From: (b) (6)
To: (b) (6)
Subject: brain cancer article
Date: Thursday, February 19, 2015 3:46:13 PM
Attachments: [EAS](#)

Looks like we need a brain cancer category.

(b) (6)

*Compensation & Pension
Environmental Health Clinician
DMA Clinical Advisory Board
Ann Arbor VAMC*

Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors.

[Salehi F](#), [Turner MC](#), [Phillips KP](#), [Wigle DT](#), [Krewski D](#), [Aronson KJ](#).

Source

McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Canada.

Abstract

Breast cancer is the most frequently diagnosed cancer among Canadian women, accounting for about 30% of all new cancer cases each year. Although the incidence of breast cancer has increased over the past 50 years, the cause of this rise is unknown. Risk factors for breast cancer may be classified into four broad categories: (1) genetic/familial, (2) reproductive/hormonal, (3) lifestyle, and (4) environmental. Established risk factors for breast cancer include older age, later age at first full-term pregnancy, no full-term pregnancies, postmenopausal obesity, and genetic factors. However, these known risk factors cannot account for the majority of cases. In the early 1990s, it was suggested that exposure to some environmental chemicals such as organochlorine compounds may play a causal role in the etiology of breast cancer through estrogen-related pathways. The relationship between organochlorines and breast cancer risk has been studied extensively in the past decade and more, and at this point there is no clear evidence to support a causal role of most organochlorine pesticides in the etiology of human breast cancer, but more evidence is needed to assess risk associated with polychlorinated biphenyls (PCBs). Future studies need to consider the combined effects of exposures, concentrate on vulnerable groups such as those with higher levels of exposure, only consider exposures occurring during the most etiologically relevant time periods, and more thoroughly consider gene-environment interactions.

Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors.

[Salehi F](#), [Turner MC](#), [Phillips KP](#), [Wigle DT](#), [Krewski D](#), [Aronson KJ](#).

Source

McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Canada.

Abstract

Breast cancer is the most frequently diagnosed cancer among Canadian women, accounting for about 30% of all new cancer cases each year. Although the incidence of breast cancer has increased over the past 50 years, the cause of this rise is unknown. Risk factors for breast cancer may be classified into four broad categories: (1) genetic/familial, (2) reproductive/hormonal, (3) lifestyle, and (4) environmental. Established risk factors for breast cancer include older age, later age at first full-term pregnancy, no full-term pregnancies, postmenopausal obesity, and genetic factors. However, these known risk factors cannot account for the majority of cases. In the early 1990s, it was suggested that exposure to some environmental chemicals such as organochlorine compounds may play a causal role in the etiology of breast cancer through estrogen-related pathways. The relationship between organochlorines and breast cancer risk has been studied extensively in the past decade and more, and at this point there is no clear evidence to support a causal role of most organochlorine pesticides in the etiology of human breast cancer, but more evidence is needed to assess risk associated with polychlorinated biphenyls (PCBs). Future studies need to consider the combined effects of exposures, concentrate on vulnerable groups such as those with higher levels of exposure, only consider exposures occurring during the most etiologically relevant time periods, and more thoroughly consider gene-environment interactions.

[CA Cancer J Clin](#). 2002 Sep-Oct;52(5):301-9.

Organochlorines and breast cancer risk.

[Calle EE](#), [Frumkin H](#), [Henley SJ](#), [Savitz DA](#), [Thun MJ](#).

Source

American Cancer Society, Atlanta, GA, USA.

Abstract

Organochlorines are a diverse group of synthetic chemicals that include polychlorinated biphenyls (PCBs), dioxins, and organochlorine pesticides such as dichlorodiphenyl-

trichloroethane (DDT), lindane, and hexachlorobenzene. Although use of DDT and PCBs has been banned in the United States since the 1970s, some organochlorine compounds have accumulated and persisted within the environment. As a result, measurable amounts can still be found in human tissue. Because some organochlorine compounds act as estrogen agonists or antagonists within in vitro and experimental animal systems, a possible association of breast cancer risk with organochlorine exposure has been hypothesized and investigated. Although a few studies support this hypothesis, the vast majority of epidemiological studies do not. While some of these compounds may have other adverse environmental or health effects, organochlorine exposure is not believed to be causally related to breast cancer. Women concerned about possible organochlorine exposure can be reassured that available evidence does not suggest an association between these chemicals and breast cancer.

[Occup Environ Med.](#) 2010 Dec;67(12):837-44. doi: 10.1136/oem.2009.052175. Epub 2010 Aug 25.

Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe.

[Villeneuve S](#), [Cyr D](#), [Lynge E](#), [Orsi L](#), [Sabroe S](#), [Merletti F](#), [Gorini G](#), [Morales-Suarez-Varela M](#), [Ahrens W](#), [Baumgardt-Elms C](#), [Kaerlev L](#), [Eriksson M](#), [Hardell L](#), [Févotte J](#), [Guénel P](#).

Source

CESP-INSERM (National Institute of Health and Medical Research), Villejuif, France.

Abstract

OBJECTIVES:

Male breast cancer is a rare disease of largely unknown aetiology. In addition to genetic and hormone-related risk factors, a large number of environmental chemicals are suspected of playing a role in breast cancer. The identification of occupations or occupational exposures associated with an increased incidence of breast cancer in men may help to identify mammary carcinogens in the environment.

METHODS:

Occupational risk factors for male breast cancer were investigated in a multi-centre case-control study conducted in eight European countries which included 104 cases and 1901 controls. Lifetime work history was obtained during in-person interviews. Occupational exposures to endocrine disrupting chemicals (alkylphenolic compounds, phthalates, polychlorinated biphenyls and dioxins) were assessed on a case-by-case basis using expert judgement.

RESULTS:

Male breast cancer incidence was particularly increased in motor vehicle mechanics (OR 2.1, 95% CI 1.0 to 4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers, and furniture manufacture workers. The OR for exposure to alkylphenolic compounds above the median was 3.8 (95% CI 1.5 to 9.5). This association persisted after adjustment for occupational exposures to other environmental oestrogens.

CONCLUSION:

These findings suggest that some environmental chemicals are possible mammary carcinogens. Petrol, organic petroleum solvents or polycyclic aromatic hydrocarbons are suspect because of the consistent elevated risk of male breast cancer observed in motor vehicle mechanics. Endocrine disruptors such as alkylphenolic compounds may play a role in breast cancer.

[Am J Ind Med.](#) 2011 Jul;54(7):499-509. doi: 10.1002/ajim.20952. Epub 2011 Apr 6.

Breast cancer risk by occupation and industry: analysis of the CECILE study, a population-based case-control study in France.

[Villeneuve S](#), [Févotte J](#), [Anger A](#), [Truong T](#), [Lamkarkach F](#), [Gaye O](#), [Kerbrat P](#), [Arveux P](#), [Miglianico L](#), [Imbernon E](#), [Guénel P](#).

Source

National Institute of Health and Medical Research, Center for Research in Epidemiology and Population Health, Environmental Epidemiology of Cancer, Villejuif, France.

Abstract

BACKGROUND:

It has been suggested that certain occupational exposures may play a role in breast cancer etiology. The recognition of high-risk occupations may give clues about potential mammary carcinogens in the work place.

METHODS:

We conducted a population-based case-control study in France including 1,230 breast cancer cases and 1,315 population controls with detailed information on lifetime work history. Odds ratios for women ever employed in an occupation or industry were adjusted for well-established risk factors for breast cancer.

RESULTS:

Adjusted odds ratios were marginally increased in some white-collar occupations, as well as in textile workers (2.4; 95% CI [0.9-6.0]), rubber and plastics product makers (1.8; 95% CI [0.9-3.5]), and in women employed for more than 10 years as nurses (1.4; 95% CI [0.9-2.1]) and as tailors/dressmakers (1.5; 95% CI [0.9-2.6]). The incidence of breast cancer was increased among women employed in the manufacture of chemicals, of non-metallic mineral products, and decreased among women in agriculture.

CONCLUSIONS:

These findings suggest a possible role of occupational exposures in breast cancer, including night-shift work, solvents and endocrine disrupting chemicals and require further studies with detailed assessment of occupational exposures.

[Rev Environ Health](#). 2008 Jan-Mar;23(1):1-37.

Environmental and occupational causes of cancer: new evidence 2005-2007.

[Clapp RW](#), [Jacobs MM](#), [Loechler EL](#).

Source

Boston University School of Public Health, Boston, MA 02118, USA. richard.clapp@gmail.com

Abstract

What do we currently know about the occupational and environmental causes of cancer? As of 2007, the International Agency for Research on Cancer (IARC) identified 415 known or suspected carcinogens. Cancer arises through an extremely complicated web of multiple causes, and we will likely never know the full range of agents or combinations of agents. We do know that preventing exposure to individual carcinogens prevents the disease. Declines in cancer rates—such as the drop in male lung cancer cases from the reduction in tobacco smoking or the drop in bladder cancer among cohorts of dye workers from the elimination of exposure to specific aromatic amines—provides evidence that preventing cancer is possible when we act on what we know. Although the overall age-adjusted cancer incidence rates in the United States among both men and women have declined in the last decade, the rates of several types of cancers are on the rise; some of which are linked to environmental and occupational exposures. This report chronicles the most recent epidemiologic evidence linking occupational and environmental exposures with cancer. Peer-reviewed scientific studies published from January 2005 to June 2007 were reviewed, supplementing our state-of-the-evidence report published in September 2005. Despite weaknesses in certain individual studies, we consider the evidence linking the increased risk of several types of cancer with specific exposures somewhat strengthened by recent publications, among them brain cancer from exposure to non-ionizing radiation, particularly radiofrequency fields emitted by mobile telephones; breast cancer from exposure to the pesticide dichlorodiphenyltrichloroethane (DDT) before puberty; leukemia from exposure to 1,3-butadiene; lung cancer from exposure to air pollution; non-Hodgkin's lymphoma (NHL) from exposure to pesticides and solvents; and prostate cancer from exposure to pesticides, polyaromatic hydrocarbons (PAHs), and metal working fluids or mineral oils. In addition to NHL and prostate cancer, early findings from the National Institutes of Health Agricultural Health Study suggest that several additional cancers may be linked to a variety of pesticides. Our report also briefly describes the toxicological evidence related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans, namely exposures to bis-phenol A and epigenetic, trans-generational effects. To underscore the multi-factorial, multi-stage nature of cancer, we also present a technical description of cancer causation summarizing current knowledge in molecular biology. We argue for a new cancer prevention paradigm, one based on an understanding that cancer is ultimately caused by multiple interacting factors rather than a paradigm based on dubious attributable fractions. This new cancer prevention paradigm demands that we limit exposure to avoidable environmental and occupational carcinogens, in combination with additional important risk factors like diet and lifestyle. The research literature related to environmental and occupational causes of cancer is constantly growing, and future updates will be carried out in light of new biological understanding of the mechanisms and new methods for studying exposures in human populations. The current state of knowledge is sufficient to compel us to act on what we know. We repeat the call of ecologist Sandra Steingraber: "From the right to know and the duty to inquire flows the obligation to act."

[Environ Health Perspect.](#) 1998 Aug;106 Suppl 4:947-53.

Tetrachloroethylene-contaminated drinking water and the risk of breast cancer.

[Aschengrau A](#), [Paulu C](#), [Ozonoff D](#).

Source

Department of Epidemiology, University School of Public Health, Boston, Massachusetts, USA.
aaschen@bu.edu

Abstract

We conducted a population-based case-control study to evaluate the relationship between cases of breast cancer and exposure to tetrachloroethylene (PCE) from public drinking water (n = 258 cases and 686 controls). Women were exposed to PCE when it leached from the vinyl lining of water distribution pipes. The relative delivered dose was estimated using an algorithm that accounted for residential history, water flow, and pipe characteristics. Only small increases in breast cancer risk were seen among ever-exposed women either when latency was ignored or when 5 to 15 years of latency was considered. No or small increases were seen among highly exposed women either when latency was ignored or when 5 years of latency was considered. However, the adjusted odds ratios (ORs) were more increased for highly exposed women when 7 and 9 years of latency, respectively, were considered (OR 1.5 95% CI 0.5-4.7 and OR 2.3, 95% CI 0.6-8.8 for the 75th percentile, and OR 2.7, 95% CI 0.4-15.8 and OR 7.6, 95% CI 0.9-161.3 for the 90th percentile). The number of highly exposed women was too small for meaningful analysis when more years of latency were considered. Because firm conclusions from these data are limited, we recently undertook a new study with a large number of more recently diagnosed cases

Link to full article: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1533339>

Risk of breast cancer following exposure to tetrachloroethylene-contaminated drinking water in Cape Cod, Massachusetts: reanalysis of a case-control study using a modified exposure assessment

Lisa G Gallagher¹, Veronica M Vieira¹, David Ozonoff¹, Thomas F Webster¹ and Ann Aschengrau^{2*}

Abstract

Background: Tetrachloroethylene (PCE) is an important occupational chemical used in metal degreasing and drycleaning and a prevalent drinking water contaminant. Exposure often occurs with other chemicals but it occurred alone in a pattern that reduced the likelihood of confounding in a unique scenario on Cape Cod, Massachusetts. We previously found a small to moderate increased risk of breast cancer among women with the highest exposures using a simple exposure model. We have taken advantage of technical improvements in publically available software to incorporate a more sophisticated determination of water flow and direction to see if previous results were robust to more accurate exposure assessment.

Methods: The current analysis used PCE exposure estimates generated with the addition of water distribution modeling software (EPANET 2.0) to test model assumptions, compare exposure distributions to prior methods, and re-examine the risk of breast cancer. In addition, we applied data smoothing to examine nonlinear relationships between breast cancer and exposure. We also compared a set of measured PCE concentrations in water samples collected in 1980 to modeled estimates.

Results: Thirty-nine percent of individuals considered unexposed in prior epidemiological analyses were considered exposed using the current method, but mostly at low exposure levels. As a result, the exposure distribution was shifted downward resulting in a lower value for the 90th percentile, the definition of "high exposure" in prior analyses. The current analyses confirmed a modest increase in the risk of breast cancer for women with high PCE exposure levels defined by either the 90th percentile (adjusted ORs 1.0-1.5 for 0-19 year latency assumptions) or smoothing analysis cut point (adjusted ORs 1.3-2.0 for 0-15 year latency assumptions). Current exposure estimates had a higher correlation with PCE concentrations in water samples (Spearman correlation coefficient = 0.65, $p < 0.0001$) than estimates generated using the prior method (0.54, $p < 0.0001$).

Conclusions: The incorporation of sophisticated flow estimates in the exposure assessment method shifted the PCE exposure distribution downward, but did not meaningfully affect the exposure ranking of subjects or the strength of the association with the risk of breast cancer found in earlier analyses. Thus, the current analyses show a slightly elevated breast cancer risk for highly exposed women, with strengthened exposure assessment and minimization of misclassification by using the latest technology.

* Correspondence: aascheng@bu.edu

²Department of Epidemiology Boston University School of Public Health 715 Albany Street, Talbot 3 East, Boston, MA 021, USA

Full list of author information is available at the end of the article



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PCE in Water

Dose Model Appendix

The personal delivered dose model (PDD) sums the contribution of dose from inhalation, ingestion, and dermal absorption for each subject over all their residences. The subject interviews provided information on duration, frequency, temperature of baths and showers, water consumption, and residency time for all residences over a forty-year period. Inhalation doses from baths or showers were calculated as the product of concentration of PCE in the air, inhalation rate, duration, frequency, and residence time, and then summed for an overall inhalation dose. The PCE concentration in air was calculated using the two-resistance theory modeled by Little [11]. The Henry's law constant was calculated using the temperature-dependent values of vapor pressure, modeled using Antoine's equation. The overall mass transfer coefficient was calculated as the sum of two resistances in series, from the air film and water film. Similar to models used by McKone [10] and Little [17], the liquid and gas-phase mass transfer coefficients were modeled to be proportional to diffusivity, but the PDD model incorporated temperature-dependent diffusivity and viscosity.

Dose from ingestion was calculated as the product of PCE concentration in the water, the volume of water consumed, and the duration of tap water consumption. No ingestion dose was calculated for years that subjects reported bottled water use. Dose from dermal absorption was calculated using a nonsteady-state application of Fick's Law developed by the Environmental Protection Agency [12] and based on theoretical work by Cleek and Bunge [18]. The traditional steady-state approach for estimating the dermally absorbed dose of organic chemicals from water was revised by EPA because PCE does not reach steady state during the relatively short contact time of water on a subject's skin during bathing. The permeability coefficient for PCE was calculated using

the equations developed by Potts and Guy [19]. The personal delivered dose model was also developed for trichloroethylene (TCE) and validated using a series of shower experiments by Giardino and Andelman [20]. Sensitivity analyses revealed that the PDD model was most influenced by the initial PCE concentration and residency time and least influenced by temperature [21].

The surgeon general report on smoking and health 50 years later: breast cancer and the cost of increasing caution.

[Glantz SA](#), [Johnson KC](#).

Author information

Abstract

Despite the Surgeon General's strong track record and the rapidly expanding body of solid scientific work demonstrating that smoking caused a wide range of diseases, the decision making process for concluding "causality" in Surgeon General reports has become increasingly cautious and defensive. Whereas, the 1964 report did not conclude that smoking caused heart disease, it recommended that "from the public health viewpoint [one should] assume that the established association has causative meaning rather than to suspend judgment until no uncertainty remains," the de facto practice has become to do just the opposite. In particular, the 2004 report reached an affirmative negative conclusion that active smoking did not cause breast cancer and the 2006 report on passive smoking only found the link "suggestive." In contrast, in 2005 the California EPA found both active and passive smoking caused breast cancer in younger women. The evidence has continued to strengthen since 2005: there are now 12 large cohort studies that consistently demonstrate a dose-response relationship with smoking before first birth and increased breast cancer risk. The Surgeon General's increasing caution is preventing young women around the world from appreciating the risks that smoking and secondhand smoke pose for developing breast cancer. *Cancer Epidemiol Biomarkers Prev*; 23(1); 37-46. ©2014 AACR.

PMID:

24420985

[PubMed - in process]

Breast cancer risk after occupational solvent exposure: the influence of timing and setting.

[Ekenga CC](#)¹, [Parks CG](#)², [D'Aloisio AA](#)², [DeRoo LA](#)³, [Sandler DP](#)².

[Author information](#)

Abstract

Organic solvents are ubiquitous in occupational settings where they may contribute to risks for carcinogenesis. However, there is limited information on organic solvents as human breast carcinogens. We examined the relationship between occupational exposure to solvents and breast cancer in a prospective study of 47,661 women with an occupational history in the Sister Study cohort. Occupational solvent exposure was categorized using self-reported job-specific solvent use collected at baseline. Multivariable Cox regression analyses were used to assess breast cancer risk, adjusting for established breast cancer risk factors. A total of 1,798 women were diagnosed with breast cancer during follow-up, including 1,255 invasive cases. Overall the risk of invasive breast cancer was not associated with lifetime exposure to solvents [HR, 1.04; 95% confidence interval (CI), 0.88-1.24]. Parous women who worked with solvents before their first full-term birth had an increased risk of estrogen receptor-positive invasive breast cancer compared with women who never worked with solvents (HR, 1.39; 95% CI, 1.03-1.86). A significantly elevated risk for estrogen receptor-positive invasive breast cancer was associated with solvent exposure among clinical laboratory technologists and technicians (HR, 2.00; 95% CI, 1.07-3.73). Occupational exposure to solvents before first birth, a critical period of breast tissue differentiation, may result in increased vulnerability for breast cancer. Our findings suggest a need for future studies in this area to focus on exposure time windows and solvent types in different occupational settings.

©2014 American Association for Cancer Research.

Male bladder cancer risk and occupational exposure according to a job-exposure matrix-a case-control study in British Columbia, Canada.

[Richardson K](#), [Band PR](#), [Astrakianakis G](#), [Le ND](#).

Source: Cancer Control Research, BC Cancer Research Centre, Vancouver, British Columbia, Canada.

Abstract

OBJECTIVES:

The authors investigated the risk of bladder cancer in association with exposure to over 12 000 occupational chemical agents, complex mixtures, and other substances (hereafter referred to as chemical agents).

METHODS: Adult males diagnosed with cancer between 1983 and 1990 in British Columbia, Canada, were surveyed. Detailed occupational histories and confounding information was provided by a self-administered questionnaire. Cancer controls were matched to bladder cancer cases, resulting in 1062 cases and 8057 controls for the analysis. An extensive United-States-based job-exposure matrix was applied to estimate cumulative exposure to occupational chemical agents. Odds ratios for bladder cancer due to exposure to chemical agents were estimated via conditional logistic regression analyses, adjusted for important confounders.

RESULTS: A significantly ($P < 0.05$) increased risk was detected for ever exposure to 635 chemical agents, and 341 chemical agents exhibited a significantly increasing dose-response relationship. Adjustment for multiple comparisons resulted in a subset of 29 chemical agents that continued to show significant results. A principal components analysis classified these 29 chemical agents into five independent groups, distinguished mainly by job. Exposures to these chemical agents were largely due to employment in the logging and construction industries and occupations involving motor vehicles. Consistent results were observed for bladder carcinogens reported in the literature.

CONCLUSIONS: This study suggests that several specific chemical agents were significantly associated with the risk of bladder cancer. The chemical agents were mainly derivatives or combustion products of fossil fuels. The results corroborate important findings from the literature and document a risk for specific chemical agents not previously reported.

Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies.

[Brennan P](#), [Bogillot O](#), [Cordier S](#), [Greiser E](#), [Schill W](#), [Vineis P](#), [Lopez-Abente G](#), [Tzonou A](#), [Chang-Claude J](#), [Bolm-Audorff U](#), [Jöckel KH](#), [Donato F](#), [Serra C](#), [Wahrendorf J](#), [Hours M](#), [T'Mannetje A](#), [Kogevinas M](#), [Boffetta P](#).

Source

International Agency for Research on Cancer, Lyon, France. Brennan@iarc.fr

Abstract

The primary risk factor for bladder cancer is cigarette smoking. Using a combined analysis of 11 case-control studies, we have accurately measured the relationship between cigarette smoking and bladder cancer in men. Available smoking information on 2,600 male bladder cancer cases and 5,524 male controls included duration of smoking habit, number of cigarettes smoked per day and time since cessation of smoking habit for ex-smokers. There was a linear increasing risk of bladder cancer with increasing duration of smoking, ranging from an odds ratio (OR) of 1.96 after 20 years of smoking (95% confidence interval [CI] 1.48-2.61) to 5.57 after 60 years (CI 4.18-7.44). A dose relationship was observed between number of cigarettes smoked per day and bladder cancer up to a threshold limit of 15-20 cigarettes per day, OR = 4.50 (CI 3.81-5.33), after which no increased risk was observed. An immediate decrease in risk of bladder cancer was observed for those who gave up smoking. This decrease was over 30% after 1-4 years, OR = 0.65 (0.53-0.79), and was over 60% after 25 years of cessation, OR = 0.37 (0.30-0.45). However, even after 25 years, the decrease in risk did not reach the level of the never-smokers, OR = 0.20 (0.17-0.24). The proportion of bladder cancer cases attributable to ever-smoking was 0.66 (0.61-0.70) for all men and 0.73 (0.66-0.79) for men younger than 60. These estimates are higher than previously calculated.

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Cancer. 1985 Feb 15;55(4):901-6.

Bladder cancer risk and pipes, cigars, and smokeless tobacco.

[Hartge P](#), [Hoover R](#), [Kantor A](#).

Abstract

Interview data from 2982 patients with bladder cancer and 5782 controls selected from the general population were used to assess the effects of non-cigarette tobacco use on bladder cancer risk. Compared to men who had never smoked, those who had smoked pipes but not cigars or cigarettes had a relative risk estimated at 1.23 (95% confidence interval [CI] = 0.75-2.00). Those who smoked cigars but not pipes or cigarettes were estimated to have a relative risk of 1.33 (95% CI = 0.92-1.94). Little evidence of dose response was observed. The excess relative risk to pipe smokers was limited to those who inhaled deeply.

Bladder cancer, a review of the environmental risk factors.

[Letašiová S¹](#), [Medve'ová A](#), [Šovčíková A](#), [Dušínská M](#), [Volkovová K](#), [Mosoiu C](#), [Bartonová A](#).

Author information

- ¹Institute of Biochemistry, Nutrition and Health Protection, Faculty of Chemical and Food Technology, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovak Republic. silvia.letasiova@gmail.com

Abstract

BACKGROUND:

Many epidemiological studies and reviews have been performed to identify the causes of bladder cancer. The aim of this review is to investigate the links between various environmental risk factors and cancer of the bladder.

METHODS:

A systematic literature search was performed using PubMed, Science Direct, Scopus, Scholar Google and Russian Google databases to identify reviews and epidemiological studies on bladder cancer risk factors associated with the environment published between 1998 and 2010. Only literature discussing human studies was considered.

RESULTS:

Smoking, mainly cigarette smoking, is a well known risk factor for various diseases, including bladder cancer. Another factor strongly associated with bladder cancer is exposure to arsenic in drinking water at concentrations higher than 300 µg/l. The most notable risk factor for development of bladder cancer is occupational exposure to aromatic amines (2-naphthylamine, 4-aminobiphenyl and benzidine) and 4,4'-methylenebis(2-chloroaniline), which can be found in the products of the chemical, dye and rubber industries as well as in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust. There are also data suggesting an effect from other types of smoking besides cigarettes (cigar, pipe, Egyptian waterpipe, smokeless tobacco and environmental tobacco smoking), and other sources of arsenic exposure such as air, food, occupational hazards, and tobacco. Other studies show that hairdressers and barbers with occupational exposure to hair dyes experience enhanced risk of bladder cancer. For example, a study related to personal use of hair dyes demonstrates an elevated bladder cancer risk for people who used permanent hair dyes at least once a month, for one year or longer.

CONCLUSION:

Smoking, in particular from cigarettes, exposure to arsenic in drinking water, and occupational exposure to aromatic amines and 4,4'-methylenebis(2-chloroaniline) are well known risk factors for various diseases including bladder cancer. Although the number of chemicals related to occupational exposure is still growing, it is worth noting that it may take several years or decades between exposure and the subsequent cancer.

Body mass index, height, and risk of lymphoid neoplasms in a large US cohort.

[Patel AV](#), [Diver WR](#), [Teras LR](#), [Birmann BM](#), [Gapstur SM](#).

Abstract

ABSTRACT Results from epidemiologic studies examining associations between body size and risk of non-Hodgkin lymphoma (NHL) are inconsistent and etiology may vary by histologic subtypes of disease. Using Cox proportional hazards regression, multivariable relative risks (RR) and 95% confidence intervals (CI) were computed for associations of body mass index (BMI) and height with NHL in the prospective American Cancer Society Cancer Prevention Study-II Nutrition Cohort. From 1992-2007, 2,074 incident NHL cases were identified among 152,423 men and women. Obese individuals (BMI $\geq 30\text{kg/m}^2$) had 23% higher incidence of NHL (95% CI 1.08-1.40) compared to normal weight (BMI 18.5- $<25\text{kg/m}^2$). Height was positively associated with NHL (RR=1.25, 95% CI 1.10-1.43, sex-specific quintile 5 vs. 1). BMI associations were strongest for diffuse large B-cell lymphoma; height was most strongly associated with chronic lymphocytic leukemia/small lymphocytic lymphoma and to a lesser extent with multiple myeloma. These findings provide further evidence that body size may play a role in the etiology of NHL, which is of public health importance given the rapid rise in obesity worldwide.

[Lancet](#). 2014 Aug 30;384(9945):755-65. doi: 10.1016/S0140-6736(14)60892-8. Epub 2014 Aug 13

Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults.

[Bhaskaran K](#)¹, [Douglas I](#)², [Forbes H](#)², [dos-Santos-Silva I](#)², [Leon DA](#)², [Smeeth L](#)³.

Abstract

BACKGROUND: High body-mass index (BMI) predisposes to several site-specific cancers, but a large-scale systematic and detailed characterisation of patterns of risk across all common cancers adjusted for potential confounders has not previously been undertaken. We aimed to investigate the links between BMI and the most common site-specific cancers.

METHODS: With primary care data from individuals in the Clinical Practice Research Datalink with BMI data, we fitted Cox models to investigate associations between BMI and 22 of the most common cancers, adjusting for potential confounders. We fitted linear then non-linear (spline) models; investigated effect modification by sex, menopausal status, smoking, and age; and calculated population effects.

FINDINGS: 5·24 million individuals were included; 166,955 developed cancers of interest. BMI was associated with 17 of 22 cancers, but effects varied substantially by site. Each 5 kg/m² increase in BMI was roughly linearly associated with cancers of the uterus (hazard ratio [HR] 1·62, 99% CI 1·56-1·69; p<0·0001), gallbladder (1·31, 1·12-1·52; p<0·0001), kidney (1·25, 1·17-1·33; p<0·0001), cervix (1·10, 1·03-1·17; p=0·00035), thyroid (1·09, 1·00-1·19; p=0·0088), and leukaemia (1·09, 1·05-1·13; p≤0·0001). BMI was positively associated with liver (1·19, 1·12-1·27), colon (1·10, 1·07-1·13), ovarian (1·09, 1·04-1·14), and postmenopausal breast cancers (1·05, 1·03-1·07) overall (all p<0·0001), but these effects varied by underlying BMI or individual-level characteristics. We estimated inverse associations with prostate and premenopausal breast cancer risk, both overall (prostate 0·98, 0·95-1·00; premenopausal breast cancer 0·89, 0·86-0·92) and in never-smokers (prostate 0·96, 0·93-0·99; premenopausal breast cancer 0·89, 0·85-0·94). By contrast, for lung and oral cavity cancer, we observed no association in never smokers (lung 0·99, 0·93-1·05; oral cavity 1·07, 0·91-1·26): inverse associations overall were driven by current smokers and ex-smokers, probably because of residual confounding by smoking amount. Assuming causality, 41% of uterine and 10% or more of gallbladder, kidney, liver, and colon cancers could be attributable to excess weight. We estimated that a 1 kg/m² population-wide increase in BMI would result in 3790 additional annual UK patients developing one of the ten cancers positively associated with BMI.

INTERPRETATION:

BMI is associated with cancer risk, with substantial population-level effects. The heterogeneity in the effects suggests that different mechanisms are associated with different cancer sites and different patient subgroups.

INFORMATION PAPER
ATSDR Mortality Study of Civilian Employees at Camp Lejeune and Camp Pendleton

Issue:

- The Department of Defense (DoD) and the Department of Veterans Affairs (VA) coordinate on the provision of medical care for veterans who formerly lived at Marine Corps Base Camp Lejeune, NC. Contaminated drinking water was discovered in the 1980s at Camp Lejeune, leading to concerns about long-term health effects.
- On 13 Aug 2014, the Agency for Toxic Substances and Disease Registry (ATSDR), which is part of the CDC, published a mortality study of civilian employees who worked at Camp Lejeune (reference below).

Discussion:

- ATSDR has been evaluating the health of previous residents of Camp Lejeune (CL) since 1991. The Navy has provided more than \$40 million to fund these ATSDR studies.
- The purpose of the study was “to determine if potential exposures of employees to contaminated drinking water at Camp Lejeune increased the risk of mortality from cancers and other chronic diseases.”
- The death rates of 4,647 civilian employees at Camp Lejeune (CL) were compared to the death rates of 4,690 civilians at Camp Pendleton (CP), as well as with death rates in the general US population.
- Both the CL and CP groups were significantly healthier than the general US population. Both groups had statistically significant decreases in mortality from all causes. There was a significant, 14% decrease in the overall death rate from all causes in the CL group, compared to the US population.
- 14.1% of the individuals in the CL group and 18.5% of the individuals in the CP group died by the end of the follow-up period in 2008. Therefore, there was a lower overall mortality rate in the CL group, compared to the control group from CP.
- ATSDR concluded there were “elevated risks” in the CL group for the following diseases: kidney cancer, leukemias, multiple myeloma, rectal cancer, oral cavity cancers, and Parkinson’s disease. However, none of these diseases showed a statistically significant increase in the CL group.
- These ATSDR conclusions about “elevated risks” of these diseases were not supported by the data.
- This mortality study was published in an obscure, on-line journal, which requires payment from authors and which has minimal scientific peer review. High-quality medical journals do not require payment for publication; and they require rigorous peer review before manuscripts are accepted.
- ATSDR published two previous Camp Lejeune studies in the same journal, a birth defects study in Dec 2013 and a mortality study in Marines in Feb 2014. These two previous studies had the same flaws as the mortality study in civilians, in that ATSDR drew conclusions that were not supported by the data.
- ATSDR will release the results of three more health studies related to CL in the next year, including a national health survey of the CL and CP populations.
- This study could have a direct impact on VA disability compensation. Congress and veterans groups are likely to pressure VA to make a presumption of service connection for the diseases in the two mortality studies, even though the ATSDR conclusions were flawed. This could lead to automatic decisions (“presumptions”) on compensation for thousands of veterans.

ATSDR study: Bove, FJ, Ruckart, PZ, Maslia, M, Larson, TC. Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environmental Health* 2014;13:68.

Dr. Kelley Brix, Defense Health Agency, Research and Development Directorate, 703-681-8211, 14 Aug 2014



RESEARCH

Open Access

Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study

Frank J Bove^{1*}, Perri Zeitz Ruckart¹, Morris Maslia² and Theodore C Larson¹

Abstract

Background: Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s 1985.

Methods: We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975 1985 and were stationed at Camp Lejeune or Camp Pendleton, California during this period. Camp Pendleton's drinking water was uncontaminated. Mortality follow up was 1979 2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune (N = 154,932) and Camp Pendleton (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the Camp Lejeune cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

Results: There were 8,964 and 9,365 deaths respectively, in the Camp Lejeune and Camp Pendleton cohorts. Compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios (HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the Camp Lejeune cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: 0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: 0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: 0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non monotonic exposure response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

Conclusion: The study found elevated HRs at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long term follow up would be necessary to comprehensively assess effects of drinking water exposures at the base.

Keywords: Mortality, Cancers, Trichloroethylene, Tetrachloroethylene, Vinyl chloride, Benzene, Drinking water

* Correspondence: fbove@cdc.gov

¹Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry (ATSDR), 4770 Buford Highway, MS F 58, Atlanta, GA 30341, USA

Full list of author information is available at the end of the article



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Background

Samples taken during 1980-1985 at United States Marine Corps (USMC) Base Camp Lejeune, North Carolina detected solvents in drinking water supplied by two of the base's eight treatment plants, Tarawa Terrace (TT) and Hadnot Point (HP). The TT supply wells were contaminated by an off-base dry cleaning business. The HP supply wells were contaminated by on-base sources: leaking underground storage tanks, industrial area spills and waste disposal sites. Contaminated supply wells in the TT and HP systems were shut down by February 1985 [1,2].

The primary contaminant in the TT distribution system was tetrachloroethylene (PCE) with a maximum measured level of 215 micrograms per liter ($\mu\text{g/L}$). Also detected were much lower levels of trichloroethylene (TCE), trans-1,2-dichloroethylene, and vinyl chloride, created when PCE degraded in ground water over time. The TT system served approximately 1,850 family housing units on base during 1975-1985 [1].

The primary contaminant in the HP distribution system was TCE with a maximum detected level of 1,400 $\mu\text{g/L}$. The maximum level of PCE was 100 $\mu\text{g/L}$, and benzene was also detected. Trans-1,2-dichloroethylene and vinyl chloride were present due to degradation of TCE in ground water [2]. During 1975-1985, the HP system served the "mainside" area of the base where a majority of bachelor's quarters ("barracks") and a few family housing units were located.

The Holcomb Boulevard system was a third system at the base, which served approximately 2,100 family housing units and was uncontaminated except for intermittent periods during dry spring-summer months when the HP system provided supplementary water. During a 2-week period in early 1985, the Holcomb Boulevard treatment plant shut down for repairs and the HP system provided water for its service area.

In each system, water from supply wells was mixed together at the treatment plant prior to distribution. Contamination levels in each system varied depending on the wells in use at a particular time.

Current U.S. maximum contaminant levels (MCLs) for TCE, PCE and benzene are 5 $\mu\text{g/L}$. The MCL for vinyl chloride is 2 $\mu\text{g/L}$. TCE has recently been classified as a human carcinogen [3,4]. Vinyl chloride and benzene are also classified as human carcinogens [5]. PCE is classified as a "likely" or "probable" human carcinogen [4,6].

Several meta-analyses and reviews assessed health effects of these chemicals [3-7]. Most of the evidence has come from occupational studies where the primary route of exposure was inhalation. Drinking water exposure to these chemicals involves contributions to total internal body dose from three routes: ingestion, inhalation and dermal. The dose from the inhalation and dermal routes may be as high

as the dose from the ingestion route. For example, an internal dose via inhalation to TCE during a 10-minute shower may equal the internal dose via the ingestion of 2 liters of TCE-contaminated drinking water [8].

The literature is limited on health effects of drinking water exposures to these chemicals. A drinking water study in NJ observed associations between TCE and leukemia and non-Hodgkin lymphoma (NHL), and PCE and NHL [9]. PCE-contaminated drinking water was associated with lung cancer, bladder cancer, leukemia, rectal cancer, and female breast cancer in a study at Cape Cod, MA [10-12]. No studies have evaluated associations between drinking water exposures to these chemicals and medically confirmed, non-cancer diseases in adults.

The purpose of this study was to determine whether exposures of Marine and Naval personnel to contaminated drinking water at Camp Lejeune increased risk of mortality from cancers and other chronic diseases.

Methods

We identified several diseases of *primary* interest: cancers of the kidney, hematopoietic system (NHL, leukemia, multiple myeloma, Hodgkin lymphoma), liver, bladder, esophagus and cervix. Kidney cancer, NHL and liver cancer were selected because the U.S. Environmental Protection Agency (EPA) and the International Agency For Research On Cancer cited evidence for a causal association with TCE exposure, although the evidence for liver cancer is "more limited" than the evidence for kidney cancer and NHL [4,7]. The National Toxicology Program (NTP) concluded that there was "evidence for consistent positive associations" between PCE and esophageal and cervical cancer, and EPA cited evidence for associations between PCE and bladder cancer and multiple myeloma [5,6]. Benzene is a known cause of leukemia.

Diseases of *secondary* interest were identified based on information from literature reviews suggesting possible associations with the contaminants or with solvents in general: aplastic anemia, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), kidney and liver diseases, Parkinson's disease, and cancers of the connective tissue, brain, pancreas, oral cavity, pharynx, lung, larynx, prostate, breast, colon and rectum [3,5-7,13].

Because this was a data linkage study with no smoking information, we evaluated smoking-related diseases not known to be associated with the contaminants to assess possible confounding: cardiovascular disease, chronic obstructive pulmonary disease (COPD), and stomach cancer.

Study population and eligibility

The Camp Lejeune cohort consisted of 154,932 Marine and Naval personnel ("Marines") who began active duty service during April 1975 – December 1985 and were stationed at Camp Lejeune anytime during this period.

A comparison cohort consisted of 154,969 Marine and Naval personnel who began active duty service during April 1975 – December 1985, were stationed anytime during this period at USMC Base Camp Pendleton, but were not stationed at Camp Lejeune during this period. Camp Pendleton, located along the Southern California coast in northern San Diego County and southern Orange County, did not have contaminated drinking water during the period when the cohort was stationed at the base [14].

We obtained data for Camp Lejeune and Camp Pendleton from Defense Manpower Data Center (DMDC) Active Duty Military Personnel Master File for April 1975–December 1985. Unit information first became available in the DMDC file in April 1975 [15]. The USMC provided a list of units stationed at Camps Lejeune and Pendleton during 1975–1985. The quarterly DMDC file contained Social Security number (SSN), date of birth, sex, race/ethnicity, education, marital status, rank, active duty start date, total months of service, and military occupation code. This study was approved by the Centers for Disease Control and Prevention Institutional Review Board.

Vital status ascertainment

Personal identifier information from the DMDC database was matched to data in the Social Security Administration (SSA) Death Master File (DMF) and SSA Office of Research, Evaluation and Statistics (ORES) Presumed Living Search to determine vital status [16,17]. For those not matched, a commercial tracing service was used to determine vital status. Identified deaths and individuals whose vital status remained unknown were then searched in the National Death Index (NDI). Those whose vital status remained unknown after the NDI search were considered “lost to follow-up” but contributed person-years to the study until the last date they were known to be alive based on commercial tracing or DMDC data. Underlying and contributing causes of death information were obtained from NDI.

Exposure assessment

Due to limited numbers of historical samples for drinking water contamination, ATSDR conducted a historical reconstruction of the contamination using ground water fate and transport and distribution system models. Monthly average estimates of contaminant concentrations in each system were computed and reported in peer-reviewed agency reports [1,2]. Table 1 summarizes the estimated monthly mean contaminant concentrations from January 1975 through February 1985. Estimated monthly mean concentrations of PCE in the Tarawa Terrace distribution system during this period ranged from 0 to 158 µg/L with a median of approximately

85 µg/L (Table 1). PCE was the primary contaminant in the Tarawa Terrace system. Estimated monthly mean concentrations of TCE in the Hadnot Point distribution system during this period ranged from 0 to 783 µg/L, with a median level of approximately 366 µg/L (Table 2). TCE was the main contaminant in the Hadnot Point system although estimated monthly levels of PCE and vinyl chloride were often considerably above their MCLs, with medians of the estimates during this period of 15 µg/L and 22 µg/L, respectively.

On average, an individual in the Camp Lejeune cohort resided at the base for 18 months. Each individual was assigned estimated monthly average contaminant concentrations in the drinking water system serving the individual's residence during the period of residence. We used several sources of information to determine an individual's residence (Figure 1).

Married Camp Lejeune cohort members resided either in base family housing or in off-base housing. We used probability and manual matching to link married cohort members to base family housing records on name, rank, occupancy dates, and dates stationed on base.

Unmarried officers resided in bachelor officers' quarters served by the Holcomb Boulevard water system during 1975–1985. Unmarried enlisted individuals resided in barracks. Unit barrack locations were identified using information provided by retired marines, base staff, and base command chronologies. Female marines resided in areas served by the HP system until June 1977 when they moved to an area with uncontaminated drinking water.

Data analysis

Follow-up began on January 1, 1979 or start of active duty service at either base, whichever was later, and continued until December 31, 2008, if the person was known to be alive, or to date of death. Those with unknown vital status were followed until the last date they were known to be alive based on available data.

We used the Life Table Analysis System (LTAS) to compute cause-specific, standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) comparing the Camp Lejeune and Camp Pendleton cohorts to age-sex-race-and calendar period-specific U.S. mortality rates for underlying and contributing causes of death [18]. In apportioning person-years to specific age-race-sex-and calendar period categories for each base, once an individual was stationed at Camp Lejeune (e.g., some began at Camp Pendleton and later transferred to Camp Lejeune), all subsequent person-years were assigned to Camp Lejeune.

- a. Comparisons between Camp Lejeune and Camp Pendleton cohorts

Table 1 Estimated monthly average contaminant concentrations in the Tarawa Terrace system, 1975 – 1985

| 1975 1985 (132 months) | | | | | | |
|--|-------------|---------------|----------------------|---------------|--------------------|--|
| Contaminant | Mean (µg/L) | Median (µg/L) | Range (µg/L) | # Months >MCL | # Months >100 µg/L | |
| Tetrachloroethylene | 75.7 | 84.9 | 0 158.1 | 117 | 16 | |
| Trichloroethylene | 3.1 | 3.5 | 0 6.6 | 11 | 0 | |
| Vinyl chloride | 5.6 | 6.2 | 0 12.3 | 117 | 0 | |
| 1975 1979 (60 months) | | | | | | |
| Tetrachloroethylene | 68.3 | 68.2 | 43.8 94.8 | 60 | 0 | |
| Trichloroethylene | 2.8 | 2.9 | 1.7 3.9 | 0 | 0 | |
| Vinyl chloride | 5.2 | 5.5 | 2.6 7.3 | 60 | 0 | |
| January 1980 January 1985 (61 months)* | | | | | | |
| Tetrachloroethylene | 96.1 | 95.5 | 0 [¥] 158.1 | 57 | 16 | |
| Trichloroethylene | 3.9 | 3.9 | 0 [¥] 6.6 | 11 | 0 | |
| Vinyl chloride | 7.0 | 7.0 | 0 [¥] 12.3 | 57 | 0 | |

*Two contaminated wells were shut down in January 1985. Estimated monthly average tetrachloroethylene levels from February through December 1985 were <4 µg/L.

[¥]One contaminated well was shut down for maintenance during 7/80 8/80 and 1/83 2/83. The other contaminated well was not in use until August 1984.

We used Cox extended regression models [19] with age as the time variable and base location as a time-varying dichotomous variable to calculate hazard ratios (HRs) comparing mortality rates between Camp Lejeune and Camp Pendleton cohorts. These analyses assumed everyone at Camp Lejeune was exposed to contaminated drinking water at their residences and/or during daily activities on base while those at Camp Pendleton were unexposed. We accounted for a “latency period” by lagging exposure to a base by 10, 15, and 20 years in addition to an analysis with no lag. For example, a 10 year lag would assign to an individual aged 29,

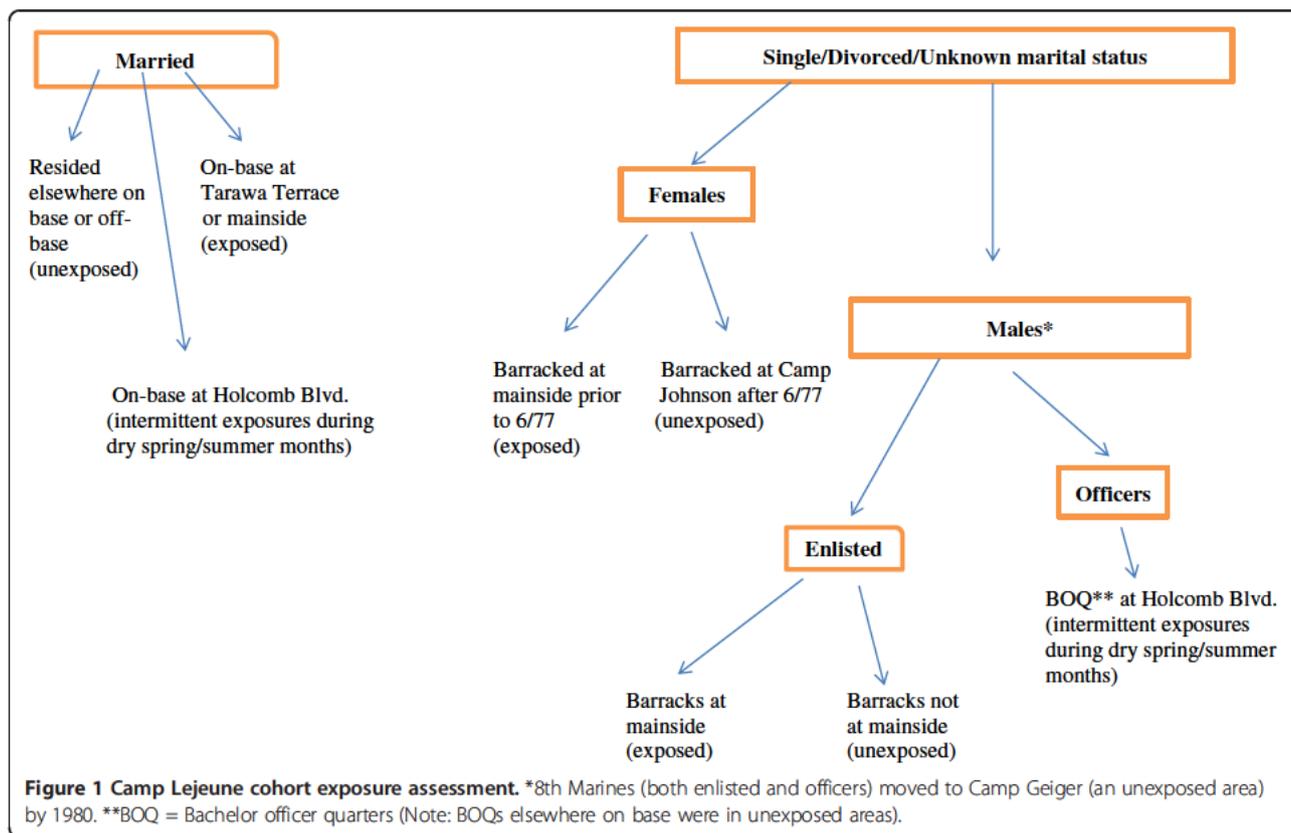
the base the individual was stationed at age 19. If this individual was not yet serving at age 19, then the person-year for age 29 was assigned to a category, “not at either base”. We used the Akaike’s information criterion (AIC), a measure of model goodness of fit, to select an appropriate lag period.

b. Analyses within the Camp Lejeune cohort
 Within the Camp Lejeune cohort, we evaluated exposure-response relationships between cumulative exposures to drinking water contaminants and cause of mortality using Cox extended regression models with age as the time variable and cumulative exposure as a time-varying variable. Estimated

Table 2 Estimated monthly average contaminant concentrations in the Hadnot Point system, 1975 – 1985

| 1975 1985 | | | | | | |
|-----------------------------|-------------|---------------|--------------|---------------|--------------------|--|
| Contaminant | Mean (µg/L) | Median (µg/L) | Range (µg/L) | # Months >MCL | # Months >100 µg/L | |
| Tetrachloroethylene | 15.7 | 15.4 | 0 38.7 | 111 | 0 | |
| Trichloroethylene | 358.7 | 365.9 | 0 783.3 | 122 | 113 | |
| Vinyl chloride | 24.0 | 22.2 | 0 67.3 | 122 | 0 | |
| Benzene | 5.4 | 4.6 | 0 12.2 | 63 | 0 | |
| 1975 1979 | | | | | | |
| Tetrachloroethylene | 12.2 | 12.0 | 1.4 24.1 | 53 | 0 | |
| Trichloroethylene | 325.1 | 327.7 | 60.6 546.3 | 60 | 55 | |
| Vinyl chloride | 17.3 | 16.5 | 2.3 33.4 | 60 | 0 | |
| Benzene | 3.5 | 3.4 | 0 5.8 | 4 | 0 | |
| January 1980 February 1985* | | | | | | |
| Tetrachloroethylene | 21.5 | 21.4 | 2.2 38.7 | 58 | 0 | |
| Trichloroethylene | 449.2 | 446.2 | 42.6 783.3 | 62 | 58 | |
| Vinyl chloride | 34.3 | 35.7 | 4.2 67.3 | 62 | 0 | |
| Benzene | 7.6 | 7.6 | 1.6 12.2 | 59 | 0 | |

*Contaminated wells were shut down after February 1985. From March through December 1985, estimated monthly average levels of trichloroethylene, tetrachloroethylene and vinyl chloride were <1 µg/L, and benzene was <4 µg/L.



monthly average contaminant concentrations in the water system serving the individual's residence and occupancy dates were used to calculate cumulative exposures ("µg/L-months") to each contaminant and to the total amount of these contaminants ("TVOC"). We evaluated untransformed and log₁₀ transformed cumulative exposures as continuous variables. The log transform is appropriate when exposure-response relationships plateau or attenuate at higher levels of exposure [20]. We added a small constant (i.e., 0.001) to the monthly average contaminant concentrations to avoid taking the logarithm of zero. A one unit increase in the log-transformed cumulative exposure corresponds to a ten-fold increase in cumulative exposure. We also evaluated cumulative exposure as categorical variable (no, low, medium, and high exposure) based on cumulative exposure distributions of each contaminant among those exposed cohort members who died of any cancer. The low to high exposure categories contained approximately equal numbers of exposed cancer deaths in order to produce similar variances for hazard ratios across exposure categories [20]. We evaluated PCE, TCE, vinyl chloride, and benzene separately because the contaminants were highly correlated and could not be included together in a

model. For example, correlations ≥ .96 were observed between cumulative exposures to TCE, VC, and benzene because the Hadnot Point system was the source of higher levels of these contaminants. Lower correlations ranging from .44 to .53 were observed between PCE and the other contaminants because the Tarawa Terrace system had high levels of PCE but low levels of other contaminants. Because of the high correlations among the contaminants, it is not possible to separate the effects of each of the individual contaminants, although TCE and PCE levels were substantially higher than the levels of the other contaminants. In order to evaluate the contaminants as a group, we created the variable, TVOC, by combining PCE, TCE, trans-1,2-dichloroethylene, vinyl chloride and benzene. To account for latency, we evaluated 10, 15, and 20 year lag periods for cumulative exposures in addition to a "no lag" period. The use of either categorical or continuous exposure variables (whether transformed or not) imposes a structure on the exposure-response relationship which may be inaccurate [20]. To obtain a more flexible, smoothed exposure-response curve, we specified a restricted cubic spline (RCS) function for cumulative exposure in the Cox extended model

[21]. Four knots were located at the 5th, 25th, 75th, and 95th percentiles among those with cumulative exposure to a contaminant >1 µg/L-months. The RCS function allowed the shape of the HR curve to vary within and between these knots and restricted the curve to be linear before the first knot and after the last knot. The resulting curve is useful for assessing whether the exposure-response relationship is adequately captured by either the categorical or continuous exposure variables. In subsequent analyses, we evaluated duration at Camp Lejeune and duration exposed to the contaminated drinking water as time-varying categorical variables, and average exposures as time-independent categorical and continuous variables.

c. Confounder assessment

DMDC and NDI data were available for sex, race, marital status, birth cohort, date of death, age at death, rank, education, and duty occupation. For confounding to occur, a risk factor must be associated with the exposure as well as with the disease of interest. To identify potential confounding, we used a “10% change in the estimate” rule [22]. Final Cox extended models included sex, race, rank, and education. Information on smoking, alcohol consumption, and occupational history prior to or after active duty service, was unavailable. We evaluated possible smoking confounding by subtracting the log HR among smoking-related diseases from the log HR of the disease of interest [23].

Because the cohorts began active duty service after 1974, none were Vietnam veterans. However, information was unavailable concerning service in later wars involving hazardous exposures.

d. Interpretation of findings

Interpretation of study findings was based on the magnitude of the adjusted SMR or HR. For analyses internal to the Camp Lejeune cohort, we also based our interpretation on the exposure-response relationship, giving more emphasis to monotonic trends in the categorical cumulative exposure variables. A monotonic trend occurs when every change in the HR with increasing category of exposure is in the same direction, although the trend could have flat segments but never reverse direction [24]. Because exposure-response trends could be distorted by biases such as exposure misclassification, we also emphasized non-monotonic exposure-response trends when an elevated HR was observed in the high exposure group.

We computed 95% confidence intervals to show the precision of the HR and regression coefficient estimates, and we included p-values for information

purposes only. We did not use statistical significance testing to interpret findings [24-28].

Results and discussion

The cohorts had similar demographics and most were under age 55 by the end of follow-up (Table 3). Each cohort contributed approximately 4 million person-years of follow-up, about 6% died during the follow-up period, and vital status was unknown for less than 2%.

Standardized mortality ratio (SMR) analyses

Because we observed similar results for contributing and underlying causes of death, only results for underlying cause of death are presented. Over a quarter of deaths in both cohorts were due to cancers and cardiovascular diseases combined (Table 4). Suicide, homicide, transportation injuries and other injuries accounted for about half of deaths in the cohorts (data not shown).

Comparing each cohort to U.S. mortality rates, most SMRs were less than 1.00 indicating a “healthy veteran effect” [29] for cancers and non-cancers (Table 4). For diseases of primary interest, we observed SMRs above 1.00 in the Camp Lejeune cohort for kidney cancer (SMR = 1.16, 95% CI: 0.84, 1.57), multiple myeloma (SMR = 1.05, 95% CI: 0.61, 1.69), and cervical cancer (SMR = 1.03, 95% CI: 0.33, 2.39). At Camp Pendleton, the only disease of primary interest with an SMR greater

Table 3 Demographics of the Camp Lejeune and Camp Pendleton cohorts

| Factor | Camp Lejeune N = 154,932 | Camp Pendleton N = 154,969 |
|-----------------------------------|-----------------------------|-------------------------------|
| Male | 94.8% | 96.4% |
| Female | 5.2% | 3.6% |
| “White” | 73.1% | 77.6% |
| African American | 24.2% | 17.0% |
| “other” or unknown | 2.7% | 5.4% |
| Median age, start of follow up | 20 | 20 |
| Median age, end of follow up | 49 | 49 |
| % ≥55 yrs, end of follow up | 2.7% | 3.2% |
| Not a high school graduate | 11.3% | 14.7% |
| High school graduate | 84.9% | 80.5% |
| College graduate | 3.8% | 4.8% |
| Enlisted | 96.4% | 95.5% |
| Officer | 3.6% | 4.5% |
| Median months active duty service | 36 | 35 |
| Total deaths | 8,964 (5.8%) | 9,365 (6.0%) |
| % deaths occurring >1995 | 55.5% | 54.7% |
| Total lost to follow up | 1,990 (1.3%) | 2,339 (1.5%) |
| Total person years of follow up | 4.14 million | 4.19 million |

Table 4 Standardized mortality ratios (SMRs), underlying cause of death

| Underlying | Camp Pendleton (reference) | | | Camp Lejeune | | |
|---|----------------------------|--------|-------------------|--------------|--------|-------------------|
| | Obs. | Exp. | SMR (95% CI) | Obs. | Exp. | SMR (95% CI) |
| Cause of death | | | | | | |
| All causes | 9,365 | 10,922 | 0.86 (0.84, 0.87) | 8,964 | 10,864 | 0.83 (0.81, 0.84) |
| All cancers | 1,008 | 1,296 | 0.78 (0.73, 0.83) | 1,078 | 1,272 | 0.85 (0.80, 0.90) |
| Diseases of primary interest | | | | | | |
| Kidney cancer | 33 | 37.20 | 0.89 (0.61, 1.25) | 42 | 36.08 | 1.16 (0.84, 1.57) |
| Bladder cancer | 14 | 13.65 | 1.03 (0.56, 1.72) | 11 | 13.04 | 0.84 (0.42, 1.51) |
| Liver* cancer | 39 | 69.21 | 0.56 (0.40, 0.77) | 51 | 69.20 | 0.74 (0.55, 0.97) |
| Esophageal cancer | 27 | 43.33 | 0.62 (0.41, 0.91) | 35 | 41.34 | 0.85 (0.59, 1.18) |
| Hematopoietic cancers | 167 | 215.93 | 0.77 (0.66, 0.90) | 165 | 211.10 | 0.78 (0.67, 0.91) |
| Hodgkin | 23 | 25.86 | 0.89 (0.56, 1.33) | 24 | 25.03 | 0.96 (0.61, 1.43) |
| NHL** | 68 | 87.56 | 0.78 (0.60, 0.98) | 58 | 85.50 | 0.68 (0.52, 0.88) |
| Multiple myeloma | 12 | 16.26 | 0.74 (0.38, 1.29) | 17 | 16.13 | 1.05 (0.61, 1.69) |
| Leukemias | 64 | 86.26 | 0.74 (0.57, 0.95) | 66 | 84.43 | 0.78 (0.60, 0.99) |
| Cervical cancer | 2 | 3.53 | 0.57 (0.07, 2.05) | 5 | 4.88 | 1.03 (0.33, 2.39) |
| Diseases of secondary interest | | | | | | |
| Pancreatic cancer | 44 | 60.05 | 0.73 (0.53, 0.98) | 57 | 58.29 | 0.98 (0.74, 1.27) |
| Colon cancer | 73 | 93.28 | 0.78 (0.61, 0.98) | 86 | 92.29 | 0.93 (0.75, 1.15) |
| Rectal cancer | 16 | 29.84 | 0.54 (0.31, 0.87) | 24 | 29.54 | 0.81 (0.52, 1.21) |
| Soft tissue cancers | 21 | 27.82 | 0.75 (0.47, 1.15) | 29 | 27.44 | 1.06 (0.71, 1.52) |
| Brain cancer | 80 | 93.36 | 0.86 (0.68, 1.07) | 74 | 88.95 | 0.83 (0.65, 1.04) |
| Laryngeal cancer | 13 | 12.15 | 1.07 (0.57, 1.83) | 6 | 11.92 | 0.50 (0.18, 1.10) |
| Lung*** cancer | 216 | 265.44 | 0.81 (0.71, 0.93) | 237 | 259.01 | 0.92 (0.80, 1.04) |
| Oral cancers**** | 35 | 37.64 | 0.93 (0.65, 1.29) | 26 | 37.38 | 0.70 (0.45, 1.02) |
| Breast (female) cancer | 7 | 14.68 | 0.48 (0.19, 0.98) | 10 | 19.62 | 0.51 (0.24, 0.94) |
| Prostate cancer | 15 | 10.68 | 1.41 (0.79, 2.32) | 18 | 10.41 | 1.73 (1.02, 2.73) |
| Liver diseases | 233 | 322.70 | 0.72 (0.63, 0.82) | 191 | 311.90 | 0.61 (0.53, 0.71) |
| Kidney diseases | 37 | 71.72 | 0.52 (0.37, 0.71) | 37 | 74.54 | 0.50 (0.35, 0.68) |
| ALS | 27 | 19.42 | 1.39 (0.92, 2.02) | 21 | 18.45 | 1.14 (0.70, 1.74) |
| Multiple sclerosis | 10 | 14.95 | 0.67 (0.32, 1.23) | 12 | 14.75 | 0.81 (0.42, 1.42) |
| Smoking related diseases (not known to be related to solvent exposure) | | | | | | |
| Stomach cancer | 29 | 41.43 | 0.70 (0.47, 1.01) | 35 | 41.88 | 0.84 (0.58, 1.16) |
| Cardiovascular disease† | 1,376 | 1,791 | 0.77 (0.73, 0.81) | 1,390 | 1,781 | 0.78 (0.74, 0.82) |
| COPD | 45 | 55.82 | 0.81 (0.59, 1.08) | 47 | 53.89 | 0.87 (0.64, 1.16) |

Not evaluated due to small numbers were Parkinson's disease and male breast cancer.

*Biliary passages, liver and gall bladder **Non Hodgkin lymphoma.

Trachea, bronchus, and lung *Oral cavity and Pharynx.

†Includes diseases of the heart and other diseases of the circulatory system.

Camp Lejeune = 154,932; person years = 4,140,042.

Camp Pendleton = 154,969; person years = 4,190,132.

than 1.00 was bladder cancer (SMR = 1.03, 95% CI: 0.56, 1.72). For diseases of secondary interest, both Camp Lejeune and Camp Pendleton cohorts had SMRs > 1.00 for prostate cancer (SMR = 1.73, 95% CI: 1.02, 2.73); and SMR = 1.41, 95% CI: 0.79, 2.32, respectively) and ALS (SMR = 1.14, 95% CI: 0.70, 1.74; and SMR = 1.39, 95% CI: 0.92, 2.02, respectively). Soft tissue sarcoma was elevated

in the Camp Lejeune cohort (SMR = 1.06, 95% CI: 0.71, 1.52) and cancer of the larynx was elevated in the Camp Pendleton cohort (SMR = 1.07, 95% CI: 0.57, 1.83). SMRs for male breast cancer and Parkinson's disease were not calculated because there were <5 cases in each cohort. We did not calculate SMRs for aplastic anemia because LTAS combined aplastic anemia with other anemias.

Comparison of Camp Lejeune with Camp Pendleton

Table 5 presents results for comparisons of mortality between the two cohorts. A 10 year lag generally had the lowest AIC values. Camp Lejeune had an elevated HR for “all cancers” (HR = 1.10, 95% CI: 1.00, 1.20). For diseases of primary interest, Camp Lejeune had elevated HRs for kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43, 95% CI: 0.85, 2.38), multiple myeloma

(HR = 1.68, 95% CI: 0.76, 3.72), leukemias (HR = 1.11, 95% CI: 0.75, 1.62), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32). Bladder cancer and NHL had HRs < 1.00.

An evaluation of leukemia subtypes was not conducted because a considerable percentage (22.7%) of the leukemias were classified as “acute leukemia, not otherwise specified” in the Camp Lejeune cohort compared to the percentage (9.4%) occurring in the Camp Pendleton cohort.

Table 5 Camp Lejeune vs Camp Pendleton: hazard ratios and 95% confidence intervals, adjusted by sex, race, rank and education, 10-year lag

| Underlying cause of death | Hazard ratio | 95% LCL | 95% UCL | p value |
|---|--------------|---------|---------|---------|
| All cancers | 1.10 | 1.00 | 1.20 | 0.02 |
| Diseases of primary interest | | | | |
| Kidney cancer | 1.35 | 0.84 | 2.16 | 0.19 |
| Bladder cancer | 0.76 | 0.34 | 1.71 | 0.50 |
| Liver* cancer | 1.42 | 0.92 | 2.20 | 0.11 |
| Esophageal cancer | 1.43 | 0.85 | 2.38 | 0.17 |
| Hematopoietic cancers | 1.05 | 0.82 | 1.33 | 0.57 |
| Hodgkin | 1.47 | 0.71 | 3.06 | 0.26 |
| NHL** | 0.81 | 0.56 | 1.18 | 0.43 |
| Multiple myeloma | 1.68 | 0.76 | 3.72 | 0.21 |
| Leukemias | 1.11 | 0.75 | 1.62 | 0.63 |
| Cervical cancer | 1.33 | 0.24 | 7.32 | 0.74 |
| Diseases of secondary interest | | | | |
| Pancreatic cancer | 1.36 | 0.91 | 2.02 | 0.13 |
| Colorectal cancers | 1.13 | 0.85 | 1.51 | 0.35 |
| Colon cancer | 1.04 | 0.75 | 1.43 | 0.76 |
| Rectal cancer | 1.60 | 0.83 | 3.07 | 0.15 |
| Soft tissue cancers | 1.38 | 0.73 | 2.64 | 0.30 |
| Brain cancer | 0.93 | 0.67 | 1.30 | 0.84 |
| Laryngeal cancer | 0.54 | 0.20 | 1.45 | 0.22 |
| Lung*** cancer | 1.16 | 0.96 | 1.40 | 0.10 |
| Oral cancers**** | 0.82 | 0.48 | 1.41 | 0.46 |
| Breast (female) cancer | 0.93 | 0.34 | 2.50 | 0.88 |
| Prostate cancer | 1.23 | 0.60 | 2.49 | 0.57 |
| Liver diseases | 0.87 | 0.71 | 1.06 | 0.18 |
| Kidney diseases | 1.00 | 0.63 | 1.63 | 0.95 |
| ALS | 0.83 | 0.47 | 1.48 | 0.54 |
| Multiple sclerosis | 1.21 | 0.50 | 2.94 | 0.65 |
| Smoking related diseases (not known to be related to solvent exposure) | | | | |
| Stomach cancer | 1.15 | 0.70 | 1.90 | 0.58 |
| Cardiovascular disease† | 1.04 | 0.95 | 1.11 | 0.31 |
| COPD | 1.08 | 0.70 | 1.67 | 0.70 |

Not evaluated due to small numbers were Parkinson's disease, male breast cancer, and aplastic anemia.

LCL: lower confidence limit UCL: upper confidence limit.

*Biliary passages, liver and gall bladder ***Trachea, bronchus, and lung.

****Oral cavity and Pharynx.

†Includes heart diseases and other diseases of the circulatory system.

We conducted additional analyses to determine whether the elevated HRs for the Camp Lejeune cohort could be explained by cumulative exposures to the contaminants or by some other factor. For these analyses, the Camp Pendleton cohort was the reference group and the Camp Lejeune cohort was split into two groupings: no/low cumulative exposure and medium/high cumulative exposure (Additional file 1: Table S3). For example, if HRs in the no/very low cumulative exposure group were higher than HRs in the medium/high cumulative exposure group, then the elevation could be due to some other factor. For kidney cancer, Hodgkin lymphoma and leukemias, those with no/very low cumulative exposures had HRs ≤ 1.00 with all of the elevation in risk occurring among those with higher cumulative exposures. For cervical cancer, the HRs were ≤ 1.12 among those with no/very low cumulative exposures, while the HRs were >5.80 among those with higher cumulative exposures. For multiple myeloma, elevated HRs did occur among those with no/very low cumulative exposures, ranging from 1.10 to 1.40, while HRs ranging from 1.60 to 1.70 occurred among those with higher cumulative exposures. For liver cancer, the HRs for no/very low and higher cumulative exposures were similar, ranging from 1.30 to 1.40, while for esophageal cancer, the no/very low cumulative exposure group had much higher HRs than the higher exposure group.

Of diseases of secondary interest, Camp Lejeune had elevated HRs for colorectal cancers, in particular, rectal cancer (HR = 1.60, 95% CI: 0.83, 3.07), pancreatic cancer (HR = 1.36, 95% CI: 0.91, 2.02), soft tissue cancers (HR = 1.38, 95% CI: 0.73, 2.64), lung cancer (HR = 1.16, 95% CI: 0.96, 1.40), prostate cancer (HR = 1.23, 95% CI: 0.60, 2.49), and multiple sclerosis (HR = 1.21, 95% CI: 0.50, 2.94). Diseases with HRs ≤ 1.00 were ALS, liver diseases, kidney diseases and brain, laryngeal and oral cancers.

The elevation in the HR for lung cancer was due entirely to those with higher cumulative exposures at Camp Lejeune (Additional file 1: Table S3). For rectal cancer, the HRs were similar for the no/very low and higher cumulative exposure groups. For soft tissue cancers, pancreatic cancer, prostate cancers and multiple sclerosis, the elevation in HRs was due primarily to those with very low cumulative exposures.

The highest HR among smoking-related diseases was for stomach cancer (HR = 1.15, 95% CI: 0.70, 1.90). Using the stomach cancer result to adjust for smoking confounding would reduce the HRs for diseases of primary and secondary interest by 13%. However, HRs for the other smoking-related diseases (COPD and cardiovascular disease) were less than 1.10, and HRs for diseases that are both smoking and solvent related (e.g., laryngeal and oral cancers) were less than 1.00. Therefore it is likely that the confounding effects of smoking

are less than 10% for the comparisons between Camp Lejeune and Camp Pendleton.

Analyses internal to the Camp Lejeune cohort

Categorizations of cumulative exposure (“ $\mu\text{g/L}$ –months”) for each contaminant are presented in Table 6. Full results for categorical and continuous cumulative exposures are in the Additional file 2: Table S1, Additional file 3: Table S2. Similar AIC values were observed for the exposure lag and no lag periods evaluated so a 10 year lag was selected. The reference group consisted of Camp Lejeune cohort members with cumulative exposures within the reference levels listed in Table 6. Both the reference group and the low cumulative exposure category had a higher percentage of females, “white” race, officers, and college graduates than the medium and high cumulative exposure categories. All analyses included these variables in the models.

We observed a monotonic exposure-response relationship for kidney cancer and the categorized cumulative exposure variable for TVOC (HR for high exposure category = 1.54, 95% CI: 0.63, 3.75) (Table 7a). A non-monotonic exposure-response trend was observed for PCE and Kidney cancer (HR for high exposure category = 1.59, 95% CI: 0.66, 3.86). Non-monotonic and weaker effects were seen for other contaminants. The \log_{10} transform had lower AIC values indicating attenuation of HRs at higher exposure levels [20], and this attenuation was reflected in the spline for TVOC and kidney cancer with HRs rising in a linear fashion to a peak value of 1.7 in mid-range level of cumulative exposure before declining at higher exposure levels. (see Additional file 4: Figure S1). The regression coefficients for the \log_{10} transform of cumulative exposure to PCE and TVOC were 0.0813 (95% CI: -0.0553, 0.2179) and 0.0633 (95% CI: -0.0481, 0.1747), respectively.

We observed monotonic exposure-response relationships for Hodgkin lymphoma and TCE and benzene with HRs at the high exposure category of 1.97 (95% CI: 0.55, 7.03) and 1.94 (95% CI: 0.54, 6.95), respectively (Table 7b). A non-monotonic relationship was found for vinyl chloride and TVOC with HRs at the high exposure category of 1.99 (95% CI = 0.56, 7.13) and 2.17 (95% CI: 0.63, 7.50), respectively. Similar AIC values were observed for untransformed and \log_{10} transformed cumulative exposures. The regression coefficients for cumulative exposures to TCE and benzene were 0.00005 (95% CI: -0.00003, 0.00013) and 0.00203 (95% CI: -0.00339, 0.00745), respectively. The spline for TCE supported the categorized results as the HRs steadily increased in a linear fashion to approximately 2.4 in the high cumulative exposure range and then fell slightly thereafter (see Additional file 4: Figure S2).

Table 6 Categorization of cumulative exposure variables (µg/L –months) within the Camp Lejeune cohort

| Category | Reference level | Low exposure | Medium exposure | High exposure |
|---|-----------------|----------------|-----------------|----------------|
| Cumulative tetrachloroethylene (for >1 µg/L months: mean = 402.6, median = 269.5) | | | | |
| Level* | ≤ 1 | >1 155 | >155 380 | >380 8,585 |
| Number (%) | 66, 582 (43.0%) | 28,230 (18.2%) | 27,255 (17.6%) | 32,865 (21.2%) |
| Cumulative trichloroethylene (for >1 µg/L months: mean = 6,369.3, median = 5,289.0) | | | | |
| Level* | ≤ 1 | >1 3,100 | >3,100 7,700 | >7,700 39,745 |
| Number (%) | 64, 584 (41.7%) | 31,069 (20.1%) | 27,638 (17.8%) | 31,641 (20.4%) |
| Cumulative vinyl chloride (for >1 µg/L months: mean = 458.9, median = 360.6) | | | | |
| Level* | ≤ 1 | >1 205 | >205 500 | >500 2,800 |
| Number (%) | 66, 470 (42.9%) | 27,651 (17.8%) | 28,063 (18.1%) | 32,748 (21.1%) |
| Cumulative benzene (for ≥2 µg/L months: mean = 104.7, median = 83.2) | | | | |
| Level* | < 2 | 2 45 | >45 110 | >110 601 |
| Number (%) | 64, 580 (41.7%) | 24,579 (15.9%) | 31,838 (20.5%) | 33,935 (21.9%) |
| Cumulative TVOC (for >1 µg/L months: mean = 9,605.1, median = 7,652.8) | | | | |
| Level* | ≤ 1 | >1 4,600 | >4,600 12,250 | >12,250 64,016 |
| Number (%) | 57, 328 (37.0%) | 35,432 (22.9%) | 29,687 (19.2%) | 32,485 (21.0%) |

*An individual's maximum amount of cumulative exposure (µg/L months) at the end of follow up. N = 154,932.

Non-monotonic exposure-response relationships were observed for leukemias, with HRs for the high exposure category of 2.33 (95% CI: 1.08, 5.03), 1.81 (95% CI: 0.85, 3.85) and 1.69 (95% CI: 0.77, 3.67) for TVOC, TCE, and benzene, respectively (Table 7c). Lower AIC

values were observed for log₁₀ transformed cumulative exposures to TCE, benzene and TVOC with regression coefficients of 0.080 (95% CI: -0.009, 0.170), 0.128 (95% CI: 0.002, 0.253), and 0.095 (95% CI: 0.003, 0.187), respectively.

Table 7 Hazard ratios (95% CI) for categorical cumulative exposure, and coefficients (95% CI) for continuous cumulative exposure

| | Low exposure | Medium exposure | High exposure | Cumulative exposure | Log ₁₀ cumulative exposure |
|-----------------------------------|------------------------|------------------------|------------------------|-----------------------------------|---------------------------------------|
| a. Kidney cancer (N=42) | | | | | |
| PCE | 1.40 (0.54, 3.58) N=8 | 1.82 (0.75, 4.42) N=11 | 1.59 (0.66, 3.86) N=11 | .00009 (0.00048, 0.00065), p=.76 | .0813 (0.0553, 0.2179), p=.24 |
| TVOC | 1.42 (0.58, 3.47) N=10 | 1.44 (0.58, 3.59) N=10 | 1.54 (0.63, 3.75) N=11 | .00001 (0.00003, 0.00005) p=.59 | .0633 (0.0481, 0.1747) p=.26 |
| b. Hodgkin lymphoma (N=24) | | | | | |
| TCE | 1.52 (0.42, 5.59) N=4 | 1.63 (0.43, 6.12) N=4 | 1.97 (0.55, 7.03) N=5 | .00005 (0.00003, 0.00013) p=.20 | .0940 (0.0650, 0.2530) p=.25 |
| VC | 1.20 (0.29, 4.94) N=3 | 2.07 (0.59, 7.27) N=5 | 1.99 (0.56, 7.13) N=5 | .00056 (0.00060, 0.00172) p=.34 | .1101 (0.0817, 0.3019) p=.26 |
| Benzene | 1.24 (0.30, 5.11) N=3 | 1.88 (0.54, 6.61) N=5 | 1.94 (0.54, 6.95) N=5 | .00203 (0.00339, 0.00745) p=.46 | .1074 (0.1088, 0.3236) p=.33 |
| TVOC | 0.66 (0.13, 3.39) N=2 | 1.77 (0.50, 6.25) N=5 | 2.17 (0.63, 7.50) N=6 | .00003 (0.00003, 0.00009) p=.24 | .0752 (0.0818, 0.2322) p=.35 |
| c. Leukemias (N=66) | | | | | |
| TCE | 2.00 (1.00, 4.00) N=16 | 1.54 (0.71, 3.36) N=11 | 1.81 (0.85, 3.85) N=13 | .00002 (0.00004, 0.00008) p=.46 | .0801 (0.0093, 0.1695) p=.08 |
| Benzene | 2.54 (1.27, 5.08) N=17 | 1.46 (0.66, 3.20) N=11 | 1.69 (0.77, 3.67) N=12 | .00168 (0.00158, 0.00494) p=.31 | .1276 (0.0020, 0.2532) p=.05 |
| TVOC | 2.50 (1.24, 5.03) N=19 | 1.33 (0.56, 3.14) N=9 | 2.33 (1.08, 5.03) N=15 | .00001 (0.00003, 0.00005) p=.44 | .0950 (0.0032, 0.1868) p=.04 |
| d. ALS (N=21) | | | | | |
| TCE | 0.91 (0.25, 3.23) N=4 | 0.87 (0.21, 3.57) N=3 | 1.93 (0.65, 5.79) N=8 | .00007 (0.00001, 0.00013) p=.04 | .0436 (0.1083, 0.1955) p=.57 |
| PCE | 0.69 (0.13, 3.55) N=2 | 1.58 (0.45, 5.50) N=5 | 1.96 (0.64, 6.02) N=8 | .00039 (0.00002, 0.00080) p=.06 | .0836 (0.1060, 0.2732) p=.39 |
| VC | 1.22 (0.33, 4.51) N=4 | 0.91 (0.22, 3.87) N=3 | 2.21 (0.71, 6.86) N=8 | .00110 (0.00020, 0.00200) p=.02 | .0724 (0.1149, 0.2597) p=.45 |
| TVOC | 1.27 (0.37, 4.41) N=5 | 0.89 (0.21, 3.82) N=3 | 2.11 (0.67, 6.68) N=8 | .00005 (0.00001, 0.00009) p=.03 | .0702 (0.0872, 0.2276) p=.38 |

TCE: Trichloroethylene **PCE:** Tetrachloroethylene (or perchloroethylene) **VC:** Vinyl chloride.

TVOC: ("total volatile organic compounds") the sum of all contaminants (TCE, PCE, trans 1,2 dichloroethylene, vinyl chloride and benzene) in the drinking water. The referent group for each contaminant consists of those Camp Lejeune cohort members with cumulative exposures within the reference level for that contaminant shown in Table 6.

Exposure lagged 10 years. Adjusted for race, sex, rank and education. Selected causes of death. Camp Lejeune cohort (N = 154,932).

Two other diseases of primary interest had HRs above 1.00 in the high exposure category but trends were non-monotonic: NHL had HRs between 1.10 and 1.20 for TVOC, TCE, vinyl chloride and PCE, and bladder cancer had an HR of 2.26 for benzene based on 3 cases, and HRs of 1.20 for TVOC and PCE (see Additional file 2: Table S1). Multiple myeloma, liver cancer and esophageal cancer had HRs ≤ 1.00 in the high exposure category for each contaminant. Cervical cancer could not be evaluated because there were only 5 deaths in the Camp Lejeune cohort.

Of diseases of secondary interest, ALS had HRs > 1.90 in the high cumulative exposure category for TVOC (HR = 2.11, 95% CI: 0.67, 6.68), TCE (HR = 1.93, 95% CI: 0.65, 5.79), PCE (HR = 1.96, 95% CI: 0.64, 6.02), and vinyl chloride (HR = 2.21, 95% CI: 0.71, 6.86) but the exposure-response trends were not monotonic (Table 7d). The splines for these contaminants and ALS had similar exposure-response trends as those observed for the categorized cumulative exposure variables. For example, the spline for cumulative exposure to vinyl chloride indicated HRs < 1.00 until the high exposure range and then rose in a linear fashion to HRs > 3.00 (Additional file 4: Figure S3a). Splines for TCE and TVOC were similar to the spline for vinyl chloride. For PCE, HRs > 1.00 were observed near the end of the middle exposure range and rose linearly to approximately 3.50, leveling off thereafter (Additional file 4: Figure S3b). For all the contaminants, the lower AIC values were observed for untransformed cumulative exposures with regression coefficients for TCE, PCE, vinyl chloride and TVOC of 0.00007 (95% CI: 0.00001, 0.00013), 0.00039 (95% CI: -0.00002, 0.00080), 0.00110 (95% CI: 0.00020, 0.00200), and 0.00005 (95% CI: 0.00001, 0.00009), respectively.

We did not observe monotonic exposure-response trends for other diseases of secondary interest. The HR for PCE in the high exposure category and oral cancers was 1.80 (95% CI: 0.59, 5.46), but this was slightly lower than the HR at the low exposure category (HR = 1.89, 95% CI: 0.63, 5.66) and the middle exposure category had an HR < 1.00 (see Additional file 2: Table S1). Other diseases of secondary interest had HRs ≤ 1.20 (see Additional file 2: Table S1). Laryngeal cancer had too few cases ($N = 4$) to evaluate.

Except for benzene, we observed monotonic exposure-response relationships for the categorized cumulative exposure variables and cardiovascular disease, with HRs ≤ 1.12 in the high exposure categories. For stomach cancer and PCE, a non-monotonic relationship was observed with HR = 1.56 (95% CI: 0.66, 3.69) at the high exposure category. The HRs for COPD were < 1.00 for the middle and high cumulative exposure categories of the contaminants (see Additional file 2: Table S1).

Analyses of duration of exposure and average exposure produced results similar to cumulative exposure and are not presented.

Discussion

The diseases of primary and secondary interest under evaluation were selected based primarily on evidence from occupational studies of solvents such as TCE. Although occupational exposures occur primarily via inhalation and levels are generally much higher than drinking water exposures, the levels of TCE in the Hadnot Point distribution system were sufficiently high to result in exposures comparable to those that may occur in some occupational settings.

For example, daily inhalation exposures to TCE between 2.2 mg/day and 9.5 mg/day could occur in occupational settings where personal monitoring measurements indicated TCE air concentrations between 1.2 and 5.1 parts per million (ppm) [3]. A marine in training under warm weather conditions could drink between 1 and 2 quarts of water per hour [30]. Combining this ingestion rate with dermal and inhalation exposures from showering twice a day, a marine could consume a liter-equivalent of up to 8 liters of drinking water per day [31]. The Hadnot Point distribution system had a median TCE monthly average level of 446 $\mu\text{g/L}$ during January 1980-February 1985 (see Table 2), thus resulting in a possible daily exposure as high as 3.6 mg/day, i.e., within the range of workday exposures that occurred in some occupational settings.

One estimate of mean TCE air concentrations across all industries from the 1950s through the 1980s was 38 parts per million (ppm) [32]. This level of exposure would be considerably higher than an exposure to a marine consuming Hadnot Point drinking water. However, TCE concentrations in industry have decreased over time in the U.S. By the 1980s, the geometric mean concentration of TCE in Danish industries was approximately 4.3 ppm [3,33], and this level of air concentration of TCE would result in exposure comparable to the drinking water exposure to TCE at Camp Lejeune. A meta-analysis of occupational studies conducted by EPA that evaluated "any TCE exposure" obtained RRs of 1.27, 1.23 and 1.29 for kidney cancer, NHL, and liver cancer, respectively [7]. Similar findings were observed in this study for kidney cancer and liver cancer, but not for NHL, when the Camp Lejeune cohort was compared to the Camp Pendleton cohort.

In the comparison between Camp Lejeune and Camp Pendleton, the HRs for several cancers of primary interest were elevated in the Camp Lejeune cohort. Of these cancers, the elevated HRs for kidney cancer, cervical cancer, leukemias and Hodgkin lymphoma occurred primarily or exclusively among those with higher cumulative exposures.

The HRs for several diseases of secondary interest were also elevated. Of these diseases, the elevated HR for lung cancer occurred exclusively among those with higher cumulative exposures.

In analyses internal to the Camp Lejeune cohort, we observed monotonic trends for cumulative exposure to one or more contaminant and kidney cancer and Hodgkin lymphoma. For ALS, HRs > 1.90 were observed in the high exposure category for all the contaminants except benzene.

Drinking water studies conducted at Cape Cod, MA found associations between PCE and several cancers: lung, bladder, rectal, leukemia, and female breast [10-12]. All these cancers except bladder cancer were also elevated in comparisons between the Camp Lejeune and Camp Pendleton cohorts. In the NJ study, associations were observed for specific subgroupings of leukemia and NHL [9]. However, NHL was not elevated in our study.

Camp Pendleton did not have contaminated drinking water, but similar to Camp Lejeune, there were NPL sites located on the base. Although a public health assessment conducted by ATSDR at Camp Pendleton found “no apparent public health hazard” from these toxic waste sites [14], there was concern that the potential for exposure could not be ruled out. Therefore, we decided to compare both the Camp Lejeune and Camp Pendleton cohorts to the U.S. mortality rates. We realized that it was unlikely that any of the mortality rates at Camp Lejeune or Camp Pendleton would be elevated compared to the U.S. mortality rates because of the healthy veteran effect bias [29]. The effect of this bias is sufficiently strong to produce SMRs of ≤ 0.80 for cancer mortality when military personnel are compared to the U.S. population [29]. Moreover, since the median age at the end of follow-up was only 49 years, we expected that it would be too soon to observe elevations in either cohort. Nevertheless, we observed SMRs > 1.0 for three diseases of primary interest in the Camp Lejeune cohort: kidney cancer, multiple myeloma, and cervical cancer.

By the end of the study, there was one death in the Camp Lejeune cohort whose underlying cause was male breast cancer. However, many cases of male breast cancer among those who resided at Camp Lejeune have been identified in media reports and by diligent work conducted by members of the exposed population. Because male breast cancer has a relatively high survival rate, ATSDR collected data from the Veterans Affairs’s cancer registry and is currently evaluating the data regarding conducting a case-control study of male breast cancer incidence.

We conducted comparisons between Camp Lejeune and Camp Pendleton to minimize the bias due to the healthy veteran effect and because of concern that

everyone at Camp Lejeune was exposed to contaminated drinking water during daily activities if not at the residence. The Camp Pendleton cohort was an appropriate comparison population. Demographics and the healthy veteran effect were similar in both cohorts. The only major difference was drinking water contamination at Camp Lejeune.

Limitations

The study had several strengths including large cohorts, small percentage of loss to follow-up, and rigorous reconstruction of historical levels of drinking water contamination. However, there were several limitations. The average residence at Camp Lejeune was about 19 months (standard deviation = 13 months, range: 3-102 months). Many had short exposure durations that likely reduced the magnitude of the effects observed and made interpretation difficult.

A serious limitation was exposure misclassification, likely non-differential since exposure assignments should be unrelated to disease status. Such misclassification could bias HRs in comparisons between Camp Lejeune (“exposed”) and Camp Pendleton (“unexposed”) toward the null value of 1.0, resulting in underestimates of true effects of exposure. In analyses within the Camp Lejeune cohort, such bias could distort exposure-response relationships, e.g., producing non-monotonic trends that attenuate or turn negative at high exposure levels [20,34].

There were several sources of exposure misclassification. First, because historical research was necessary to identify units stationed at each base, errors in base assignment likely occurred. Second, determining a unit’s barrack location at Camp Lejeune was based primarily on recollections of retired marines. Third, family housing data inaccuracies hindered matching of married individuals to base housing, so some may have been wrongly assigned as living off-base and unexposed. Fourth, many stationed at Camp Lejeune spent time away from the base for training or deployment.

For the comparisons between the Camp Lejeune and Camp Pendleton cohorts, it is likely that the sensitivity of the exposure classification would be very high (e.g., >0.95) and the false-negative proportion would be very low because very few of those classified as “unexposed” (i.e., the Camp Pendleton cohort) would have an exposure to these contaminants. On the other hand, the specificity of the exposure classification would be much lower (e.g., between 0.70 and 0.85) because all members of the Camp Lejeune cohort were considered “exposed” although it is likely that some were not exposed. To apply a method to correct for non-differential exposure misclassification bias [35], we created a two-by-two contingency table by ignoring censoring, making the base location a time-independent variable, and forced the resulting odds ratio

to be similar to the observed hazard ratio. Assuming a sensitivity of 0.98 and a specificity ranging from 0.70 to 0.85, the kidney cancer HR of 1.35 in the comparison between Camp Lejeune and Camp Pendleton could increase between 6% and 18% (i.e., the misclassification-corrected HR could increase between 1.43 and 1.59).

Disease misclassification bias (both false positives and false negatives) is also a possibility. For example, some cancers of the digestive system and oral cavity/pharynx appear to be underreported on death certificates compared to cancer registry data, whereas cancers of the esophagus, lung, liver and brain may be over reported compared to cancer registry data [36]. However, it is likely that such disease misclassification was non-differential and would tend to bias the effect measures towards the null.

Another limitation was lack of information on smoking and other risk factors. Such risk factors, if associated with exposure status, could be confounders, biasing HRs in either direction and distorting exposure-response relationships. However, both bases had similar demographics so it is unlikely that confounding was a major source of bias in comparisons between the two bases. It is also unlikely that unmeasured risk factors would be associated with contaminant cumulative exposure levels.

We evaluated smoking-related diseases not known to be associated with solvent exposure to evaluate possible confounding by smoking. In comparisons between the two cohorts, we observed an HR of 1.15 for stomach cancer suggesting that the confounding effect of smoking would be no more than 13% and within the range observed in occupational studies [37]. However, we observed very slight elevations in HRs for COPD and cardiovascular disease, and HRs below 1.00 for oral and laryngeal cancers, suggesting that the confounding effect of smoking would likely be less than 10%.

For the comparisons of cumulative exposure within Camp Lejeune, there is mixed evidence of confounding by smoking. For example, the HRs for oral cancers and stomach cancer are between 1.4 and 1.8 which would indicate the potential for considerable confounding by smoking. On the other hand, the HRs for COPD, esophageal cancer, and pancreatic cancer are all less than 1.00 indicating no confounding by smoking, and the results for lung cancer, bladder cancer and cardiovascular disease (i.e., HRs between 1.10 and 1.20) indicate that confounding by smoking would be no more than 15%. Given these results, the cumulative exposure comparisons within the Camp Lejeune cohort should be minimally affected by confounding due to smoking.

Many HR estimates lacked precision, as indicated by wide confidence intervals, due to small numbers of specific causes of death. Lack of precision in the HR

estimates indicates uncertainty about the actual magnitude of the effects of the drinking water exposures on specific causes of death. Despite the large sizes of the cohorts, there were relatively small numbers of specific causes of death due to the healthy veteran effect and because most people in the cohort were younger than 55 at the end of follow-up.

Conclusion

The study found elevated HRs in the Camp Lejeune cohort for several causes of mortality including kidney cancer, liver cancer, esophageal cancer, cervical cancer, multiple myeloma, Hodgkin lymphoma, and ALS. However, the precision of many HR estimates was low as indicated by wide confidence intervals. Approximately 97% of the Camp Lejeune cohort was under the age of 55 and less than 6% had died by the end of the study. Long-term follow-up would be necessary for a comprehensive assessment of the effects of exposures to the contaminated drinking water at the base.

Additional files

Additional file 1: Table S3. Categorical cumulative exposures, Camp Lejeune compared to Camp Pendleton (referent).

Additional file 2: Table S1. Categorical Cumulative Exposures and Underlying Cause of Death.

Additional file 3: Table S2. Cumulative Exposures and Underlying Cause of Death.

Additional file 4: Figures S1 S3. Splines of selected causes of death and cumulative exposures.

Abbreviations

ATSDR: Agency for toxic substances and disease registry; AIC: Akaike's information criterion; ALS: Amyotrophic lateral sclerosis; COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; DMF: Death master file; DMDC: Defense manpower data center; HP: Hadnot point; HR: Hazard ratio; ICD: International classification of diseases; LTAS: Life table analysis system; MCL: Maximum contaminant level; $\mu\text{g/L}$: Micrograms per liter; mg/day: Milligrams per day; MS: Multiple sclerosis; NDI: National death index; NHL: Non Hodgkin lymphoma; NTP: National toxicology program; ORES: Office of research, evaluation and statistics; ppm: Parts per million; RCS: Restricted cubic spline functions; SSN: Social Security number; SSA: Social Security Administration; SMR: Standardized mortality ratio; TT: Tarawa Terrace; TVOC: Total amount of the contaminants; TCE: Trichloroethylene; PCE: Tetrachloroethylene or perchloroethylene; USMC: United States Marine Corps; EPA: United States Environmental Protection Agency.

Competing interests

All authors declare they have no actual or potential competing financial interest.

Authors' contributions

FJB participated in the study design, data collection, analysis and interpretation of data, and drafted the manuscript. PZR participated in the study design, data collection, interpretation of data, and helped draft the manuscript. MM conducted the water modeling. TCL assisted with analysis and interpretation of data. All authors read and approved the final manuscript.

Acknowledgement

The authors would like to thank Dana Flanders and Kyle Steenland of Emory University, Rollins School of Public Health for their statistical advice in preparing this manuscript. The authors thank Walter M. Grayman and the members of the Camp Lejeune water modeling team: Robert E. Faye, Jason B. Sautner, René J. Suárez Soto, Barbara A. Anderson, Mustafa M. Aral, Jinjun Wang, Wonyong Jang, Amy Krueger, Claudia Valenzuela, and Joseph W. Green, Jr. The authors would also like to thank Kerry Grace Morrissey, Sigurd Hermansen, Vanessa Olivo, and Tim McAdams of WESTAT for preparing the data for analyses.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

Author details

¹Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry (ATSDR), 4770 Buford Highway, MS F 58, Atlanta, GA 30341, USA. ²ATSDR, Division of Community Health Investigations, 4770 Buford Highway, MS F 59, Atlanta, GA 30341, USA.

Received: 9 December 2013 Accepted: 11 February 2014

Published: 19 February 2014

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doi:10.1186/1476-069X-13-10

Cite this article as: Bove et al.: Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study. *Environmental Health* 2014 **13**:10.

Full Text

Benzene and multiple myeloma: appraisal of the scientific evidence

1. [Daniel E. Bergsagel](#),
2. [Otto Wong](#),
3. [P. Leif Bergsagel](#),
4. [Raymond Alexanian](#),
5. [Kenneth Anderson](#),
6. [Robert A. Kyle](#), and
7. [Gerhard K. Raabe](#)

Blood August 15, 1999 vol. 94 no. 4 1174-1182

The recent paper by Bergsagel et al raised questions of scope, content, and provenance.^{[1](#)} Goldstein and Shalat have addressed many of the issues of scope and content in their review, and a response to their letter has been received from the authors of the paper.^{[2](#)} We will not address those issues again. However, the issue of the article's provenance has not been addressed, and it is to that provenance we now turn.

When the Bergsagel review was published, one of us wrote to the editor to ask what the source of funding for this paper might have been. The editor responded at that time that since *Blood* did not have a policy that required financial disclosure, he had no information on the source or sources of funding for the paper. He recommended that we write the authors to obtain this information. Two letters to the authors went unanswered. Further inquiry to the editor provided welcome assurance that *Blood's* editorial policy had been changed [New policy follows the response to this letter—Ed]. *Blood* will require financial disclosure in the future. However, the policy could not fairly be applied retroactively. Because the provenance of the Bergsagel paper remained at issue, the editor invited a letter to encourage the authors to provide the financial support information.

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

[Abdul Khalade](#),¹ [Maritta S Jaakkola](#),² [Eero Pukkala](#),^{3,4} and [Jouni JK Jaakkola](#)^{1,5}

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Abstract

Background

A substantial number of epidemiologic studies have provided estimates of the relation between exposure to benzene at work and the risk of leukemia, but the results have been heterogeneous. To bridge this gap in knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of leukemia, including all types combined and the four main subgroups acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

Methods

A systematic literature review was carried out using two databases 'Medline' and 'Embase' from 1950 through to July 2009. We selected articles which provided information that can be used to estimate the relation between benzene exposure and cancer risk (effect size).

Results

In total 15 studies were identified in the search, providing 16 effect estimates for the main analysis. The summary effect size for any leukemia from the fixed-effects model was 1.40 (95% CI, 1.23-1.57), but the study-specific estimates were strongly heterogeneous ($I^2 = 56.5\%$, Q stat = 34.47, $p = 0.003$). The random-effects model yielded a summary- effect size estimate of 1.72 (95% CI, 1.37-2.17). Effect estimates from 9 studies were based on cumulative exposures. In these studies the risk of leukemia increased with a dose-response pattern with a summary-effect estimate of 1.64 (95% CI, 1.13-2.39) for low (< 40 ppm-years), 1.90 (95% CI, 1.26-2.89) for medium (40-99.9 ppm-years), and 2.62 (95% CI, 1.57-4.39) for high exposure category (> 100

ppm-years). In a meta-regression, the trend was statistically significant ($P = 0.015$). Use of cumulative exposure eliminated heterogeneity. The risk of AML also increased from low (1.94, 95% CI, 0.95-3.95), medium (2.32, 95% CI, 0.91-5.94) to high exposure category (3.20, 95% CI, 1.09-9.45), but the trend was not statistically significant.

Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

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[Abdul Khalade](#),¹ [Maritta S Jaakkola](#),² [Eero Pukkala](#),^{3,4} and [Jouni JK Jaakkola](#)^{1,5}

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[Go to:](#)

Background

Le Noire and Claude published in 1897 the first report on the possible role of occupational exposure to benzene in the development of leukemia [1]. Since then a substantial number of epidemiologic studies in different occupational groups have assessed benzene exposure and made attempts to quantify the magnitude of risk related to such exposure. In 2005, Schnatter and colleagues published a systematic review of the available 22 epidemiologic studies of the relation between benzene exposure and leukemia subtypes [2]. They concluded that there was consistent evidence that the risk of acute myeloid leukemia (AML) is related to benzene exposure with an indication of a dose-response pattern, and a suggestion for chronic lymphoid leukemia (CLL), whereas the data for chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL) are sparse. They did not present any quantitative assessment of these relations. To our knowledge there are no previous meta-analyses that have estimated the effect of exposure to benzene on the risk of leukemia taking into account the cumulative exposure from individual studies. To bridge this gap in current knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of any leukemia and the risks of main subtypes of leukemia in adults, including AML, ALL, CLL, and CML.

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Methods

Search strategy and inclusion criteria

We conducted a systematic literature review using Medline and Embase databases from 1950 through July 2009. The following search terms were applied: benzene [Benzene derivatives, Polycyclic aromatic hydrocarbons]; occupational exposure, [Inhalation exposure, Maximum allowable concentration, Threshold limit values] and cancer [Neoplasms]. The search command was further refined to include any leukemia combined [leukemia, lymphoid] and the subgroups of leukemia, including AML, CML, and CLL. The Newcastle-Ottawa-Scale (NOS) was used to

assess the quality of papers. The articles from the search were then screened according to the following *a priori* inclusion criteria:

- (1) Provides information that can be used to estimate the relation between benzene exposure and cancer risk (effect size) in terms of odds ratio (OR), relative risk (RR), standardized mortality ratio (SMR), standardized relative risk (SRR), cumulative incidence ratio (CIR), or standardized incidence rate ratio (SIR);
- (2) Original study;
- (3) Provides comparable measures of effect estimates and/or cumulative exposure to benzene
- (4) Is a cohort, case-control or cross-sectional study in design; and
- (5) Includes occupationally active adults as a study population.

The selection of studies was based on a clearly defined search strategy. In addition to the primary Medline and Embase searches, we identified references that were cited by the articles identified in the primary database searches. Many of these secondary references directly investigated the relation between benzene exposure and cancer risk with leukemia being the main cancer. Two observers independently checked the eligibility of the studies according to *a priori* set inclusion and exclusion criteria, and identified the most appropriate effect or prevalence estimates. There was little disagreement between the two observers and these were settled by discussion. Incompatibility of the exposure or outcome criteria with our preset criteria was the main reason for exclusion.

Duplicate reports of studies were rejected and the study with the longest follow-up period or the most recent study of the cohort were chosen. All studies providing sufficient information on the relation between work exposure to benzene and leukemia were included, irrespective of whether this question was their primary or secondary objective, as measuring benzene alone was very unlikely due to fact that other chemicals were often present in the workplace alongside. The references of all included and excluded studies were further screened to identify any relevant papers. The definitions of the outcomes were based on the codes of the International Classification of Diseases (ICD) Revision 10 as follows any leukemia (C91-95), acute lymphocytic leukemia (C91.0), chronic lymphocytic leukemia (C91.1), acute myeloid leukemia (C92.0) and chronic myeloid leukemia (C92.1). A total of 15 papers which provided 16 effect estimates for the risk of leukemia in relation to benzene exposure were selected. Of these three studies applied codes of ICD revision 8, ten studies used revision 9, one revision 8 onwards, and one revision 6-9. There were no studies reporting classifications based on ICD-10 although it was available for use from 1992.

Data extraction

Two co-authors (AK, JJ) independently examined the papers and identified and recorded the main characteristics of the study including: (1) author(s) with the year of publication; (2) study design; (3) size of study population; (4) study group; (5) geographical location; (6) time window

of exposure; (7) exposure assessment; (8) study outcome; (9) effect estimate for given exposure category; (10) study selection criteria; (11) comparability in terms of confounders accounted for in the studies, for example smoking, age, socio-economic status; (12) the outcome for cohort studies and the exposure ascertained for case-control studies; and (13) the overall quality of the based on (10), (11) and (12). We defined the categories for cumulative exposure on as low from > 0 to < 40 , medium from 40 to < 100 and high 100+ parts per million (ppm)-years. The two sets of data were then grouped together to identify any discrepancy in recording of the findings, and such discrepancies were then reviewed and re-assessed for the final recording.

Assessment of study quality

We applied the Newcastle-Ottawa Scale (NOS) to assess the quality of the specific studies. The NOS for cohort and case-control studies includes the following items: 1) representativeness of the exposed cohort/adequacy of case definition; 2) selection of the non-exposed cohort/representativeness of the cases; 3) ascertainment of exposure/selection of controls; 4) demonstration that outcome of interest was not present at start of study/definition of controls; 5) comparability of cohorts on the basis of the design or analysis/comparability of cases and controls on the basis of the design or analysis; 6) assessment of outcome/ascertainment of exposure; 7) sufficiency of follow-up for outcomes to occur/similarity of method of ascertainment for cases and controls; and 8) adequacy of follow-up of cohorts/non-response rate. A star can be awarded for good quality for each item (except 1-2 stars for item 5) resulting in a range of 0-9 stars, more stars indicating higher quality.

Statistical methods

We first calculated summary effect estimates for the four outcomes (Leuk, AML, CLL, CML) by using both the fixed-effects and random-effects models. The fixed-effects model applied the general variance-based method with inverse variances of individual study effect estimates as weights [3]. The random-effects model applied the method of DerSimonian and Laird [3]. The natural log of the effect estimates and its standard error were calculated from the effect estimates and confidence intervals (CI) presented in the articles. We ran the Stata version 10 for the fixed- and random-effects models by using the "meta" command. The Q statistics and subgroup analysis were then applied to address potential heterogeneity between study-specific effect estimates. Finally, we conducted a dose-response analysis in a meta-regression model of $\ln(\text{effect estimate})$ by average cumulative exposure in the exposure category.

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Results

Studies

The Medline and Embase search identified a total of 466 articles. We screened the abstracts, and excluded 287 as being clearly irrelevant or duplicates of the same study. The remaining 179 abstracts were then evaluated using *a priori* inclusion criteria (see Methods). A total of 14

articles met the selection criteria for inclusion and 165 were excluded. The reasons for exclusion were: no information on the relation of interest (n = 121) and/or no quantitative effect estimate or sufficient figures to calculate an effect estimate (n = 29) and/or duplicate publication of the same data (n = 7). Some studies provided no information on cumulative exposure to benzene (n = 8). The included articles cited additional 23 seemingly relevant articles of which one was included. The meta-analysis was based on 15 articles with 16 effect estimates summarized in Additional File [1](#): Table S1. Similar review produced 8 articles with 9 effect estimates for AML, 10 for CLL, 6 for CML and no articles for ALL. These fifteen studies were grouped according to the weighted average of the cumulative exposure. Additional file [2](#) lists the studies cited in the narrative systematic review by Schnatter et al. [[2](#)] but not included in the present meta-analysis.

Design characteristics

From the 15 included studies, 10 were published in 1996-2004, [[4-14](#)] and the remaining five were published more recently in 2005-2008 (Additional File [1](#):Table S1) [[15-19](#)]. A total of 12 studies were cohort studies, and the remaining three were case-control studies. Seven studies were carried out in Europe (United Kingdom, Netherlands Sweden, Norway, Italy), one in Canada, five in the United States of America, one in China, and one in Australia. Additional File [1](#): Table S1 shows the workplace settings where the benzene exposure took place.

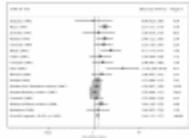
Exposure assessment and effect estimates

The exposure assessment of 9 studies was based on workplace exposure measurements and/or job exposure matrix. Three studies used work histories and/or benzene air concentrations. The remaining three studies defined exposure on the basis of employment in a given industry, and compared cancer mortality between the industry and general population. A total of 9 studies presented cumulative exposure.

Ten studies provided effect estimates in relative risks and odds ratios and five studies presented SMRs. SMRs were converted into relative risks to provide uniform estimates of the effect size (ES) for the meta-analysis. The effect estimates from the studies varied considerably from ES of 0.96 (95% CI, 0.20-4.67) to ES of 11.3 (95% CI, 2.85-45.1). Most studies presented effect estimates for several different cancer types, however only effect estimates for "any leukemia", AML, CLL and CML were extracted for this analysis.

Benzene exposure and the risk of any of leukemia

Additional File [1](#): Table S1 illustrates the study-specific effect estimates for any leukemia, as well as for the three leukemia subgroups used in the meta-analysis. Nine studies provided effect estimates based on cumulative exposure to benzene, which were categorized in to low, medium, and high exposure. The remaining five studies presented SMRs comparing mortality rates between exposed cohorts and general population. Figure [Figure11](#) shows a forest plot of all the study-specific effect estimates, the weights of the studies, and the summary effect estimate with the 95% confidence interval. Additional File [3](#): Table S3 presents the summary-effect estimates based on all 15 available studies (16 estimates), 9 studies with cumulative exposure categories, and 5 studies without quantitative exposure information.



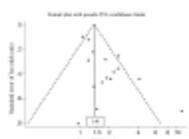
[Figure 1](#)

Forest plot showing the studies providing an estimate of the relation between exposure to benzene and the risk of any leukemia. The overall effect estimate is from the fixed-effects model.

In the fixed-effects model the summary effect size for benzene exposure was 1.40 (95% CI, 1.23-1.57), indicating a significantly increased risk of leukemia. However, both the I^2 index (56.5%) and Q statistics (34.47) revealed strong heterogeneity between the study-specific estimates (Additional File 3: Table S3). The random-effects model that allowed for heterogeneity yielded a summary ES of 1.72 (95% CI, 1.37-2.17). Additional File 3: Table S3 shows also summary-effect estimates for three levels of exposure, low (based on 8 studies), medium (6 studies), and high exposure (7 studies). Taking into account the average level of cumulative exposure in each study practically eliminated heterogeneity, so the variable exposure levels seemed to explain the heterogeneity observed in the overall estimate. The summary-effect estimates for low (1.64, 95% CI 1.13-2.39), medium (1.90, 95% CI 1.26-2.89), and high exposure (2.62, 95% CI 1.57-4.39) showed a clear dose-response pattern. The summary-effect estimate based on studies providing no dose information was slightly lower, 1.25 (95% CI 1.09-1.44).

To further elaborate the dose-response pattern we fitted a meta-regression model for $\ln(\text{effect estimate})$ by average cumulative exposure to benzene. There were several effect estimates for different contrasts: eight estimates for low vs. reference, six for medium vs. reference and seven for high vs. reference category. The meta-regression model showed a moderate, statistically significant association with the R-squared value of 37% and P value of < 0.05 .

The potential for publication bias was assessed by producing a funnel plot shown in Figure [Figure22](#). The vertical line indicates the summary-effect estimate from the fixed-effects model (1.40), and the corresponding pseudo 95% confidence limits converging as a function of the standard error (SE) of the effect estimate. The smaller studies with large SEs of $\ln \text{OR}$ seem to be scattered symmetrically around the summary-effect estimate, whereas the funnel plot shows substantial heterogeneity among the large studies with small SEs, with an imbalance toward large positive effect estimate. The pattern differs from a typical publication bias, in which the effect estimate from the small studies would be biased towards large positive values.



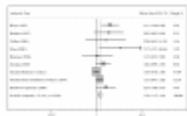
[Figure 2](#)

Funnel plot showing the effect estimates ($\ln \text{OR}$) by their standard errors (SE of $\ln \text{OR}$).

The vertical line indicates the summary effect estimate (1.40) from the fixed-effects model, and the dashed lines show pseudo 95% confidence limits for the summary ...

Benzene exposure and the risk of acute myeloid leukemia (AML)

The study-specific effect estimates for the relation between benzene exposure and the risk of AML appear in Additional File [1](#):Table S1. Additional File [3](#): Table S3 summarizes the results of the meta-analysis on AML. In the main analysis based on 9 articles, the fixed-effects model yielded a summary-effect estimate of 1.38 (95% CI, 1.15-1.64), and the study-specific effect estimates were homogeneous (I^2 index 51.4%, Q statistic of 16.46, P 0.036) (Figure [\(Figure3\).3](#)). Four studies provided information on dose, and the dose-specific effect estimates were homogeneous and presented a clear dose-response pattern (low: 1.94, 95% CI 0.95-3.95; medium 2.32, 95% CI 0.90-5.94; high: 3.20, 95% CI 1.09-9.45).



[Figure 3](#)

Forest plot showing the studies providing an estimate of the relation between exposure to benzene and the risk of acute myeloid leukemia. The summary effect estimate is from the fixed-effects model.

The meta-regression model for AML was based on four effect estimates for low vs. reference category, two for medium vs. reference and two for high vs. reference category. The model for the relation between cumulative exposure to benzene and the risk of AML showed no association (R-squared value of 3% and P value 0.813).

Benzene exposure and the risk of chronic myeloid leukemia (CML)

The summary-effect estimate for CML was 1.05 (95% CI, 0.83-1.34), and the study-specific estimates were homogeneous. There were no studies applying cumulative exposure. The Egger's statistics did not indicate any publication bias (P value 0.57).

Benzene exposure and the risk of chronic lymphocytic leukemia (CLL)

A total of 10 study-specific effect estimates yielded a summary-effect estimate of 1.31 (95% CI, 1.09-1.57). There was no indication of heterogeneity, and the random-effects model produced similar results (Additional File [3](#): Table S3). Six studies provided effect estimates based on cumulative exposure (dose). The summary-effect estimate for low exposure was 1.83 (95% CI 0.75-4.48), for medium exposure 1.67 (0.86-3.24), and for high exposure 3.50 (0.90-13.2), the latter was based on only one study available. There was no indication of publication bias (Egger's statistics: P value 0.06).

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Discussion

This systematic review and meta-analysis based on 15 available epidemiologic studies provides evidence of an association between benzene exposure at work and leukemia risk. The summary estimate from the fixed-effects model was 1.40 (95% CI 1.23-1.57), but the study-specific estimates were heterogeneous. Focusing on 9 studies that provided information on cumulative exposures and stratifying the effect estimates according to the magnitude of cumulative exposure eliminated the heterogeneity. The summary-effect estimate was 1.64 (1.13-2.39) for low, 1.90 (1.26-2.89) for medium, and 2.62 (1.57-4.39) for high exposure, showing evidence of a dose-response relation. The summary effect estimate for the studies which did not have dose information was lower 1.25 (1.09-1.44). Also the meta-regression model was consistent with a dose-response pattern. The results provided some evidence of an increased risk for AML and CLL. The meta-analysis indicated consistently a lack of association between benzene exposure and the risk of CML. There was not sufficient information on ALL.

The outcome assessment in all the specific studies was based on an ICD-diagnosis. Although there was a significant association between exposure to benzene and the broad category of any leukemia (ICD C91-95), there was substantial heterogeneity in the effects on specific leukemia ranging from a strong summary effect for AML to no effect for CML. Our results indicate that the use of the broad category of any leukemia underestimates the magnitude of the effect on AML. Although the summary-effect estimates for any leukemia, as well as for AML and CLL indicated an increased risk, the study-specific effect estimates presented strong heterogeneity.

We were able to retrieve some type of quantitative estimate for cumulative exposure to benzene from 9 studies. Additional File 1: Table S1 displays estimates of cumulative exposure for different exposure categories. Although exposure assessment varied between the studies, each study applied similar approaches to different levels of exposure. Use of exposure categories based on cumulative exposure reduced or practically eliminated this heterogeneity, suggesting that different amounts of benzene exposure in different studies explained the heterogeneity observed in the overall risk estimates. For example, for any leukemia the effect estimate for better quality studies (NOS 6-9) was 1.32 (95% CI 1.15-1.51), and for others (NOS 0-5) 1.79 (1.34-2.38). The summary-effect estimates for studies without dose information were presented mainly as standardized mortality ratios using external cancer mortality rates as the reference group. Their estimates were systematically lower than those from the studies providing data for dose-response analyses. A funnel plot analysis of studies on benzene exposure and leukemia risk did not show any suggestion of publication bias [20].

Several studies have been published since the most recent systematic reviews [2,21,22] on benzene and leukemia, and ours is to our knowledge the first meta-analysis on this topic.

In 1989, Lamm and colleagues published a risk assessment based on a large cohort study conducted by NIOSH (including 9 cases of leukemia), and compared their results with those of the other available large studies [21]. They concluded that AML can be caused by excessive benzene exposure, meaning a peak benzene exposure greater than 20 ppm or an estimated cumulative benzene exposure greater than 250 ppm-years. This finding was consistent across the reviewed studies except a Chinese study by Wong. This early review reported no consistent evidence for ALL, CML, or CLL in relation to benzene exposure. In 1997, Savitz and Andrews reviewed epidemiologic research on lymphatic and hematopoietic cancers. They identified 14

studies, three community-based and 11 industry-based, on benzene and total leukemia and 16 studies, nine community-based and seven industry-based, on benzene and specific histologic types of leukemia [22]. However, they did not conduct any meta-analyses. They concluded that the "epidemiologic evidence linking benzene to leukemia in the aggregate, as well as acute and chronic lymphocytic and myeloid leukemia, is no less persuasive than that for AML alone", but did not suggest any quantitative estimates.

In the most recent systematic review published in 2005, Schnatter and colleagues assessed 22 industry-based cohort and case-control studies. A high and significant AML risk was reported across study designs, especially in more highly exposed workers of rubber, shoe, and paint industry. Results on CLL were controversial with an increased risk in nested case-control studies, but with no increase in cohort studies. Data for ALL and CML were deemed sparse and inconclusive [2].

The results of our systematic review both strengthen the evidence of the effect of benzene exposure on leukemia risk, and provide quantitative estimates of effect size. We detected substantial heterogeneity between the different types of leukemia, which reduces the relevance of the overall estimate. Thus we also assessed the leukemia-specific effect sizes. The risk of AML was estimated to be two-fold for cumulative exposure below 40 ppm-years, 2.3-fold for exposures from 40 ppm-years to below 100 ppm-years, and over 3-fold for exposures 100 ppm-years and above. These estimates indicated an increased risk related to substantially lower dose than that suggested by Lamm and colleagues [21]. As a new contribution, our results also show that the available evidence is consistent with no effect on CML. Our results strengthen the evidence that benzene exposure also increases the risk of CLL, suggesting a dose-response pattern, although the effect estimate for the highest exposure category is based on a single study. Consistently with the previous reports, we found that there is no sufficient evidence to make any inference on the effects of benzene exposure to ALL.

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Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. The results showed some evidence of an increased risk for AML and CLL. The meta-analysis indicated consistently a lack of association between benzene exposure and the risk of CML. The evidence was insufficient to make any inference on the effects on ALL. For the purposes of clinical, occupational health, and policy implications, it is important to note that a significantly increased risk of any leukemia and AML was observed already in relation to the low benzene exposure and that the risk varied according to the type of leukemia.

In 1946, The American Conference of Governmental Industrial Hygienists set the first occupational exposure limit for benzene to 325 mg/m³ (100 ppm), and in 1963 the limit was reduced to 35 ppm. Currently most European and North American countries have harmonised the limit to 1.63-3.25 mg/m³ (0.5-1 ppm) This recent figure was agreed within the European Union in 1997 and was adopted within standard setting committee [23].

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Abbreviations

ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; CIR: Cumulative incidence ratio; ICD: International Classification of Diseases; OR: Odds ratio; NOS: Newcastle-Ottawa Scale; RR: Relative risk; SIR: Standardized incidence rate ratio; SRR: Standardized relative rate; SMR: Standardized mortality ratio.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AK conducted the literature search, reviewed the articles, conducted the statistical analyses, and drafted the manuscript. MSJ and EP made substantial contributions to interpretation of data, and were involved in drafting the manuscript or revising it critically for important intellectual content. JJKJ conceived and designed the study, reviewed the articles, and supervised the work in all phases. All authors read and approved the final manuscript.

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Supplementary Material

Additional file 1:

Table S1. Design characteristics of studies included in the meta-analysis

[Click here for file](#) ^(162K, DOC)

Additional file 2:

Table S2. Studies not included and the reasons for exclusion

[Click here for file](#) ^(43K, DOC)

Additional file 3:

Table S3. Summary of effect size for the relation between benzene exposure and risk of leukaemia and dose-response analysis

[Click here for file](#) ^(102K, DOC)

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Acknowledgements

The first author was funded by a PhD scholarship and travel award from the Medical & Public Health School of the University of Birmingham, UK. Many thanks also go out to the Center for Environmental and Respiratory Health Research, Institute of Health Sciences University of Oulu Finland for use of their facilities while there.

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Subject: article to share
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J Periodontol. 2005 Mar;76(3):406-10.

Is periodontitis associated with oral neoplasms?

Tezal M1, Grossi SG, Genco RJ.

Author information

Abstract

BACKGROUND:

Infections have been suggested in the etiology of oral cancer. This study was carried out to evaluate the effect of periodontal disease on oral soft tissue lesions.

METHODS:

A total of 13,798 subjects aged 20 years and older with at least six natural teeth and who participated in the Third National Health and Nutrition Examination Survey (NHANES III) constituted the study population. Severity of periodontal disease was represented by clinical attachment loss (CAL) and was dichotomized as $<$ or $=1.5$ mm versus >1.5 mm according to its distributions in the NHANES III population. Three separate dependent variables were employed: 1) tumor (non-specific); 2) precancerous lesions; and 3) any oral soft tissue lesion. The independent effect of CAL on those three dependent variables was assessed by weighted multiple logistic regression analyses adjusting for the effects of number of filled teeth, number of decayed teeth, presence of prosthesis, age, gender, race/ethnicity, education, tobacco, alcohol, occupational hazard, and interaction term "tobacco*occupational hazard." Odds ratios (OR) and their 95% confidence intervals (CI) were calculated.

RESULTS:

CAL was not related to the presence of any soft tissue lesion (OR = 1.09, 95% CI: 0.91 to 1.31), but was specifically related to the presence of tumor (OR = 4.57, 95% CI: 2.25 to 9.30) and precancerous lesions (OR = 1.55, 95% CI: 1.06 to 2.27).

CONCLUSION:

This study suggests associations between periodontal disease and the risk for precancerous lesions and tumors generating a hypothesis about a possible relationship between periodontal disease and oral neoplasms. Prospective or well-designed case-control studies with histologically confirmed incident oral cancer cases are necessary to confirm this relationship.

PMID: 15857075 [PubMed - indexed for MEDLINE]

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Compensation & Pension

Environmental Health Clinician

DMA Clinical Advisory Board
Ann Arbor VAMC

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This is a good one

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*Compensation & Pension
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Subject: Articles for CLCW library
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Attachments: [EAS](#)

FYI

From: (b) (6)
Sent: Tuesday, September 16, 2014 12:43 PM
To: VHA CO CLCW SME
Subject: CLCW: Bove Article Abstracts

Good Afternoon,

Per the monthly call, I have included the abstracts for the two controversial Bove et al articles on Camp Lejeune. We will discuss these at the monthly call next week.

(b)

[Environ Health](#). 2014 Aug 13;13:68. doi: 10.1186/1476-069X-13-68.

Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study.

[Bove FJ](#)¹, [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

[Author information](#)

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of 4,647 civilian, full-time workers employed at Camp Lejeune during 1973-1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 Camp Pendleton workers employed during 1973-1985 and unexposed to contaminated drinking water. Mortality follow-up period was 1979-2008. Cause-specific standardized mortality ratios utilized U.S. age-, sex-, race-, and calendar period-specific mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune and Camp Pendleton workers and assess the effects of estimated cumulative contaminant exposures within the Camp Lejeune cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at Camp Lejeune. The confidence interval (CI) indicated precision of effect estimates.

RESULTS:

Compared to Camp Pendleton, Camp Lejeune workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the Camp Lejeune cohort, monotonic exposure-response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure-response relationships.

CONCLUSION:

The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the Camp Lejeune cohort died by end of follow-up, producing small numbers of ca

[Environ Health](#). 2014 Feb 19;13(1):10. doi: 10.1186/1476-069X-13-10.

Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study.

[Bove FJ](#)¹, [Ruckart PZ](#), [Maslia M](#), [Larson TC](#).

[Author information](#)

Abstract

BACKGROUND:

Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

METHODS:

We conducted a retrospective cohort mortality study of Marine and Naval personnel who began service during 1975-1985 and were stationed at Camp Lejeune or Camp Pendleton, California during this period. Camp Pendleton's drinking water was uncontaminated. Mortality follow-up was 1979-2008. Standardized Mortality Ratios were calculated using U.S. mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune (N = 154,932) and Camp Pendleton (N = 154,969) cohorts and assess effects of cumulative exposures to contaminants within the Camp Lejeune cohort. Models estimated monthly contaminant levels at residences. Confidence intervals (CIs) indicated precision of effect estimates.

RESULTS:

There were 8,964 and 9,365 deaths respectively, in the Camp Lejeune and Camp Pendleton cohorts. Compared to Camp Pendleton, Camp Lejeune had elevated mortality hazard ratios

(HRs) for all cancers (HR = 1.10, 95% CI: 1.00, 1.20), kidney cancer (HR = 1.35, 95% CI: 0.84, 2.16), liver cancer (HR = 1.42, 95% CI: 0.92, 2.20), esophageal cancer (HR = 1.43 95% CI: 0.85, 2.38), cervical cancer (HR = 1.33, 95% CI: 0.24, 7.32), Hodgkin lymphoma (HR = 1.47, 95% CI: 0.71, 3.06), and multiple myeloma (HR = 1.68, 95% CI: 0.76, 3.72). Within the Camp Lejeune cohort, monotonic categorical cumulative exposure trends were observed for kidney cancer and total contaminants (HR, high cumulative exposure = 1.54, 95% CI: 0.63, 3.75; $\log_{10} \beta = 0.06$, 95% CI: -0.05, 0.17), Hodgkin lymphoma and trichloroethylene (HR, high cumulative exposure = 1.97, 95% CI: 0.55, 7.03; $\beta = 0.00005$, 95% CI: -0.00003, 0.00013) and benzene (HR, high cumulative exposure = 1.94, 95% CI: 0.54, 6.95; $\beta = 0.00203$, 95% CI: -0.00339, 0.00745). Amyotrophic Lateral Sclerosis (ALS) had HR = 2.21 (95% CI: 0.71, 6.86) at high cumulative vinyl chloride exposure but a non-monotonic exposure-response relationship ($\beta = 0.0011$, 95% CI: 0.0002, 0.0020).

CONCLUSION:

The study found elevated HRs at Camp Lejeune for several causes of death including cancers of the kidney, liver, esophagus, cervix, multiple myeloma, Hodgkin lymphoma and ALS. CIs were wide for most HRs. Because <6% of the cohort had died, long-term follow-up would be necessary to comprehensively assess effects of drinking water exposu

Attachments:

jama_259_15_037.pdf (687315 Bytes)

Good pasture syndrome & Solvent Exp.pdf (809930 Bytes)

Occupational Exposures in rare cancer.pdf (2181007 Bytes)

Camp Lejeune Health Studies

Evaluation of mortality among Marines and Navy personnel exposed to contaminated drinking water at USMC Base Camp Lejeune: A retrospective cohort study

Study Purpose

The purpose of this study was to determine whether residential exposures of Marines and Navy personnel to contaminated drinking water at Camp Lejeune increased risk of mortality from cancers and other chronic diseases.

What Was Studied

The study evaluated specific causes of death in 154,932 Marines and Navy personnel who began service during 1975-1985¹ and were stationed at Camp Lejeune anytime during this period. We also evaluated a comparison group of 154,969 Marines and Navy personnel from Camp Pendleton. The Camp Pendleton group was not exposed to contaminated drinking water, but was otherwise similar to the Camp Lejeune group.

Cause of death data from 1979-2008 was used to study the Camp Lejeune and Camp Pendleton cohorts. Information on causes of death was obtained from the National Center for Health Statistics National Death Index (NDI). The study included all underlying causes of death that other studies have shown associations with one or more of the chemicals found in the drinking water at Camp Lejeune. Causes of death were selected based on literature reviews conducted by the U.S. Environmental Protection Agency (EPA), the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), and ATSDR.

The causes of death studied include:

- Amyotrophic lateral sclerosis (ALS)
- Cancers of the bladder, brain, cervix, colon, esophagus, female breast, kidney, larynx, liver, lung, oral cavity, pancreas, prostate, rectum, and soft tissue
- Hematopoietic cancers
 - Hodgkin's Lymphoma
 - Leukemias
 - Multiple myeloma
 - Non-Hodgkin's lymphoma
- Non-cancerous kidney diseases
- Non-cancerous liver diseases
- Multiple sclerosis

¹Unit information with location for marines and navy personnel was not available in the Defense Manpower Data Center personnel database prior to 1975. The most heavily contaminated wells were shut down in 1985.

Continued on next page

Also included in the study were three causes of death that are known to be caused by cigarette smoking but are not known to be associated with the drinking water contaminants: cardiovascular disease, chronic obstructive pulmonary disease (COPD), and stomach cancer. These causes of death were included to assess the possible impact of smoking on the findings because we did not have information on smoking status for study subjects.

Features of this Study

The study included a comparison population from Camp Pendleton that was similar to the Camp Lejeune cohort on risk factors such as military training, occupations, and smoking. Camp Pendleton did not have a contaminated drinking water supply.

Residential cumulative exposure to each contaminant was based on results from the water modeling and the location and duration of residence.

Key Results

Compared to Camp Pendleton, the Camp Lejeune group had higher mortality rates for the following causes of death:

- Cancers of the cervix, esophagus, kidney, liver, lung, pancreas, prostate, rectum, and soft tissue
- Hodgkin's lymphoma
- Leukemias
- Multiple myeloma
- Multiple sclerosis

The higher rates for kidney cancer, cervical cancer, Hodgkin's lymphoma, leukemias, multiple myeloma, and lung cancer were mainly among those with higher cumulative exposures to the contaminants. However, the precision of the estimated rates of many of these conditions was low.

The findings for the smoking-related causes of death such as stomach cancer, cardiovascular disease, and COPD suggested that smoking would have only a slight impact on the associations between causes of death and exposure to the drinking water contaminants at Camp Lejeune.

Conclusion

The study found increased risk of death in the Camp Lejeune cohort for several causes including cancers of the cervix, esophagus, kidney, and liver, Hodgkin's lymphoma, and multiple myeloma. This study makes an important contribution to the body of evidence about harm caused by these chemicals. However, due to its limitations it does not provide definitive evidence for causality nor can it answer the question whether an individual has been affected by these exposures at Camp Lejeune.



RESEARCH

Open Access

Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study

Frank J Bove^{1*}, Perri Zeitz Ruckart¹, Morris Maslia² and Theodore C Larson¹

Abstract

Background: Two drinking water systems at U.S. Marine Corps Base Camp Lejeune, North Carolina were contaminated with solvents during 1950s-1985.

Methods: We conducted a retrospective cohort mortality study of 4,647 civilian, full time workers employed at Camp Lejeune during 1973–1985 and potentially exposed to contaminated drinking water. We selected a comparison cohort of 4,690 Camp Pendleton workers employed during 1973–1985 and unexposed to contaminated drinking water. Mortality follow up period was 1979–2008. Cause specific standardized mortality ratios utilized U.S. age, sex, race, and calendar period specific mortality rates as reference. We used survival analysis to compare mortality rates between Camp Lejeune and Camp Pendleton workers and assess the effects of estimated cumulative contaminant exposures within the Camp Lejeune cohort. Ground water contaminant fate/transport and distribution system models provided monthly estimated contaminant levels in drinking water serving workplaces at Camp Lejeune. The confidence interval (CI) indicated precision of effect estimates.

Results: Compared to Camp Pendleton, Camp Lejeune workers had mortality hazard ratios (HRs) >1.50 for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34), leukemias (HR = 1.59, 95% CI: 0.66, 3.84), multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58), rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.81). Within the Camp Lejeune cohort, monotonic exposure response relationships were observed for leukemia and vinyl chloride and PCE, with mortality HRs at the high exposure category of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32), respectively. Cumulative exposures were above the median for most deaths from cancers of the kidney, esophagus, rectum, prostate, and Parkinson's disease, but small numbers precluded evaluation of exposure response relationships.

Conclusion: The study found elevated HRs in the Camp Lejeune cohort for several causes of death including cancers of the kidney, rectum, oral cavity, leukemias, multiple myeloma, and Parkinson's disease. Only 14% of the Camp Lejeune cohort died by end of follow up, producing small numbers of cause specific deaths and wide CIs. Additional follow up would be necessary to comprehensively assess drinking water exposure effects at the base.

Keywords: Mortality, Cancers, Trichloroethylene, Tetrachloroethylene, Vinyl chloride, Benzene, Drinking water

* Correspondence: fbove@cdc.gov

¹Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology and Human Health Sciences, 4770 Buford Highway, MS F 58, Atlanta, GA 30341, USA

Full list of author information is available at the end of the article



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Background

United States Marine Corps (USMC) Base Camp Lejeune is located in Onslow County, North Carolina. Samples taken during 1980 through 1985 at Camp Lejeune detected solvents in drinking water supplied by the Hadnot Point (HP) treatment plant serving the main area (“main-side”) of the base where most workplaces were located. The HP supply wells were contaminated by an on-base landfill used for chemical dumping as well as underground storage tank leaks and waste disposal practices at the base’s industrial area [1]. The highly contaminated HP supply wells were shut down by early February 1985.

The primary contaminant in the HP distribution system was trichloroethylene (TCE) with a maximum detected level of 1,400 micrograms per liter ($\mu\text{g/L}$). The maximum level of tetrachloroethylene (PCE) in the HP drinking water was 100 $\mu\text{g/L}$ and benzene was also detected. Trans-1,2-dichloroethylene (DCE) and vinyl chloride were present in the HP system due to the degradation of TCE in ground water [1].

Between 20 and 30 supply wells were operating in the HP system at any one time since the system began operation in 1942 [1]. Water from all the supply wells serving the HP system was mixed together at the treatment plant prior to distribution. A majority of the supply wells in the HP system were not contaminated, so contamination levels varied depending on the wells in use at a particular time [1].

Current U.S. maximum contaminant levels (MCLs) for TCE, PCE and benzene are 5 $\mu\text{g/L}$; the MCL for vinyl chloride is 2 $\mu\text{g/L}$; and the MCL for DCE is 100 $\mu\text{g/L}$. TCE has recently been classified as a human carcinogen [2-4]. Vinyl chloride and benzene are also classified as human carcinogens [5]. PCE is classified as a “likely” or “probable” human carcinogen [3,6,7].

Several meta-analyses and reviews have assessed the effects of these chemicals on cancers and other chronic diseases [2-7]. Most of the evidence has come from occupational studies where the primary route of exposure was inhalation. On the other hand, drinking water exposure to these chemicals usually involves contributions to total internal body dose from three routes: ingestion, inhalation and dermal. The dose from the inhalation and dermal routes may be as high as the dose from the ingestion route. For example, an internal dose via inhalation to TCE during a 10-minute shower may equal the internal dose via the ingestion of 2 liters of TCE-contaminated drinking water [8]. If a worker at Camp Lejeune consumed cold tap water at his/her workplace, then the route of exposure would be primarily via ingestion. However, if a worker used hot water at the workplace, for example, in tea or coffee, washing hands, or showering (e.g., after exercising or at the end of the shift), then the inhalation and dermal routes of exposure would be important.

The literature is limited on health effects of drinking water exposures to these chemicals. A drinking water study in New Jersey observed associations between TCE and the incidence of leukemia and non-Hodgkin lymphoma (NHL), and between PCE and NHL incidence [9]. PCE-contaminated drinking water was associated with the incidence of lung cancer, bladder cancer, leukemia, rectal cancer, and female breast cancer in a study at Cape Cod, MA [10-12]. No studies have evaluated associations between drinking water exposures to these chemicals and medically confirmed, non-cancer diseases in adults.

The purpose of this study was to determine whether potential exposures of employees to contaminated drinking water at Camp Lejeune increased risk of mortality from cancers and other chronic diseases.

Methods

We identified *a priori* several diseases of primary interest: cancers of the kidney, hematopoietic system (NHL, leukemia, multiple myeloma, Hodgkin lymphoma), liver, bladder, esophagus and cervix. Kidney cancer, NHL and liver cancer were selected because the U.S. Environmental Protection Agency (EPA) and the International Agency For Research On Cancer cited evidence for a causal association with TCE exposure, although the evidence for liver cancer is “more limited” than the evidence for kidney cancer and NHL [2-4]. The National Toxicology Program (NTP) concluded that there was “evidence for consistent positive associations” between PCE and esophageal and cervical cancer, and EPA cited evidence for associations between PCE and bladder cancer, NHL, and multiple myeloma [3,5-7]. Benzene is a known cause of leukemia.

Diseases of secondary interest were identified *a priori* based on information from literature reviews suggesting possible associations with the contaminants or with solvents in general: aplastic anemia, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), kidney and liver diseases, Parkinson’s disease, and cancers of the connective tissue, brain, pancreas, oral cavity, pharynx, lung, larynx, prostate, breast, colon and rectum [2,4-7,13-15]. Because this was a data linkage study with no smoking information, we evaluated smoking-related diseases not known to be associated with the contaminants to assess possible confounding: cardiovascular disease, chronic obstructive pulmonary disease (COPD) which includes emphysema and chronic bronchitis, and stomach cancer.

Study population and eligibility

The Camp Lejeune cohort consisted of 4,647 full time civilian employees who began working at the base any time between April 1973 and December 1985. A comparison cohort from USMC Base Camp Pendleton consisted of 4,690 full time civilian employees who met

the same criteria, but were not employed at Camp Lejeune during April 1973–December 1985. Camp Pendleton is located along the Southern California coast in northern San Diego County and southern Orange County. Both bases had similar types of occupations but Camp Pendleton did not have a contaminated drinking water supply [16].

We obtained the Defense Manpower Data Center (DMDC) quarterly personnel files for employees at Camp Lejeune and Camp Pendleton. The DMDC began data collection in the last quarter of 1972. There was a gap in the dataset for the first quarter of 1973 and the quarterly data resumed continuously from the second quarter of 1973 onward. Because we had no information on the employment history of those who were employed at either base prior to 1973, we limited the study to those who were not included in the DMDC dataset for the last quarter of 1972 but who were in the dataset anytime from April 1973 through December 1985. We assumed that those not in the DMDC dataset in the last quarter of 1972 were first employed at either base on or after 1973. Personnel transaction codes indicating changes in employment status (e.g., hiring, promotions, retirement) were available in the DMDC dataset beginning in the second quarter of 1974 but could not be used to determine employment start dates because of missing data and coding problems.

For each individual, the quarterly DMDC data contained full name (starting in the last quarter of 1981), Social Security number (SSN), location of employment (city, state, and zip codes), date of birth, sex, race/ethnicity, highest education level attained, paygrade, and occupation code. This study was approved by the Centers for Disease Control and Prevention Institutional Review Board.

Vital status ascertainment

Personal identifier information from the DMDC database (i.e., name when available, SSN, date of birth, and sex) was matched using a customized algorithm to data in the Social Security Administration (SSA) Death Master File (DMF) and SSA Office of Research, Evaluation and Statistics (ORES) Presumed Living Search to determine vital status [17,18]. Of the combined Camp Lejeune and Camp Pendleton cohorts, almost 50% could not be uniquely matched to the ORES file or their vital status was listed as “unknown” in the ORES file. For these individuals, a commercial tracing service was used to obtain information on their vital status. Identified deaths and individuals whose vital status remained unknown were then searched in the National Death Index (NDI). Those whose vital status remained unknown after the NDI search were considered “lost to follow-up” but contributed person-years to the study until the last date they were included in our DMDC database or the last

date they were known to be alive based on the commercial tracing service information. Underlying and contributing causes of death information were obtained from the NDI Plus.

Exposure assessment

Due to the limited number of historical drinking water samples for volatile organic compounds, the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a historical reconstruction of the spatial and temporal distribution of the contaminants. Details of the methodology and results have been summarized in a peer-reviewed published report [1]. Briefly, we used ground water fate and transport and distribution system models to compute monthly average estimates of the concentrations of the contaminants in the Hadnot Point distribution system [1]. The estimated monthly average concentrations of contaminants in the Hadnot Point water system increased over time during 1973–1985 (Table 1).

Virtually all civilian workers at Camp Lejeune resided off-base. The contamination at Camp Lejeune did not affect off-base drinking water supplies. Exposure to the contaminated drinking water would occur only when the civilians were at work at the base. The mainside area of the base contained maintenance shops, administrative offices, commissaries, storage yards and warehouses. Most of the workplaces were located at mainside. Therefore, we assumed that most civilian workers at Camp Lejeune spent the major portion of their workday in the mainside area, which was served by the Hadnot Point water system. We also assumed that workers at Camp Lejeune were exposed to contaminated drinking water via consumption and/or other uses while at their workplaces during the workday. Since this was a data linkage study, we did not have information on water usage by the workers at Camp Lejeune. For example, we had no information on ingestion or whether the workers showered after their shift or during exercise breaks on base.

We assigned the estimated monthly average contaminant concentrations in the Hadnot Point drinking water to each employee during the period of employment at Camp Lejeune. The median length of employment during 1973–1985 for employees in the Camp Lejeune cohort was about 2.5 years.

Data analysis

Follow-up began on January 1, 1979 (when NDI began data collection) or the start of employment at either Camp Lejeune or Camp Pendleton, whichever was later. Follow-up continued until the end of the study period, December 31, 2008, if the person was known to be alive, or to the date of death. Those with unknown vital status were followed until the last date they were known to be alive based on available data. We used IBM SPSS Statistics 20

Table 1 Estimated Monthly Average Contaminant Concentrations in the Hadnot Point system, 1973 – 1985

| April 1973* | | January 1985** | | | |
|-----------------------------------|-------------|----------------|--------------|----------------|--------------------|
| Contaminant | Mean (µg/L) | Median (µg/L) | Range (µg/L) | # Months > MCL | # Months >100 µg/L |
| Tetrachloroethylene | 14.9 | 14.5 | 0 38.7 | 114 | 0 |
| Trichloroethylene | 355.5 | 356.6 | 30.9 783.3 | 142 | 127 |
| Vinyl Chloride | 23.3 | 20.3 | 1.0 67.3 | 140 | 0 |
| Benzene | 5.2 | 4.1 | 0 12.2 | 63 | 0 |
| April 1973* December 1979 | | | | | |
| Tetrachloroethylene | 9.7 | 9.6 | 0 24.1 | 56 | 0 |
| Trichloroethylene | 280.4 | 274.1 | 30.9 546.3 | 81 | 69 |
| Vinyl Chloride | 14.7 | 14.3 | 1.0 33.4 | 79 | 0 |
| Benzene | 3.3 | 3.2 | 0 5.8 | 4 | 0 |
| January 1980 January 1985* | | | | | |
| Tetrachloroethylene | 21.8 | 21.8 | 2.2 38.7 | 58 | 0 |
| Trichloroethylene | 455.2 | 449.1 | 42.6 783.3 | 61 | 58 |
| Vinyl Chloride | 34.7 | 36.0 | 4.2 67.3 | 61 | 0 |
| Benzene | 7.7 | 7.6 | 1.6 12.2 | 59 | 0 |

*First quarter of continuous DMDC quarterly personnel data on DOD employees.

**Contaminated wells were shut down in February 1985. From March through December 1985, estimated monthly average levels of trichloroethylene, tetrachloroethylene and vinyl chloride were <1 µg/L, and benzene was <4 µg/L.

for data manipulation and data management and SAS 9.3 for data analyses.

We used the Life Table Analysis System (LTAS) to compute cause-specific, standardized mortality ratios (SMRs) and 95% confidence intervals comparing the Camp Lejeune and Camp Pendleton cohorts to the age- sex- race-and calendar period-specific U.S. mortality rates for underlying and multiple (contributing) causes of death [19].

We could not calculate SMRs for aplastic anemia because LTAS combined aplastic anemia with “anemias of other and unspecified type”. SMRs also could not be calculated for specific leukemias because LTAS combines the leukemias. LTAS also combines liver cancers with cancers of the biliary passages and gall bladder, therefore a separate SMR for liver cancer could not be calculated.

a) Comparisons between Camp Lejeune and Camp Pendleton cohorts

We used Cox extended regression models with age as the time variable and base location as a time-varying dichotomous variable to calculate hazard ratios (HRs) comparing mortality rates between the Camp Lejeune and Camp Pendleton cohorts [20]. These analyses avoided a possible “healthy worker effect” bias which occurs when comparing mortality rates in relatively healthy workers to the U.S. mortality rates for cancers and other chronic diseases [21].

We accounted for a “latency period” by lagging exposure to a base by 10, 15, and 20 years in addition to an analysis with no lag. For example, a 10 year lag would assign to an individual aged 29, the base the individual was employed at age 19. If this individual was not yet

employed at age 19, then the person-year for age 29 was assigned to a category “not employed at either base”. We used the Akaike’s information criterion (AIC), a measure of model goodness of fit, to select an appropriate lag period.

Supplementary analyses were conducted comparing the Camp Lejeune cohort to the Camp Pendleton cohort stratified by sex, by “white” race, and by occupation (blue collar vs white collar).

b) Analyses within the Camp Lejeune cohort

Within the Camp Lejeune cohort, we evaluated estimated exposure-response relationships between cumulative exposures to drinking water contaminants and cause of mortality using Cox extended regression models with age as the time variable and cumulative exposure as a time-varying variable. Estimated monthly average contaminant concentrations in the Hadnot Point water system and the dates of employment at Camp Lejeune were used to calculate cumulative exposures (“µg/L-years”) to each contaminant and to the total amount of these contaminants (“TVOC”).

We evaluated cumulative exposures as continuous variables, both untransformed and using the log base 10 transformation. The log transform of cumulative exposure can capture exposure-response relationships in which the response plateaus or attenuates at higher levels of cumulative exposure (Steenland and Deddens 2004). We added a small constant, 0.1 µg/L-years, to the log transformed cumulative exposure to avoid taking the logarithm of zero [22]. A one unit increase in the log-transformed cumulative exposure

variable corresponds to a ten-fold increase in cumulative exposure. We restricted the analyses of the continuous cumulative exposure variables to diseases with at least 5 deaths in the Camp Lejeune cohort.

We also categorized cumulative exposures into tertiles and dichotomous (above or below the median) variables based on the cohort's distribution of maximum cumulative exposure. Because of small numbers resulting in HRs of zero or infinity, some of the causes of death could not be evaluated using the tertile and/or dichotomous categorization.

The cumulative exposure analyses focused on PCE, TCE, vinyl chloride, benzene and TVOC. Because cumulative exposures to the contaminants were correlated, making it difficult to distinguish which contaminant might have caused an association with a disease, each Cox regression model included only one contaminant at a time or TVOC.

We accounted for a latency period between the drinking water exposures and the occurrence of death by lagging the exposure over a specified period. We assessed exposure lag periods of 10, 15, and 20 years as well as a "no lag" period. For example, when a 10-year exposure lag was used, an individual at age 29 would be assigned a cumulative exposure level the individual experienced as of age 19. We used the AIC value to select an appropriate exposure lag period.

The use of either categorical or continuous exposure variables (whether transformed or not) imposes a structure on the exposure-response relationship which may be inaccurate [22]. To obtain a more flexible, smoothed exposure-response curve, we specified a restricted cubic spline (RCS) function for cumulative exposure in the Cox extended model [23]. For the analysis of each contaminant, knots were located at the 5th, 50th, and 95th percentiles among those with any cumulative exposure to the contaminant. We selected these percentiles because they were symmetric for the distribution of those with any cumulative exposure to the contaminant and encompassed most of the range of cumulative exposures [22,23]. Placing the knots at these percentiles also separated those with very low cumulative exposure and those with very high cumulative exposure from the rest of the distribution. (Splines using knots at the 10th, 50th, and 90th percentiles and at the 20th, 50th and 80th percentiles were also explored, but the shape of the HR curves did not differ appreciably from splines with knots at the 5th, 50th, and 95th percentiles.) The RCS function allowed the shape of the HR curve to vary within and between these knots and restricted the curve to be linear before the first knot and after the last knot. The resulting curve is useful for assessing whether the exposure-response relationship is adequately captured by either the categorical or continuous exposure variables. Splines were restricted to those diseases with at least 10 deaths.

In subsequent analyses, we evaluated duration at Camp Lejeune and duration exposed to contaminated drinking water as time-varying categorical variables. We assessed exposure intensity by computing time-independent, continuous and categorical variables for average exposure.

c) Confounder assessment

DMDC and NDI data were available for sex, race, date of death, age at death, paygrade, education level, and occupation. For confounding to occur, a risk factor must be associated with the exposure as well as with the disease of interest. To identify potential confounding, we used a "10% change in the estimate" rule [24]. Final Cox extended models included sex, race, occupation (blue collar vs white collar), and education level.

Information on smoking, alcohol consumption, and occupational history prior to or after employment at either base, was not available from the databases used in this study. We evaluated the magnitude of possible smoking confounding by subtracting the log HR among smoking-related diseases from the log HR of the disease of interest [25].

d) Interpretation of findings

Interpretation of study findings was based on the magnitude of the adjusted SMR or HR. For analyses internal to the Camp Lejeune cohort, we also based our interpretation on the exposure-response relationship, giving more emphasis to monotonic trends in the categorical cumulative exposure variables. A monotonic trend occurs when every change in the HR with increasing category of exposure is in the same direction, although the trend could have flat segments but never reverse direction [26]. Because exposure-response trends could be distorted by biases such as exposure misclassification, we also emphasized non-monotonic exposure-response trends when an elevated HR was observed in the high exposure group.

We computed 95% confidence intervals to show the precision of the HR and regression coefficient estimates, and we included p-values for informational purposes only. We did not use statistical significance testing to interpret findings [26-30].

Results

The Camp Lejeune and Camp Pendleton cohorts were similar on type of occupation, number of months employed at either base, and percent with at least a high school education, but differed somewhat on race and sex (Table 2). Slightly over one-third of both cohorts were employed at their bases during the study period (1973–1985) for one year or less. About 37% of the Camp Lejeune cohort and 33% of the Camp Pendleton cohort were employed at their bases for more than 4 years during the study period.

Table 2 Demographics of the Camp Lejeune and Camp Pendleton cohorts

| Factor | Camp Lejeune N = 4,647 | Camp Pendleton N = 4,690 |
|-----------------------------------|---------------------------|-----------------------------|
| Male | 42.8% | 49.3% |
| Female | 57.2% | 50.7% |
| “white” | 82.2% | 78.8% |
| African American | 15.4% | 9.0% |
| “other” or unknown | 2.4% | 12.3% |
| Median age, start of follow up | 31 | 34 |
| Median age, end of follow up | 58 | 60 |
| % ≥65 yrs, end of follow up | 28.1% | 37.4% |
| Not a high school graduate | 6.8% | 3.9% |
| High school graduate | 70.6% | 84.5% |
| College graduate | 22.6% | 11.7% |
| White Collar | 69.7% | 64.8% |
| Blue Collar | 30.3% | 35.2% |
| % Construction Trades | 15.1% | 12.5% |
| % Maintenance/Mechanics | 8.7% | 12.7% |
| % Firefighters | 2.5% | 3.9% |
| % Laundry Workers | 1.3% | 1.0% |
| % Vehicle/Equipment Operation | 1.7% | 2.2% |
| % Other | 1.0% | 2.9% |
| % Occupation as painter | 1.1% | 1.0% |
| % Worked with solvents | 27.1% | 27.7% |
| % Worked in food preparation | 1.1% | 2.2% |
| Median months employed, 1973-1985 | 29 | 27 |
| Total Deaths | 654 (14.1%) | 869 (18.5%) |
| % deaths occurring >1995 | 69.4% | 67.0% |
| Total lost to follow up | 62 (1.3%) | 95 (2.0%) |
| Total person years of follow up | 123,659 | 123,065 |

Both cohorts had similar median ages at the start and end of follow-up but differed somewhat on the percent sixty-five and older at the end of follow-up. Both cohorts were relatively young with a substantial majority under the age of 65 at the end of follow-up.

In the Camp Lejeune and Camp Pendleton cohorts, 654 deaths (14.1%) and 869 deaths (18.5%) occurred respectively. Vital status at the end of follow-up was unknown for ≤2% in the cohorts, and these individuals were lost to follow-up after their last date in our DMDC database or last date that information was available from the SSA or commercial tracing service.

Standardized Mortality Ratio (SMR) analyses

We found the results for the contributing (or multiple) causes of death to be similar to the results for the

underlying cause of death, so only the results for underlying cause of death are shown. Comparing each cohort to the U.S. mortality rates, we observed that the majority of the SMRs were less than 1.00, indicating a healthy worker effect for cancers and non-cancers (Table 3). For the diseases of primary interest, we observed SMRs above 1.00 in the Camp Lejeune cohort for kidney cancer (SMR = 1.30, 95% CI: 0.52, 2.67) and the hematopoietic cancers (SMR = 1.15, 95% CI: 0.74, 1.71), in particular, leukemias and multiple myeloma (SMR = 1.55, 95% CI: 0.80, 2.71; and SMR = 1.50, 95% CI: 0.55, 3.28, respectively). Leukemias were also elevated in the Camp Pendleton cohort (SMR = 1.33, 95% CI: 0.72, 2.22) as was liver cancer (SMR = 1.12, 95% CI: 0.56, 2.00). Of the diseases of secondary interest, both the Camp Lejeune and Camp Pendleton cohorts had SMRs > 1.00 for cancers of the brain and pancreas. Other causes of death with SMRs > 1.00 included ALS in the Camp Pendleton cohort, and Parkinson’s disease and cancer of the larynx, lung, prostate and rectum in the Camp Lejeune cohort. There were no deaths from male breast cancer at either base.

Of the smoking related diseases not known to be related to solvent exposure, only COPD was elevated in the Camp Lejeune cohort (SMR = 1.33, 95% CI: 0.95, 1.82).

Comparison of Camp Lejeune with Camp Pendleton

We used Cox extended regression models with age as the time variable to compare the mortality rates in the Camp Lejeune cohort with the Camp Pendleton cohort (Table 4). A 10-year lag of person-years at a base was selected because it had a slightly lower AIC value compared to other lags and no lag, and the HRs were adjusted for sex, race, education and occupation (blue collar vs white collar).

Camp Lejeune had an elevated HR for “all cancers” (HR = 1.12, 95% CI: 0.92, 14.36). Of the diseases of primary interest, Camp Lejeune had elevated HRs for kidney cancer (HR = 1.92, 95% CI: 0.58, 6.34) and hematopoietic cancers (HR = 1.40, 95% CI: 0.76, 2.59), in particular multiple myeloma (HR = 1.84, 95% CI: 0.45, 7.58) and leukemias (HR = 1.59, 95% CI: 0.66, 3.84).

Each cohort had 6 deaths due to acute nonlymphocytic leukemia (ANLL) but less than 5 deaths due to each of the other leukemia subgroups. The HR for ANLL was 2.13 (95% CI: .57, 7.95) when Camp Lejeune was compared to Camp Pendleton.

No other diseases of primary interest were elevated in the Camp Lejeune cohort. Because there were only 3 deaths due to the combined grouping of cancers of the liver, gall bladder and biliary passages in the Camp Lejeune cohort, we did not evaluate liver cancer separately. Hodgkin lymphoma and cervical cancer could not be evaluated because there was only 1 death in the Camp Lejeune cohort and no deaths in the Camp Pendleton cohort.

Table 3 Standardized Mortality Ratios (SMRs), Underlying cause of death

| Underlying Cause of Death | Camp Pendleton (reference) | | | Camp Lejeune | | |
|---|----------------------------|--------|-------------------|--------------|--------|-------------------|
| | Obs. | Exp. | SMR (95% CI) | Obs. | Exp. | SMR (95% CI) |
| All Causes | 869 | 1,084 | 0.80 (0.75, 0.86) | 654 | 765 | 0.86 (0.79, 0.92) |
| All Cancers | 257 | 322 | 0.80 (0.70, 0.90) | 229 | 237 | 0.97 (0.84, 1.10) |
| Diseases of Primary Interest | | | | | | |
| Kidney Cancer | 6 | 7.27 | 0.82 (0.30, 1.80) | 7 | 5.40 | 1.30 (0.52, 2.67) |
| Bladder Cancer | 4 | 5.78 | 0.69 (0.19, 1.77) | 2 | 3.76 | 0.53 (0.06, 1.92) |
| Liver* Cancer | 11 | 9.84 | 1.12 (0.56, 2.00) | 3 | 7.23 | 0.42 (0.09, 1.21) |
| Esophageal Cancer | 8 | 8.78 | 0.91 (0.39, 1.80) | 4 | 6.21 | 0.64 (0.18, 1.65) |
| Cervical Cancer | 0 | 2.94 | 0 (0.00, 1.25) | 1 | 2.98 | 0.34 (0.01, 1.87) |
| Hematopoietic Cancers | 25 | 28.83 | 0.87 (0.56, 1.28) | 24 | 20.89 | 1.15 (0.74, 1.71) |
| Hodgkin Lymphoma | 0 | 0.96 | 0.00 (0.00, 3.86) | 1 | 0.83 | 1.20 (0.03, 6.69) |
| NHL** | 8 | 11.50 | 0.70 (0.30, 1.37) | 5 | 8.34 | 0.60 (0.19, 1.40) |
| Multiple Myeloma | 3 | 5.81 | 0.52 (0.11, 1.51) | 6 | 3.99 | 1.50 (0.55, 3.28) |
| Leukemias | 14 | 10.56 | 1.33 (0.72, 2.22) | 12 | 7.73 | 1.55 (0.80, 2.71) |
| Diseases of Secondary Interest | | | | | | |
| Pancreatic Cancer | 22 | 16.39 | 1.34 (0.84, 2.03) | 12 | 11.77 | 1.02 (0.53, 1.78) |
| Colon Cancer | 13 | 25.32 | 0.51 (0.27, 0.88) | 12 | 17.61 | 0.68 (0.35, 1.19) |
| Rectal Cancer | 4 | 5.07 | 0.79 (0.22, 2.02) | 4 | 3.76 | 1.06 (0.29, 2.72) |
| Soft Tissue Cancers | 2 | 2.10 | 0.95 (0.12, 3.44) | 1 | 1.75 | 0.57 (0.01, 3.19) |
| Brain Cancer | 9 | 7.94 | 1.13 (0.52, 2.15) | 7 | 6.68 | 1.05 (0.42, 2.16) |
| Laryngeal Cancer | 1 | 3.09 | 0.32 (0.01, 1.80) | 4 | 2.16 | 1.85 (0.50, 4.74) |
| Lung*** Cancer | 82 | 101.60 | 0.81 (0.64, 1.00) | 80 | 73.20 | 1.09 (0.87, 1.36) |
| Oral Cancers**** | 2 | 6.15 | 0.33 (0.04, 1.18) | 4 | 4.43 | 0.90 (0.25, 2.31) |
| Breast (female) Cancer | 14 | 23.46 | 0.60 (0.33, 1.00) | 21 | 21.42 | 0.98 (0.61, 1.50) |
| Prostate Cancer | 12 | 15.65 | 0.77 (0.40, 1.34) | 10 | 9.16 | 1.09 (0.52, 2.01) |
| Liver Diseases | 19 | 22.64 | 0.84 (0.50, 1.31) | 9 | 18.85 | 0.48 (0.22, 0.91) |
| Kidney Diseases | 7 | 13.98 | 0.50 (0.22, 1.00) | 7 | 9.00 | 0.78 (0.34, 1.54) |
| ALS | 4 | 2.96 | 1.35 (0.37, 3.46) | 1 | 2.29 | 0.44 (0.01, 2.44) |
| Multiple Sclerosis | 1 | 1.92 | 0.52 (0.01, 2.91) | 1 | 1.89 | 0.53 (0.01, 2.95) |
| Parkinson's Disease | 4 | 4.54 | 0.88 (0.24, 2.26) | 5 | 2.28 | 2.19 (0.71, 5.11) |
| Smoking related Diseases (not known to be related to solvent exposure) | | | | | | |
| Stomach Cancer | 7 | 7.88 | 0.89 (0.36, 1.83) | 4 | 5.50 | 0.73 (0.20, 1.86) |
| Cardiovascular Disease† | 317 | 380.45 | 0.83 (0.75, 0.93) | 210 | 244.37 | 0.86 (0.75, 0.98) |
| COPD | 47 | 47.29 | 0.99 (0.73, 1.32) | 40 | 29.99 | 1.33 (0.95, 1.82) |

*Biliary passages, liver and gall bladder ** Non Hodgkin Lymphoma.

Trachea, bronchus, and lung *Buccal cavity and Pharynx.

†Includes diseases of the heart and other diseases of the circulatory system.

Camp Lejeune = 4,647; person years = 123,659.

Camp Pendleton = 4,690; person years = 123,065.

Diseases of secondary interest that had HRs > 1.50 included Parkinson's disease (HR = 3.13, 95% CI: 0.76, 12.86), oral cavity cancers (HR = 1.93, 95% CI: 0.34, 10.81), and rectal cancer (HR = 1.65, 95% CI: 0.36, 7.44). Not evaluated due to small numbers (<2 deaths at either base) were aplastic anemia (one death at Camp Lejeune only), multiple sclerosis, laryngeal cancer, and cervical cancer. For

most of the causes of death, the confidence intervals for the HRs were wide because of small numbers of deaths.

Supplementary analyses stratified by sex, race, and occupation (blue collar vs white collar) were conducted (Additional file 1: Tables S3a-c). The elevated HRs for the hematopoietic cancers were observed among males. Leukemias were elevated among blue collar workers but

Table 4 Camp Lejeune vs Camp Pendleton: Hazard ratios and 95% confidence intervals, adjusted by sex, race, occupation (blue collar vs white collar) and education, 10-year lag

| Underlying Cause of Death | Hazard Ratio | 95% LCL | 95% UCL | p value | CL # | CP # |
|---|--------------|---------|---------|---------|------|------|
| All Cancers | 1.12 | 0.92 | 1.36 | 0.27 | 197 | 234 |
| Diseases of Primary Interest | | | | | | |
| Kidney Cancer | 1.92 | 0.58 | 6.34 | 0.28 | 7 | 5 |
| Bladder Cancer | 0.65 | 0.12 | 3.65 | 0.62 | 2 | 4 |
| Liver* Cancer | 0.62 | 0.16 | 2.45 | 0.49 | 8 | 10 |
| Esophageal Cancer | 0.58 | 0.15 | 2.22 | 0.43 | 3 | 8 |
| Hematopoietic Cancers | 1.40 | 0.76 | 2.59 | 0.28 | 22 | 23 |
| Non Hodgkin Lymphoma | 0.83 | 0.26 | 2.67 | 0.76 | 5 | 8 |
| Multiple Myeloma | 1.84 | 0.45 | 7.58 | 0.40 | 6 | 3 |
| Leukemias | 1.59 | 0.66 | 3.84 | 0.30 | 10 | 12 |
| Diseases of Secondary Interest | | | | | | |
| Pancreatic Cancer | 0.54 | 0.24 | 1.20 | 0.13 | 9 | 21 |
| Colorectal Cancers | 1.14 | 0.54 | 2.39 | 0.73 | 14 | 16 |
| Colon Cancer | 1.01 | 0.43 | 2.38 | 0.98 | 10 | 13 |
| Rectal Cancer | 1.65 | 0.36 | 7.44 | 0.52 | 4 | 3 |
| Brain Cancer | 0.65 | 0.21 | 2.04 | 0.46 | 5 | 8 |
| Lung** Cancer | 1.25 | 0.89 | 1.75 | 0.19 | 69 | 74 |
| Oral Cancers*** | 1.93 | 0.34 | 10.81 | 0.46 | 4 | 2 |
| Breast (female) Cancer | 1.21 | 0.58 | 2.51 | 0.61 | 18 | 14 |
| Prostate Cancer | 1.17 | 0.49 | 2.82 | 0.72 | 10 | 12 |
| Liver Diseases | 0.87 | 0.34 | 2.25 | 0.78 | 8 | 10 |
| Kidney Diseases | 1.23 | 0.39 | 3.87 | 0.72 | 6 | 7 |
| Parkinson's Disease | 3.13 | 0.76 | 12.86 | 0.11 | 5 | 4 |
| Smoking related Diseases (not known to be related to solvent exposure) | | | | | | |
| Stomach Cancer | 0.71 | 0.17 | 2.96 | 0.64 | 3 | 6 |
| Cardiovascular Disease† | 0.93 | 0.77 | 1.13 | 0.46 | 185 | 288 |
| COPD | 1.21 | 0.78 | 1.88 | 0.40 | 38 | 46 |

Diseases not evaluated due to small numbers include: laryngeal cancer, Hodgkin lymphoma, cervical cancer, soft tissue cancers, multiple sclerosis, ALS, and aplastic anemia.

CL #: number of deaths in the Camp Lejeune cohort.

CP #: number of deaths in the Camp Pendleton cohort.

LCL: lower confidence limit UCL: upper confidence limit.

*Biliary passages, liver and gall bladder **Trachea, bronchus, and lung.

***Buccal cavity and Pharynx.

†Includes heart diseases and other diseases of the circulatory system.

not white collar workers. Five of the 10 deaths due to prostate cancer in the Camp Lejeune cohort were African Americans whereas there were no deaths among African Americans in the Camp Pendleton cohort.

Among the smoking-related diseases not known to be associated with solvent exposure, only COPD was elevated in the Camp Lejeune cohort with HR of 1.21. Using the HR for COPD to adjust for the possible confounding effects of smoking would reduce the HRs for the diseases of primary and secondary interest by approximately 17.5%. Some diseases of secondary interest that were also smoking-related diseases, such as lung

cancer and oral cancers, were elevated in the Camp Lejeune cohort, indicating possible confounding by smoking. However, HRs for other smoking-related diseases such as cardiovascular disease, and cancers of the bladder, esophagus, stomach, pancreas, and liver were <1.0 in the Camp Lejeune cohort, indicating no confounding by smoking.

Analyses internal to the Camp Lejeune cohort

To assess whether there was an exposure-response relationship between estimated cumulative exposure (“µg/L –years”) to each of the contaminants, (and total contaminants,

“TVOC”) and cause of death, analyses were restricted to the Camp Lejeune cohort. Cumulative exposure was evaluated as an untransformed and transformed (log base 10) continuous variable (Additional file 2: Tables S1a-b) as well as categorized into tertiles and dichotomous variables (Additional file 3: Tables S2a-b). We selected a 10-year exposure lag period because in most instances it had the lowest AIC value.

We observed a monotonic exposure-response relationship for leukemias and the tertile categorization of cumulative exposure to VC and PCE with HRs of 1.01 and 1.00 in the middle exposure category, and HRs of 1.72 (95% CI: 0.33, 8.83) and 1.82 (95% CI: 0.36, 9.32) at the high category exposure level, respectively (Table 5a). A monotonic exposure-response relationship was also found for leukemias and the tertile categorization of average exposure to VC with HRs of 1.64 (95% CI: 0.31, 8.73) and 1.95 (95% CI: 0.37, 10.43) in the middle and high exposure level. Nine of the 12 leukemia deaths had cumulative exposures to each contaminant above the median. Splines for leukemias and cumulative exposures to PCE and VC indicated a steady rise in HRs to a maximum of about 2.2 to 2.3 at the 85th percentile of cumulative exposure and thereafter declining to HRs of about 1.6 (Additional file 4: Figures S1a-b). This decline in the HRs could be due to exposure misclassification bias [22]. The beta coefficients for untransformed cumulative exposure were positive, but the log base 10 beta coefficients were negative (Table 5a). The untransformed and transformed cumulative exposure models had similar AIC values. Of the 6 ANLL deaths, 4 had cumulative exposures above the median for each contaminant.

All kidney cancer deaths (n = 7) among the Camp Lejeune cohort had cumulative exposures above the median for PCE, TCE, and VC. Only 1 kidney cancer was below the median for cumulative exposure to TVOC and two were below the median for benzene. Only 1 kidney cancer was below the median average exposure to each of the contaminants. Because of the small numbers and high cumulative and average exposures of kidney cancers, categorical analyses resulted in infinite HRs for some of the contaminants (Table 6a). The AIC values for the untransformed and transformed cumulative exposure models were similar and the beta coefficients were positive.

Three of the four esophageal cancer deaths had cumulative exposures above the median for each of the contaminants. HRs for the dichotomous cumulative exposure variables (<median, ≥median) for each of the contaminants were above 2.1 with very wide confidence intervals (Additional file 3: Table S2b).

Although no association was observed for cumulative exposure and multiple myeloma, a monotonic relationship was observed for the tertile categorization of average exposure to benzene with HRs of 1.39 (95% CI: 0.12, 15.65) and 3.15 (95% CI: 0.32, 30.82) in the middle and high exposure level, respectively. The tertile categorization of average exposure could not be evaluated for the other contaminants due to small numbers. Four of the six multiple myeloma deaths had higher than the median average exposure for TCE, VC and TVOC with HRs > 1.8 and very wide confidence intervals for the dichotomous average exposure variables.

No other diseases of primary interest were associated with cumulative or average exposures to the contaminants.

Table 5 Hazard ratios (95% CI) for tertiles of maximum cumulative exposure and coefficients (95% CI) for continuous cumulative exposure (µg/L-year)

| a. Leukemias (N = 12) | | | | |
|------------------------------------|--------------------------|--------------------------|------------------------------------|---------------------------------------|
| Contaminant | Medium Exposure | High Exposure | Cumulative Exposure | Log ₁₀ Cumulative Exposure |
| PCE | 1.00 (0.14, 7.39) N = 2 | 1.82 (0.36, 9.32) N = 8 | 0.0010 (0.0080, 0.0101) p = .82 | 0.0498 (0.7053, 0.6056) p = .88 |
| TCE | 0.94 (0.13, 6.97) N = 2 | 1.65 (0.32, 8.49) N = 8 | <0.00001 (0.0004, 0.0004) p = .84 | 0.1712 (0.6390, 0.2966) p = .47 |
| Vinyl Chloride | 1.01 (0.14, 7.45) N = 2 | 1.72 (0.33, 8.83) N = 8 | 0.0008 (0.0051, 0.0067) p = .80 | 0.0982 (0.7363, 0.5398) p = .76 |
| Benzene | 0.36 (0.04, 3.52) N = 1 | 1.25 (0.31, 5.10) N = 8 | 0.0043 (0.0206, 0.0292) p = .73 | 0.1221 (0.9360, 0.6918) p = .77 |
| TVOC | 0.94 (0.13, 6.97) N = 2 | 1.68 (0.33, 8.67) N = 8 | <0.00001 (0.0002, 0.0003) p = .83 | 0.2334 (0.7150, 0.2483) p = .34 |
| b. Prostate Cancer (N = 10) | | | | |
| Contaminant | Medium Exposure | High Exposure | Cumulative Exposure | Log ₁₀ Cumulative Exposure |
| PCE | 3.46 (0.38, 31.65) N = 4 | 2.08 (0.23, 18.91) N = 5 | 0.0039 (0.0059, 0.0137) p = .44 | 0.3618 (0.4945, 1.2181) p = .41 |
| TCE | 2.55 (0.26, 25.15) N = 3 | 2.39 (0.27, 21.14) N = 6 | 0.0002 (0.0002, 0.0006) p = .37 | 0.4394 (0.4270, 1.3058) p = .32 |
| Vinyl Chloride | 3.54 (0.39, 32.37) N = 4 | 2.00 (0.22, 18.21) N = 5 | 0.0023 (0.0042, 0.0088) p = .49 | 0.3317 (0.5040, 1.1674) p = .44 |
| Benzene | 1.60 (0.26, 9.79) N = 3 | 1.13 (0.21, 6.19) N = 5 | 0.0083 (0.0188, 0.0354) p = .55 | 0.2962 (0.6663, 1.2587) p = .55 |
| TVOC | 2.65 (0.27, 26.15) N = 3 | 2.47 (0.28, 21.82) N = 6 | 0.0001 (0.0001, 0.0003) p = .39 | 0.4298 (0.4438, 1.3034) p = .33 |

Exposure lagged 10 years. Adjusted by sex, race, occupation (blue collar vs white collar) and education. Selected causes of death. Camp Lejeune cohort (N = 4,647). Reference group consists of Camp Lejeune civilian employees in the lowest tertile level of maximum cumulative exposure.

Table 6 Hazard ratios (95% CI) for categorized (<median (ref.), ≥median) maximum cumulative exposure and coefficients (95% CI) for continuous cumulative exposure (µg/L-year)

| a. Kidney Cancer (N = 7) | | | |
|---------------------------------------|--------------------------|----------------------------------|---------------------------------------|
| Contaminant | ≥ Median Exposure | Cumulative Exposure | Log ₁₀ Cumulative Exposure |
| Benzene | 1.82 (0.34, 9.78) N = 5 | 0.0240 (0.0080, 0.0559) p = .14 | 1.3595 (0.3324, 3.0515) p = .11 |
| TVOC | 4.44 (0.52, 38.19) N = 6 | 0.0002 (0.0001, 0.0006) p = .13 | 1.3626 (0.4550, 3.1801) p = .14 |
| PCE | Inf. N = 7 | 0.0100 (0.0019, 0.0219) p = .10 | 1.4753 (0.2983, 3.2489) p = .10 |
| TCE | Inf. N = 7 | 0.0004 (0.0001, 0.0009) p = .12 | 1.3551 (0.4666, 3.1768) p = .14 |
| Vinyl Chloride | Inf N = 7 | 0.0063 (0.0015, 0.0141) p = .11 | 1.4370 (0.3327, 3.2066) p = .11 |
| b. Parkinson's Disease (N = 5) | | | |
| Contaminant | ≥ Median Exposure | Cumulative Exposure | Log ₁₀ Cumulative Exposure |
| PCE | 2.68 (0.22, 33.28) N = 4 | 0.0199 (0.0005, 0.0393) p = .04 | 1.9718 (0.8134, 4.7569) p = .16 |
| TCE | 2.51 (0.21, 30.76) N = 4 | 0.0009 (0.0001, 0.0017) p = .04 | 2.6244 (0.7668, 6.0156) p = .13 |
| Vinyl Chloride | 2.81 (0.23, 34.11) N = 4 | 0.0129 (0.0005, 0.0253) p = .04 | 2.0982 (0.7936, 4.9900) p = .15 |
| Benzene | 2.52 (0.20, 31.59) N = 4 | 0.0490 (0.0008, 0.0971) p = .05 | 2.0910 (0.7578, 4.9398) p = .15 |
| TVOC | 2.52 (0.21, 30.83) N = 4 | 0.0005 (<0.0001, 0.0011) p = .04 | 2.6729 (0.7448, 6.0905) p = .12 |

Exposure lagged 10 years. Adjusted by sex, race, occupation (blue collar vs white collar) and education. Selected causes of death. Camp Lejeune cohort (N = 4,647).

Among the diseases of secondary interest, four of the five cases of Parkinson's disease were above the median cumulative exposure for each of the contaminants. Reflecting this fact, the HRs for the dichotomous cumulative exposure variables were >2.50 (Table 6b). The majority of the cases were also above the median average exposure for each of the contaminants. The AIC values for the untransformed and transformed cumulative exposure models were similar, and the beta coefficients were positive.

Of the ten cases of prostate cancer, eight were above the median cumulative exposure for TCE, PCE, and benzene and seven were above the median for VC, and TVOC. The exposure-response relationships based on the tertiles of cumulative exposures were not monotonic, but the HRs were ≥2.00 in the middle and high exposure categories for PCE, TCE, VC and TVOC (Table 5b). Seven cases were also above the median average exposure for TCE and TVOC. The coefficients for the untransformed and log base 10 transformed cumulative exposure variables were positive and the AIC values were similar for these models.

Of the four cases of rectal cancer, all were above the median cumulative exposure for VC, and three out of four were above the median cumulative exposure for the other contaminants. The HRs for the dichotomous cumulative exposure variables were ≥1.75 for each of the contaminants but could not be calculated for VC or PCE (Additional file 3: Table S2b). All of the rectal cancer cases were also above the median average exposure for each of the contaminants.

None of the other diseases of secondary interest were associated with cumulative or average exposure to the contaminants.

Of the smoking-related diseases not known to be associated with solvent exposure, stomach cancer had elevated HRs for the benzene and vinyl chloride dichotomous cumulative exposure variables but not for the other contaminants. The HRs for the cumulative exposures and COPD and cardiovascular disease were less than 1.0 (Additional file 3: Tables S2 a-b).

Discussion

Diseases of primary interest that were elevated in the Camp Lejeune cohort compared to Camp Pendleton were kidney cancer and the hematopoietic cancers, leukemias and multiple myeloma.

In addition, several of the diseases of secondary interest were also elevated in the Camp Lejeune cohort compared to Camp Pendleton including cancers of the rectum, lung, breast, prostate and oral; Parkinson's disease and kidney diseases. Confidence intervals were wide due to small numbers of individual causes of death. In analyses internal to the Camp Lejeune cohort, we observed monotonic trends between cumulative exposures to VC and PCE and leukemias. Most or all of the deaths from cancers of the kidney, esophagus, rectum, and prostate, and Parkinson's disease had cumulative exposures above the median for each of the contaminants and TVOC. Although multiple myeloma was not associated with cumulative exposure, a monotonic exposure-response relationship was observed for average exposure to benzene, and most of the deaths had average exposures above the median for each of the contaminants and TVOC.

There was some consistency between the findings in this study and the findings in a previous mortality study of Marines and Navy personnel at Camp Lejeune [31]. For example, in the previous study, elevated risks were found for kidney cancer, multiple myeloma, leukemia, rectal cancer, lung cancer and prostate cancer when the Camp Lejeune cohort was compared to the Camp Pendleton cohort. These cancers were also elevated in the current study. In both studies, risks were not elevated for bladder cancer, non-Hodgkin lymphoma, colon cancer, and brain cancer. However, the two studies differed on some cancers. For example, cancers of the liver, esophagus, soft tissue, and pancreas were elevated in the previous study but not the current study. In the current study, cancers of the breast and oral cavity were elevated but not in the previous study. Any conclusions concerning the consistency of the findings in the two studies should be tentative because most of the members of the cohorts in these studies were alive at the end of follow-up.

Studies conducted at Cape Cod, MA found associations between PCE contamination and the incidence of several cancers: lung, bladder, rectal, leukemia, and female breast cancer [10-12]. In the comparison between Camp Lejeune and Camp Pendleton, we also observed elevated HRs for lung cancer, rectal cancer, leukemia and breast cancer but not for bladder cancer. In the New Jersey studies, associations were observed for the incidence of specific subgroupings of leukemia and NHL [9]. We did observe elevations in leukemias, but not NHL, in the current study.

When comparing results across these drinking water studies, it must be kept in mind that the exposure situations were very different. New Jersey and Cape Cod populations were exposed to the contaminants for a much longer time than most of the Camp Lejeune cohort and were primarily exposed at their residences rather than their workplaces. Second, the levels and mixtures of contaminants differed among the studies. At Cape Cod, the only contaminant was PCE, and some of the detected levels of PCE in the Cape Cod drinking water were much higher than those detected or estimated at Camp Lejeune. Similar to Camp Lejeune, some of the towns in the New Jersey study had mixtures of TCE, PCE and other contaminants. However, the maximum detected level of TCE in the Hadnot Point drinking water was considerably higher than the maximum levels detected in the drinking water of the New Jersey towns.

The Camp Pendleton cohort appeared to be an appropriate reference population for the Camp Lejeune cohort because the two bases had somewhat similar demographic and occupational characteristics and the healthy worker effect would be similar in both cohorts. Confounding due to unmeasured risk factors would likely be

minimal because of the similarities between the two cohorts. The key difference between the cohorts was the drinking water contamination at Camp Lejeune [16].

The strengths of the study included the small percentage of lost to follow-up and a rigorous reconstruction of historical levels of contamination in the Hadnot Point water system. An additional strength was the inclusion of the Camp Pendleton cohort.

One serious limitation of the study was the small numbers of most causes of death which resulted in wide confidence intervals for the measures of effect. Moreover, because of small numbers, it was not possible to evaluate exposure-response relationships for many of the causes of death within the Camp Lejeune cohort. There were small numbers because of the small size of the cohorts, the fact that a majority were under the age of 65 and only 14% had died by the end of the study, and the healthy worker effect bias. Many of the diseases of interest have relatively long survival rates (e.g., cancers of the kidney, bladder, colon, rectal, breast, prostate, soft tissue and non-Hodgkin lymphoma, and Parkinson's disease) and would require long-term follow-up of the Camp Lejeune cohort to fully evaluate the health impacts of the drinking water exposures. In addition, some cancers of the digestive system and oral cavity/pharynx appear to be underreported on death certificates compared to cancer registry data [32]. There is also evidence that Parkinson's disease is underreported on death certificates to a higher extent in the southern U.S. than in other areas of the U.S. [33].

Another serious limitation of the study was exposure misclassification bias. There were several sources of exposure misclassification. For example, due to a lack of information on workplace locations, we assumed that all the Camp Lejeune workers were located, or spent considerable time during the work day, at the mainside area of the base served by the Hadnot Point treatment plant. Although this assumption was true for most workers, undoubtedly some did not work in the mainside area.

In addition, we lacked information on water usage of the Camp Lejeune workers. Workers likely varied in their use of drinking water during the workday. Some workers in the mainside area of the base may have been unexposed because they did not use the drinking water for any purpose during the workday.

The exposure misclassification bias was likely considerable but non-differential, i.e., the errors in assigning exposures were likely to be unrelated to disease status. Non-differential exposure misclassification could bias the HRs comparing Camp Lejeune to Camp Pendleton towards the null value of 1.00, resulting in underestimates of the true effect of the exposures [26]. In the analyses of cumulative exposures internal to the Camp Lejeune cohort, such bias could distort exposure-response relationships, for example

producing a curve that plateaus or tails off at higher levels of cumulative exposure [22].

Another limitation was the lack of information on smoking and other risk factors such as occupational exposures prior to or after employment at Camp Lejeune or Camp Pendleton. Such risk factors, if associated with exposure status, could act as confounders, biasing the HR towards or away from the null value of 1.00 and distorting exposure-response relationships. Camp Lejeune and Camp Pendleton workers had similar demographics and occupations so it is unlikely that confounding would be a major source of bias in the comparisons between the two bases. It is also unlikely that unmeasured risk factors would be associated with cumulative exposures in the analyses that were conducted internal to the Camp Lejeune cohort.

We evaluated smoking-related diseases that were not known to be associated with solvent exposure to get some idea of the extent of the possible confounding effects of smoking. We observed a slight elevation for COPD in the Camp Lejeune cohort compared to the Camp Pendleton cohort. Based on this finding, the confounding effect of smoking on the HRs comparing Camp Lejeune and Camp Pendleton would be less than 18% which is in the range of what other occupational health studies have observed for the confounding effects of smoking [34]. In the analyses internal to Camp Lejeune, the smoking-related diseases were for the most part negatively associated with cumulative exposure.

Another possible confounder is alcohol consumption. Kidney cancer and the hematopoietic cancers are not known to be associated with alcohol consumption. A recent study also indicated that Parkinson's disease is unrelated to alcohol consumption [35]. On the other hand, several of the diseases that were elevated in the Camp Lejeune cohort compared to the Camp Pendleton cohort have been associated with alcohol consumption: cancers of the oral cavity, breast, and rectum. Other diseases that have been associated with alcohol consumption were not elevated in the Camp Lejeune cohort compared to the Camp Pendleton cohort: cancers of the liver, esophagus, and colon, cardiovascular diseases and liver diseases. Therefore it does not appear that alcohol was a confounder for the comparisons between Camp Lejeune and Camp Pendleton. Within the Camp Lejeune cohort, cumulative exposures were related to esophageal and rectal cancers but not for other alcohol-related cancers or diseases. Therefore, it does not appear that alcohol was a confounder for these comparisons internal to the Camp Lejeune cohort.

Conclusion

The study found elevated HRs in the Camp Lejeune cohort for several causes of death, including kidney cancer, leukemia, multiple myeloma, rectal cancer, and

Parkinson's disease. Because only 14% of the Camp Lejeune cohort had died by the end of the study, the number of cause-specific deaths was small resulting in wide confidence intervals. Additional follow-up would be necessary to comprehensively assess effects of drinking water exposures at the base.

Additional files

Additional file 1: Camp Lejeune vs Camp Pendleton stratified by sex, race, and occupation.

Additional file 2: Cumulative Exposures (untransformed and log base 10 transformed), 10 year lag, adjusted. Camp Lejeune Cohort (N = 4,647) (Causes of death with N ≥ 5).

Additional file 3: Adjusted Hazard ratios for categorizations of Cumulative exposures, 10 year lag. (Reference group has no/low cumulative exposure). Camp Lejeune cohort (N = 4,647).

Additional file 4: 1 Spline of leukemias and cumulative exposure to PCE and vinyl chloride.

Abbreviations

ATSDR: Agency for toxic substances and disease registry; AIC: Akaike's information criterion; ALS: Amyotrophic lateral sclerosis; COPD: Chronic obstructive pulmonary disease; CI: Confidence interval; DMF: Death master file; DMD: Defense manpower data center; HP: Hadnot point; HR: Hazard ratio; LTAS: Life table analysis system; MCL: Maximum contaminant level; µg/L: Micrograms per liter; NDI: National death index; NHL: Non Hodgkin lymphoma; NTP: National toxicology program; ORES: Office of research, evaluation and statistics; ppm: Parts per million; RCS: Restricted cubic spline functions; SSN: Social security number; SSA: Social security administration; SMR: Standardized mortality ratio; TVOC: Total amount of the contaminants; TCE: Trichloroethylene; PCE: Tetrachloroethylene or perchloroethylene; USMC: United States Marine Corps; EPA: United states environmental protection agency.

Competing interests

All authors declare they have no actual or potential competing financial interest.

Authors' contributions

FJB participated in the study design, data collection, analysis and interpretation of data, and drafted the manuscript. PZR participated in the study design, data collection, interpretation of data, and helped draft the manuscript. MM conducted the water modeling. TCL assisted with analysis and interpretation of data. All authors read and approved the final manuscript.

Acknowledgement

The authors would like to thank Dana Flanders and Kyle Steenland of Emory University, Rollins School of Public Health for their statistical advice in preparing this manuscript. The authors thank Walter M. Grayman and the members of the Camp Lejeune water modeling team: Robert E. Faye, Jason B. Sautner, René J. Suárez Soto, Barbara A. Anderson, Mustafa M. Aral, Jinjun Wang, Wonyong Jang, Amy Krueger, Claudia Valenzuela, and Joseph W. Green, Jr. The authors would also like to thank Kerry Grace Morrissey, Sigurd Hermansen, Vanessa Olivo, and Tim McAdams of WESTAT for preparing the data for analyses.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

Author details

¹Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology and Human Health Sciences, 4770 Buford Highway, MS F 58, Atlanta, GA 30341, USA. ²ATSDR, Division of Community Health Investigations, 4770 Buford Highway, MS F 59, Atlanta, GA 30341, USA.

Received: 2 June 2014 Accepted: 5 August 2014

Published: 13 August 2014

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doi:10.1186/1476-069X-13-68

Cite this article as: Bove et al.: Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study. *Environmental Health* 2014 **13**:68.

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Annals of Oncology
Volume 24, Issue 2
Pp. 301-308.
Light alcohol drinking and cancer: a meta-analysis

V. Bagnardi
University of Milan-Bicocca,

Abstract

Background There is convincing evidence that alcohol consumption increases the risk of cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx. Most of the data derive from studies that focused on the effect of moderate/high alcohol intakes, while little is known about light alcohol drinking (up to 1 drink/day).

Patients and methods We evaluated the association between light drinking and cancer of the colorectum, breast, larynx, liver, esophagus, oral cavity and pharynx, through a meta-analytic approach. We searched epidemiological studies using PubMed, ISI Web of Science and EMBASE, published before December 2010.

Results We included 222 articles comprising ~92 000 light drinkers and 60 000 non-drinkers with cancer. Light drinking was associated with the risk of oropharyngeal cancer [relative risk, RR = 1.17; 95% confidence interval (CI) 1.06–1.29], esophageal squamous cell carcinoma (SCC) (RR = 1.30; 95% CI 1.09–1.56) and female breast cancer (RR = 1.05; 95% CI 1.02–1.08). We estimated that ~5000 deaths from oropharyngeal cancer, 24 000 from esophageal SCC and 5000 from breast cancer were attributable to light drinking in 2004 worldwide. No association was found for colorectum, liver and larynx tumors.

Conclusions Light drinking increases the risk of cancer of oral cavity and pharynx, esophagus and female breast.

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Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis.

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Author information <<http://www.ncbi.nlm.nih.gov/pubmed/23723297>>

- Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20852, USA.

Abstract

The carcinogenic potential of trichloroethylene (TCE) continues to generate much controversy, even after the US Environmental Protection Agency raised its classification to 'carcinogenic to humans'. We conducted a meta-analysis of published cohort and case-control studies exploring occupational TCE exposure in relation to five different lymphatic and haematopoietic cancers: non-Hodgkin's lymphoma (NHL, N=24), Hodgkin's lymphoma (HL, N=13), multiple myeloma (MM, N=11), leukaemia (N=12) and chronic/small lymphocytic leukaemia (CLL/SLL, N=7). Studies published between 1950 and 2011 were identified through a PubMed Medline search. All studies included in analyses were classified as those that assessed either occupational TCE exposure specifically ('TCE-exposure' studies) or a broader classification of all chlorinated solvents ('chlorinated solvent-exposure' studies). A significantly raised summary estimate for NHL was seen for all cohort and case-control 'TCE-exposure' studies combined (N=19; relative risk (RR)=1.32, 95% CI 1.14

to 1.54; I(2)=25.20; p-heterogeneity=0.12) and for cohort 'TCE-exposure' studies (N=10; RR=1.52, 95% CI 1.29 to 1.79; I(2)=7.09; p-heterogeneity=0.63). A non-significant but raised summary estimate was seen for NHL case-control 'TCE-exposure' studies. No significant association with NHL risk was detected overall for any 'chlorinated solvent-exposure' studies. Summary estimates for occupational TCE exposure were not associated with risk of HL, MM, leukaemia or CLL/SLL. Our updated meta-analysis of NHL, which incorporates new analytical results from three cohort and four case-control studies, supports an association between occupational TCE exposure and NHL.

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*“The best reason for having dreams is that in dreams no reasons are necessary.”
Ashleigh Brilliant*

FULL TEXT

[Ann Oncol](#). 2013 Mar;24(3):807-16. doi: 10.1093/annonc/mds508. Epub 2012 Oct 26.

Alcohol drinking and all cancer mortality: a meta-analysis.

[Jin M¹](#), [Cai S](#), [Guo J](#), [Zhu Y](#), [Li M](#), [Yu Y](#), [Zhang S](#), [Chen K](#).

Author information

Abstract

BACKGROUND:

Epidemiological studies have suggested an inconsistent relationship between alcohol drinking and risk of all cancer mortality. As far as we know, no meta-analysis has been conducted to explore this issue.

PATIENTS AND METHODS:

We carried out a PubMed search to find relevant articles published before April 2012 in English. Categorical and dose-response meta-analyses were conducted to identify the impact of alcohol drinking on all cancer mortality. Potential sources of heterogeneity were detected by meta-regression and stratification analyses. Sensitivity and cumulative meta-analyses were also carried out.

RESULTS: <http://annonc.oxfordjournals.org/content/24/3/807.long>

Eighteen independent cohort studies met the inclusion criteria. Compared with non/occasional drinkers, the pooled relative risks (RRs) were 0.91 [95% confidence interval (CI) 0.89-0.94] for light, 1.02 (95% CI 0.99-1.06) for moderate, and 1.31 (95% CI 1.23-1.39) for heavy drinkers. Former drinkers presented a higher risk (RR = 1.32, 95% CI 1.15-1.50) than current drinkers (RR = 1.06, 95% CI 0.98-1.16). There was a J-shaped relationship between all cancer mortality and alcohol consumption in males but not in females.

CONCLUSIONS:

This meta-analysis confirms the health hazards of heavy drinking (≥ 50 g/day) and benefits of light drinking (≤ 12.5 g/day). Large-sample, well-designed, prospective epidemiological studies, especially on heavy drinking among women, should be developed in future.

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

[Abdul Khalade](#)¹, [Maritta S Jaakkola](#)², [Eero Pukkala](#)^{3,4} and [Jouni JK Jaakkola](#)^{1,5}

¹Institute of Occupational and Environmental Medicine, University of Birmingham, UK

²Center for Environmental and Respiratory Health Research, Respiratory Medicine Unit, Department of Internal Medicine, Institute of Clinical Medicine, University of Oulu, P.O. B. 5000, 90014 Oulu, Finland

³Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Pieni Roobertinkatu 9, Helsinki, Finland

⁴School of Public Health, University of Tampere, Tampere, Finland

⁵Center for Environmental and Respiratory Health Research, Institute of Health Sciences, University of Oulu, P.O. B. 5000, 90014 Oulu, Finland

Corresponding author.

Abdul Khalade: AXK042@bham.ac.uk ; Maritta S Jaakkola: maritta.jaakkola@oulu.fi ; Eero Pukkala: eero.pukkala@cancer.fi ; Jouni JK Jaakkola: jouni.jaakkola@oulu.fi

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Received August 19, 2009; Accepted June 28, 2010.

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Abstract

Background

A substantial number of epidemiologic studies have provided estimates of the relation between exposure to benzene at work and the risk of leukemia, but the results have been heterogeneous. To bridge this gap in knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of leukemia, including all types combined and the four main subgroups acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

Methods

A systematic literature review was carried out using two databases 'Medline' and 'Embase' from 1950 through to July 2009. We selected articles which provided information that can be used to estimate the relation between benzene exposure and cancer risk (effect size).

Results

In total 15 studies were identified in the search, providing 16 effect estimates for the main analysis. The summary effect size for any leukemia from the fixed-effects model was 1.40 (95% CI, 1.23-1.57), but the study-specific estimates were strongly heterogeneous ($I^2 = 56.5\%$, $Q \text{ stat} = 34.47$, $p = 0.003$). The random-effects model yielded a summary- effect size estimate of 1.72 (95% CI, 1.37-2.17). Effect estimates from 9 studies were based on cumulative exposures. In these studies the risk of leukemia increased with a dose-response pattern with a summary-effect estimate of 1.64 (95% CI, 1.13-2.39) for low (< 40 ppm-years), 1.90 (95% CI, 1.26-2.89) for medium (40-99.9 ppm-years), and 2.62 (95% CI, 1.57-4.39) for high exposure category (> 100 ppm-years). In a meta-regression, the trend was statistically significant ($P = 0.015$). Use of cumulative exposure eliminated heterogeneity. The risk of AML also increased from low (1.94, 95% CI, 0.95-3.95), medium (2.32, 95% CI, 0.91-5.94) to high exposure category (3.20, 95% CI, 1.09-9.45), but the trend was not statistically significant.

Conclusions

Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

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