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

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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 tetrachloroethylene exposure 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; three studies; 463 exposed cases). For employment as a dry cleaner, the overall mRR was 1.47 (95% CI: 1.16, 1.85; seven studies; 139 exposed cases), and for smoking-adjusted studies, the mRR was 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 approaches in exposure assessment in the studies of “tetrachloroethylene-exposed workers” may have attenuated the relative risks.

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Introduction

Bladder cancer is the ninth most common cancer diagnosis worldwide, with > 330,000 estimated new cases and > 130,000 estimated deaths each year ([Ferlay et al. 2010](#)). Although cigarette smoking is the most important risk factor for bladder cancer, accounting for approximately 66% of new cases in men and 30% of the cases in women in industrialized populations ([Burger et al. 2013](#)), an increased risk of bladder cancer has also been reported among persons employed in certain industries (e.g., rubber production, aluminum production, textile and dye manufacturing) and occupations (e.g., painter, hair dresser/barber, dry cleaners) [[Guha et al. 2010](#); [International Agency for Research on Cancer \(IARC\) 2009b](#)], and in relation to exposure to specific chemicals (e.g., aromatic amines, polycyclic aromatic hydrocarbons, arsenic, tetrachloroethylene) [[Guha et al. 2012](#); [IARC 2009a](#); U.S. Environmental Protection Agency (EPA) 2012].

Tetrachloroethylene (also referred to as perchloroethylene) is one of the most important chlorinated solvents worldwide and has been produced commercially since the early 1900s. Currently the primary use of tetrachloroethylene is as a raw material for the production of fluorocarbons ([Guha et al. 2012](#)). However, between the 1950s and 1980s, most of the tetrachloroethylene that was produced was used in dry cleaning ([Doherty 2000](#)), with smaller amounts used for degreasing metals and in the production of chlorofluorocarbons.

Epidemiological studies of workers provide a good platform for identifying individuals with considerable exposure to tetrachloroethylene. To date, few epidemiological studies assessing bladder cancer risk have included quantitative estimates of occupational exposure to tetrachloroethylene. However, some insight into the relationship between bladder cancer risk and exposure to tetrachloroethylene can be gained by studies of workers in the dry-cleaning industry.

CAREX, an international, country-specific survey of occupational exposure to carcinogens, reported that the majority of the workers occupationally exposed to tetrachloroethylene were employed in dry-cleaning shops ([Kauppinen et al. 2000](#)). The prevalence of exposure among dry cleaners was reported at 70% in the United States in 2007 ([Halogenated Solvents Industry Alliance 2008](#)), and 90% in France and two-thirds in Denmark in 2012 ([European Chlorinated Solvent Association 2013](#)). Although limited quantitative exposure data are available, some dry cleaners may have been heavily exposed to tetrachloroethylene. Before the 1960s, most dry cleaners manually moved garments immersed in tetrachloroethylene from washers to dryers—a practice that may still exist today among those using older equipment ([Garetano and Gochfeld 2000](#))—that may result in high dermal exposure.

Epidemiological findings of an increased risk of bladder cancer in dry cleaners exposed to tetrachloroethylene led an expert working group assembled by the Monographs Programme at IARC to reaffirm the classification of tetrachloroethylene as “probably carcinogenic to humans” (Group 2A) in October 2012 and to newly identify the bladder as a target organ ([Guha et al. 2012](#)). For this assessment, the working group carefully reviewed the data on human exposure, carcinogenesis bioassays in experimental animals, and the mechanisms of carcinogenesis, in addition to the epidemiological findings of cancer in humans ([Guha et al. 2012](#)). There were no mechanistic data to inform the increased risk of bladder cancer in people exposed to tetrachloroethylene. The working group did identify several potential genotoxic and nongenotoxic mechanisms of carcinogenesis for tetrachloroethylene in the liver from cancer bioassays in mice and toxicity studies in rodents that could operate in humans. In rats, tetrachloroethylene has been shown to induce neoplasms of the hematopoietic system, testes, kidney, and brain, although the human cancer data were not as strong for these sites ([Guha et al. 2012](#); [U.S. EPA 2012](#)).

To complement the systematic IARC review, we conducted meta-analyses of published studies that specifically assessed occupational exposure to tetrachloroethylene or studies of dry-cleaning workers to further evaluate evidence for the risk of bladder cancer associated with tetrachloroethylene exposure. We qualitatively assessed exposure–response relationships from the limited number of studies available.

Methods

We conducted a literature search for publications in any language that reported risk estimates for bladder cancer in relation to occupational exposure to tetrachloroethylene or provided enough information for their calculation. We identified studies from the 2012 IARC evaluation of the carcinogenicity of tetrachloroethylene ([Guha et al. 2012](#)) and the U.S. EPA review of tetrachloroethylene ([U.S. EPA 2012](#)). In addition, we searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) using the following keywords: “dry cleaners,” “dry cleaning,” “occupation,” “tetrachloroethylene,” “bladder cancer,” “bladder carcinoma,” and “urothelial carcinoma” in various combinations. Searches using common variations on these keywords did not result in the identification of additional studies.

We included studies that reported a risk estimate specifically for “tetrachloroethylene-exposed workers” or for employment as a “dry cleaner,” because of historical information indicating that many dry cleaners were exposed to tetrachloroethylene but generally not to other known or suspected occupational bladder carcinogens ([IARC 1995](#)). We included risk estimates that were reported for men and women combined. If a study reported risk estimates for men and women separately, we included both risk estimates separately in the meta-analyses. If a study reported results stratified by exposure groups and not for “any occupational exposure” versus “background exposure,” we pooled the risk estimates by conducting a within-study random-effects meta-analysis of the nonreference exposure groups. Several studies reported results only for the occupational category “dry-cleaning and laundry workers.” We conducted a sensitivity analysis with the expectation that laundry workers were unexposed to tetrachloroethylene or were exposed only at background levels; therefore, risk estimates would be biased toward the null for a combined occupational category of dry-cleaning and laundry workers because of unexposed or lightly exposed individuals misclassified as exposed.

We excluded studies that reported proportional mortality analyses because the risk estimates are potentially biased. When several publications were available from a single study population, we considered only the most complete or recent publication. Four overlapping papers in the U.S. National Cancer Institute (NCI) National Bladder Cancer Study reported findings for bladder cancer risk in dry cleaners and/or laundrers ([Schoenberg et al. 1984](#); [Silverman et al. 1989, 1990](#); [Smith et al. 1985](#)). Of these, only two ([Silverman et al. 1989, 1990](#)) were included in the sensitivity analysis for laundry and dry-cleaning workers because of the significant, but not clearly specified, overlap between the study populations and because of information indicating that laundry and dry-cleaning workers were combined by [Schoenberg et al. \(1984\)](#), which was not stated in the article (Silverman D, personal communication). Publications included in the meta-analysis are listed in [Table 1](#).

Zheng T, Cantor KP, Zhang Y, Lynch CF. Occupation and bladder cancer: a population-based, case-control study in Iowa. *J Occup Environ Med.* 2002;44:685–691. [[PubMed](#)] [[Google Scholar](#)]