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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 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.

Introduction

Bladder cancer is the 9th most common cancer diagnosis worldwide, with more than 330,000 estimated new cases and more than 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; 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. 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 is as a feedstock for 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.

Epidemiologic 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 among workers in the dry cleaning industry.

CAREX, a 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 as 70% in the United States in 2007 (Halogenated Solvents Industry Alliance 2008), 90% in France and two-thirds in Denmark in 2012 (European Chlorinated Solvent Association 2013). Although little quantitative exposure data is available, some dry cleaners may have been heavily exposed to tetrachloroethylene. Prior to 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) and may also 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 the International Agency for Research on Cancer (IARC) to re-affirm the classification of tetrachloroethylene as *probably carcinogenic to humans* (Group 2A) in October 2012 and newly identify the bladder as a target organ (Guha et al. 2012). To make this assessment, the working group also 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 non-genotoxic 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 induces 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 tetrachloroethylene exposure 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 2012 United States Environmental Protection Agency (U.S. EPA) review of tetrachloroethylene (U.S. EPA 2012). In addition, a 'PubMed' literature search was conducted including the following keywords: "dry cleaners, dry cleaning, occupation, tetrachloroethylene, bladder cancer, bladder carcinoma, urothelial carcinoma" in various combinations and also including common variations on these keywords, but 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 "dry cleaner" because of historical information indicating that many dry cleaners were exposed to tetrachloroethylene, but generally not to other known/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, both risk estimates were included separately in the meta-analysis. 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 non-reference exposure groups. A considerable number of 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 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 reporting proportional mortality analyses since the risk estimates are potentially biased. When several publications were available from a single study population, only the most complete or recent publication was considered. There were 4 overlapping papers reporting findings for bladder cancer risk in dry cleaners and/or launderers in the United States National Cancer Institute (US NCI) National Bladder Cancer Study (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 laundry and dry-cleaning workers' sensitivity analysis because of the significant, but not clearly specified, overlap between the study populations and information indicating that laundry and dry cleaning workers were combined in the paper by Schoenberg *et al.;* this was not stated in the report (Debra Silverman, personal communication). (Table 1)

We conducted random-effects meta-analyses to pool the relative risks (RRs) reported in the included publications (Table 2). We analyzed separately the studies reporting on 'tetrachloroethylene exposed workers' and the studies reporting on dry cleaning workers. An α of 0.05 was used to assess whether meta-relative risks (mRRs) were significantly elevated. Inconsistency among the studies was quantified using the I^2 statistic (Higgins et al. 2003). I^2 values of 25%–50% indicate moderate inconsistency, while values larger than 50% reflect large inconsistencies among studies. We assessed the sensitivity of the outcome of the meta-analysis by excluding individual studies one at a time and also restricting the analyses to certain subgroups (i.e. studies reporting a RR for 'employment as dry cleaner', cohort studies, case-control studies, and studies that adjusted for smoking). We assessed publication bias visually

through a funnel plot and quantitatively with Egger's graphical test (evidence for publication bias if p-value Egger's test: < 0.05) (Egger et al. 1997). We compared mRRs by strata using a test of interaction (Altman and Bland 2003).

We qualitatively summarized the exposure-response data (e.g., duration of employment as dry cleaner or duration or intensity of exposure to tetrachloroethylene) because of the limited number of studies available (Table 3). We conducted all statistical analyses in Stata (version 11; StataCorp LP, College Station, TX, USA).

Results

We identified 38 publications from 26 studies that assessed the risk of bladder cancer among tetrachloroethylene exposed workers or among dry cleaning workers (13 case-control studies, 11 cohort studies, one meta-analysis, and one cluster analysis). We excluded 20 publications from the meta-analyses because they reported standardized mortality odds ratios (1 study) or proportionate mortality ratios (4 studies), because the extent of exposure to tetrachloroethylene was unclear (4 studies), because the publication was superseded by a more recent publication (1 study), because of overlap of the study population with that of another publication (9 studies), or because it was a meta-analysis (1 study). We provide an overview of these publications and the rationale for excluding them from the meta-analysis in the Supplemental material, Table S1. In Table 1 we provide more details of the studies that were included in the present meta-analyses.

Tetrachloroethylene exposed workers

We included one cohort study (Lipworth et al. 2011) and two case-control studies (Christensen et al. 2012; Pesch et al. 2000) that assessed the risk of bladder cancer among tetrachloroethylene exposed workers (Table 1). Risk estimates were adjusted for smoking in both case-control

studies, but not in the cohort study. With the exception of one study that reported results for urothelial cancer (Pesch et al. 2000), all studies reported results for all bladder cancer subtypes combined.

To allow inclusion into the meta-analysis, we had to pool multiple non-reference exposure group specific ORs in the Pesch et al. (2000) study, which reported results based on a job exposure matrix (JEM) and also on a (more precise) job task exposure matrix (JTEM). Because the JEM results were based on a much larger number of cases than for the JTEM (445 versus 106), we included these in the meta-analysis while also assessing the sensitivity of the meta-relative risk (mRR) for this decision. The overall mRR for bladder cancer in studies of tetrachloroethylene exposed workers was 1.08 (95% CI: 0.82, 1.42) (Table 2). Substituting the JEM based results from Pesch et al. (odds ratio, OR=1.19; 95% CI: 1.06, 1.34) with the JTEM based results (OR=1.24; 95% CI: 0.91, 1.69) resulted in a mRR of 1.05 (95% CI: 0.76, 1.47) (Table 2). There was no evidence for between study heterogeneity ($I^2 < 30\%$) or publication bias (p-value Egger's test: > 0.05) in the studies included. Considering the limited number of studies available, we did not conduct a separate meta-analysis on the two available case-control studies.

Dry cleaning worker studies

We included 3 cohort studies (Blair et al. 2003; Calvert et al. 2011; Pukkala et al. 2009) and 11 case-control studies (Burns and Swanson 1991; Colt et al. 2011; Dryson et al. 2008; Gaertner et al. 2004; Kogevinas et al. 2003; Siemiatycki 1991; Silverman et al. 1989, 1990; Smith et al. 1985; Steineck et al. 1990; Teschke et al. 1997; Zheng et al. 2002) that assessed the risk of bladder cancer among dry cleaning workers, or dry cleaning and laundry workers (Table 1).

The overall mRR for bladder cancer in studies with laundry and/or dry cleaning workers was 1.20 (95% CI: 1.06, 1.36). The mRR among cohort studies was 1.17 (95% CI: 0.95, 1.44) and among case-control studies was 1.54 (95% CI: 1.17, 2.04) (Table 2). One study reported results for urothelial cancer (Steineck et al. 1990), the other studies reported results for all bladder cancer subtypes combined. We did not observe evidence for between study heterogeneity (I^2 < 30%). Some evidence for publication bias was observed using Egger's test: p = 0.013) in this meta-analysis.

We included eight risk estimates from seven studies that assessed the risk of bladder cancer among dry cleaning workers only (Blair et al. 2003; Burns and Swanson 1991; Calvert et al. 2011; Colt et al. 2011; Gaertner et al. 2004; Lynge et al. 2006; Steineck et al. 1990) (Table 1, Figure 1). One publication reported gender-specific risk estimates (Colt et al. 2011), which we included for men and women separately. In this analysis we included (Lynge et al. 2006) instead of (Pukkala et al. 2009) due to the considerable overlap between the cohorts studied in these publications. Lynge and colleagues (Lynge et al. 2006) reported results for dry cleaning workers only whereas Pukkala and colleagues (Pukkala et al. 2009) reported results for the combined category of laundry or dry cleaning workers.

The overall mRR for bladder cancer in studies of dry cleaning workers was 1.47 (95% CI: 1.16, 1.85). The mRR among cohort studies was 1.46 (95% CI: 1.14, 1.87) and among case-control studies was 1.50 (95% CI: 0.80, 2.84) (Table 2, Figure 1). All case-control studies in this analysis adjusted risk estimates for smoking. Although smoking was not adjusted for in the cohort studies, one study used unexposed laundry workers as the comparison group to indirectly control for tobacco use since the smoking pattern in those two groups are expected to be similar

(Lynge et al. 2006). We did not observe evidence for between study heterogeneity (I^2 < 30%) or publication bias (*p*-value Egger's test: > 0.05) in this meta-analysis. Although one study had considerable weight (60.6%) in the meta-analysis (Lynge et al. 2006), excluding it did not have a considerable impact on the meta-relative risk (mRR = 1.51; 95% CI: 1.05, 2.18; 6 studies) (Table 2).

Exposure-response information reported in the published studies

Five studies included in the meta-analyses provided information on the exposure-response relationship with exposure to tetrachloroethylene (2 studies) or duration of employment as dry cleaner (3 studies) and bladder cancer risk (Blair et al. 2003; Calvert et al. 2011; Christensen et al. 2012; Lynge et al. 2006; Pesch et al. 2000). Exposure group specific risk estimates for these studies are reported in Table 3. In general, we observed some evidence for an exposure-response association in the few studies that provided information on exposure-response (e.g., duration of employment as dry cleaner or duration or intensity of exposure to tetrachloroethylene).

Only Pesch et al. (Pesch et al. 2000) provide some evidence for an upward trend in ORs with increasing exposure index (product of duration, probability, and intensity of exposure to tetrachloroethylene). For men, ORs based on the JTEM exposure assessment increased with exposure index: 1.0 (95% CI: 0.7, 1.5; 37 cases) for medium exposure (higher than the 30th percentile of the distribution of exposure among exposed controls), 1.2 (95% CI: 0.8, 1.7; 47 cases) for high exposure (higher than the 60th percentile of the distribution of exposure among exposed controls), 1.8 (95% 1.1, 3.1; 22 cases) for substantial exposure (higher than the 90th percentile of the distribution of exposure among exposed controls). ORs based on the JEM exposure assessment (405 exposed cases) also increased with increasing exposure index,

although less pronounced. For women (40 exposed cases), only results based on the JEM exposure assessment were reported and no upward trend was observed. Lynge et al. (Lynge et al. 2006) reported RRs by duration of exposure. For workers exposed for less than a year the RR was 1.50 (95% CI: 0.57, 3.96), 2.39 (95% CI: 1.09, 5.22) for 2-4 years, 0.91 (95% CI: 0.52, 1.59) for 5-9 years, and 1.57 (95% CI: 1.07, 2.29) for ≥10 years. In the remaining studies (Blair et al. 2003; Calvert et al. 2011; Christensen et al. 2012) assessment of the exposure-response relationship was impaired by the limited number of cases.

Discussion

In this meta-analysis we assessed studies of dry cleaning (and laundry) workers to gain insight into the potential association between exposure to tetrachloroethylene and bladder cancer risk. Ideally, the highest quality evidence to assess this association would come from studies that conducted quantitative assessment of exposure to tetrachloroethylene (Vlaanderen et al. 2008). However, we identified only three studies that estimated exposure to tetrachloroethylene specifically (Christensen et al. 2012; Lipworth et al. 2011; Pesch et al. 2000), none of which reported estimates of risk per unit of exposure to tetrachloroethylene. These studies used relatively crude methods to generate exposure estimates (i.e. using only job title information to assign exposure), which would likely result in considerable non-differential misclassification of exposure, thereby biasing the risk estimates towards the null (Blair et al. 2007).

Several different approaches were used to classify individuals into occupational categories in studies of dry cleaners. Because of the large number of small shops and the high turnover in this industry, two studies assembled cohorts through union records (Blair et al. 2003; Calvert et al. 2011). In these studies information was only available on job-title at entry into the cohort (i.e.

data at entry into the union). Both studies augmented job-title information with monitoring data. In (Blair et al. 2003) monitoring data from other studies of the dry cleaning industry were used to assign an exposure score to the jobs held. In (Calvert et al. 2011) monitoring data was used to verify exposure to tetrachloroethylene and other dry cleaning solvents, and to exclude workers who had been exposed to carbon tetrachloride or trichloroethylene. A similar approach was used by (Lynge et al. 2006) where census and registry data were supplemented with implied exposure status (working as a dry-cleaner or in a dry-cleaning shop), based on original texts from the census forms (Denmark and Norway), interviews (Sweden), and pension scheme data (Finland). In the case-control studies (Burns and Swanson 1991; Colt et al. 2011; Gaertner et al. 2004; Steineck et al. 1990) classification into occupational categories was based on information from interviewers. Available information, including a full occupational history, complete description of the duties performed, and the dates each job began and ended, was categorized using occupational classification standards.

Differences in exposure assessment strategies reflect the design of the studies. While information on the full working history would be preferred over a "snapshot" of an individual's job-title at a specific point in time, acquiring such information is often difficult in large cohort studies.

Our finding of a lower mRR in studies that combined laundry and dry cleaning workers than among studies including only dry cleaning workers supports our hypothesis that laundry workers may have received little or no exposure to tetrachloroethylene. A possible explanation for the higher mRR among the dry cleaning worker studies than among the 'tetrachloroethylene exposed workers' studies would be co-exposure to a yet unidentified occupational bladder carcinogen, although there are no clear candidates. It is also possible that dry cleaning workers have lifestyle

factors that could account for the observed excess. In the study by Blair and colleagues (Blair et al. 2003), a higher bladder cancer mortality in dry cleaners was observed after the introduction of tetrachloroethylene, supporting that tetrachloroethylene may in fact be responsible for the cancer excess. Further, relatively crude exposure assessment approaches in the 'tetrachloroethylene exposed workers' studies might have attenuated the relative risks. Finally, the differences in the mRRs between these groups are not large and may just be due to chance occurrences (p-value for test for interaction = 0.11).

Smoking is the most important risk factor for bladder cancer and accounts for approximately half of all cases (Burger et al. 2013). None of the cohort studies included in the meta-analysis specifically controlled for tobacco smoking, although the study by Lynge et al. (Lynge et al. 2006) used unexposed laundry workers as the comparison group as an indirect proxy for bladder cancer risk factors such as tobacco use. The assumption is that the socioeconomic status of launderers and dry cleaners is similar, which should provide some control for socioeconomic status related factors. Among the subgroup of dry-cleaning workers only, the mRR for the case-control studies that adjusted for tobacco smoking was similar to the mRR for the cohort studies, indicating that there is little evidence of confounding by tobacco smoking. One case-control study assessed and reported no interaction between the OR for tobacco smoking and the OR for dry cleaning workers (Colt et al. 2011).

Finally, it is important to note that although dry cleaners were exposed to other chemicals, they were primarily exposed to tetrachloroethylene. Before 1960 dry cleaning workers could also have been exposed to carbon tetrachloride or Stoddard solvent (IARC 1995), although neither of these chemicals have been classified as bladder carcinogens by the International Agency for

Research on Cancer (IARC). (IARC did classify carbon tetrachloride as *possibly carcinogenic to humans*, based on excess liver and mammary neoplasms in experimental animals exposed to carbon tetrachloride (IARC 1999)). Although occupational exposure to aromatic amines, arsenic, and possibly polycyclic aromatic hydrocarbons are other risk factors for bladder cancer (IARC 2009a, 2009b), they are unlikely to be confounders since dry cleaning workers are generally not occupationally exposed to these agents. However, it is possible that exposure to these agents may have occurred during jobs held before or after employment as a dry cleaning worker.

Our finding of an increase in bladder cancer risk among dry cleaning workers is consistent with two other reviews. In a meta-analysis of 14 studies of dry cleaners and launderers (our analysis includes 13 studies) by Reulen et al. (Reulen et al. 2008) a mRR of 1.27 (95% CI: 0.95, 1.71) was reported. A recent systematic literature review by the USEPA also concluded that bladder cancer was one of the human tumor types associated with tetrachloroethylene exposure. The USEPA characterized tetrachloroethylene as 'likely to be carcinogenic to humans' based on suggestive evidence of carcinogenicity in epidemiological studies and conclusive evidence of tumorigenicity in rodents. (U.S. EPA 2012).

In conclusion, we observed a significantly elevated risk of bladder cancer in a meta-analysis of seven studies among dry cleaning workers. This excess occurred in cohort and case-control studies. The outcome of the meta-analysis was not excessively sensitive to individual studies or study types. Among studies with the necessary information, the excesses did not appear to be confounded by smoking behaviour. In the few studies that provided information on exposure-response (e.g., duration of employment as dry cleaner or duration or intensity of exposure to tetrachloroethylene), we observed no clear patterns. Our results demonstrate that workers in the

dry cleaning industry experienced an elevated risk of bladder cancer. Dry cleaners were exposed to a mixture of solvents, with tetrachloroethylene being the only component of the mixture identified as a potential bladder carcinogen. Therefore, the higher risk of bladder cancer in dry cleaners may have been due to tetrachloroethylene exposure, the primary solvent used in dry cleaning. However, with limited evidence from studies that specifically assessed exposure to tetrachloroethylene, we were not able to corroborate this hypothesis.

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Table 1. Overview of publications included in the meta-analysis.

Study #	Reference	Country	Study design	Sex	Disease classification	Exposure definition	Exposure period[a,b]	Smoking adjusted[c]	N exposed cases	I/M[d]	Risk estimate
1	Blair et al. 2003	USA	cohort	both	188 (ICDA-8[e])	dry cleaning	<1979[f]	no	12	M	SMR[g]
2	Calvert et al. 2011	USA	cohort	both	188, 189.3-189.9 (ICD-9[h])	dry cleaning	<1982[i]	no	10	M	SMR[g]
3	Lipworth et al. 2011	USA	cohort	both	188, 189.3-189.9 (ICD-9[h])	tetrachloroethylene	<1996	no	17	M	SMR[f]
4	Lynge et al. 2006[j]	D,N,S,F[k]	cohort	both	C67 (ICD-O2[l])	dry cleaning	<1970	no	93	I	RR[m]
4	Pukkala et al. 2009[j]	D,N,S,F[k]	cohort	both	181 (ICD-7)	laundry or dry cleaning	<1970	no	186	I	SIR[n]
5	Burns and Swanson 1991	USA	case-control	both	not reported	dry cleaning	<1991[o]	yes	8	I	OR[p]
6	Siemiatycki 1991	Canada	case-control	men	188 (ICD-9[h])	laundry or dry cleaning	<1985	yes	10	I	OR[p]
6	Christensen et al. 2012[q]	Canada	case-control	men	188 (ICD-9[h])	tetrachloroethylene	<1985	yes	2	I	OR[p]
7	Colt et al. 2011	USA	case-control	men	[r]	dry cleaning	<2004	yes	4	I	OR[p]
7	Colt et al. 2011	USA	case-control	women	[r]	dry cleaning	<2004	yes	6	I	OR[p]
8	Dryson 2008	New Zealand	case-control	both	not reported	laundry or dry cleaning	<2004	yes	3	I	OR[p]
9	Gaertner et al. 2004	Canada	case-control	men	[s]	dry cleaning	<1997	yes	4	I	OR[p]
10	Kogevinas 2003	Western Europe[t]	case-control	men		laundry or dry cleaning	<1995	yes	19	I	OR[p]
11	Pesch et al. 2000	Germany	case-control	both	[u]	tetrachloroethylene	<1995	yes	444	I	OR[p]

Study #	Reference	Country	Study design	Sex	Disease classification	Exposure definition	Exposure period[a,b]	Smoking adjusted[c]	N exposed cases	I/M[d]	Risk estimate
12	Silverman 1989[v]	USA	case-control	Non-white men	[s]	laundry or dry cleaning	<1978	yes	11	I	OR[p]
12	Silverman 1990[v]	USA	case-control	women	[s]	laundry or dry cleaning	<1978	yes	23	I	OR[p]
13	Steineck et al. 1990	Sweden	case-control	men	[v]	dry cleaning	<1987	yes	2	I	OR[p,w]
14	Teschke 1997	Canada	case-control	both	188 (ICD-O)	laundry or dry cleaning	<1991	yes	5	I	OR[p]
15	Zheng 2002	USA	case-control	women	[s]	laundry or dry cleaning	<1989	yes	3	I	OR[p]

[a]Assumed date of last exposure, based on last reported date of case inclusion. [b]Prior to 1960 exposures could have included other solvents such as carbon tetrachloride or Stoddard solvent. [c]Included relative risk smoking adjusted (yes/no). [d]Incidence (I) / mortality (M). [e]Adapted version of ICD-8, used in the United States. [f]Earliest date of entry into cohort was 1948. [g]Standardized mortality ratio. [h]World Health Organization International Classification of Diseases. [i]Mean year first employed was 1953; Monitoring data was used to exclude workers who had been exposed to carbon tetrachloride or trichloroethylene. [j]There is considerable overlap between the cohort used for Pukkala et al. 2009 and the cohort used for Lynge et al. 2006. Therefore the risk estimates are not combined in the meta-analysis. Pukkala et al. 2009 reports results for laundry or dry cleaning workers, while Lynge et al. 2006 reports results for dry cleaning workers only. Accordingly the studies are included in the respective meta-analyses. [k]Denmark, Norway, Sweden, Finland. [l]International Classification of Diseases for Oncology. 2nd ed. [m]Rate ratio. [n]Standardized incidence ratio. [o]Based on date of publication. No case inclusion dates reported. [p]Odds ratio. [q]Results based on population controls are included (results based on hospital controls also reported). [r]Histologically confirmed carcinoma of the urinary bladder (including carcinoma *in situ*). [s]Histologically confirmed bladder cancer. [t]Denmark, France, Germany, Italy, Spain. [u]Histologically confirmed cancer of the urinary bladder, ureter, renal pelvis. [v]Urothelial cancer and/or squamous-cell carcinoma in the lower urinary tract. [w]Results from conditional logistic regression.

Table 2. Meta-analysis of studies reporting exposure to tetrachloroethylene or employment in dry cleaning and the risk of bladder cancer.

Study base	N studies	N exposed cases	mRR (95% CI)	I^2	Studies included[d]
Tetrachloroethylene exposed workers					
With Pesch et al. 2000 JEM results	3	463	1.08 (0.82, 1.42)	25.3%	3,6,11
With Pesch et al. 2000 JTEM[a] results	3	125	1.05 (0.76, 1.47)	19.6%	3,6,11
Laundry and dry cleaning workers	13	306	1.20 (1.06, 1.36)	0.0%	1,2,4,5,6,7,8,9,10,12,13,14,15
Cohort studies[b]	3	208	1.17 (0.95, 1.44)	13.1%	1,2,4
Case control studies[c]	11	98	1.54 (1.17, 2.04)	0.0%	4,5,6,7,8,9,10,12,13,14,15
Dry cleaning workers	7	139	1.47 (1.16, 1.85)	0.0%	1,2,4,5,7,9,13
Excluding Lynge et al. 2006	6	46	1.51 (1.05, 2.18)	0.0%	1,2,5,7,9,13
Cohort studies[b]	3	115	1.46 (1.14, 1.87)	0.0%	1,2,4
Case control studies[c]	4	24	1.50 (0.80, 2.84)	0.0%	5,7,9,13

[a]Job Task Exposure Matrix. [b]None of the cohort studies were directly adjusted for smoking behavior. [c]All case-control analyses were adjusted for smoking behavior. [d]Numbers refer to study # in Table 1.

Table 3. Exposure-response information available in studies included in the meta-analysis.

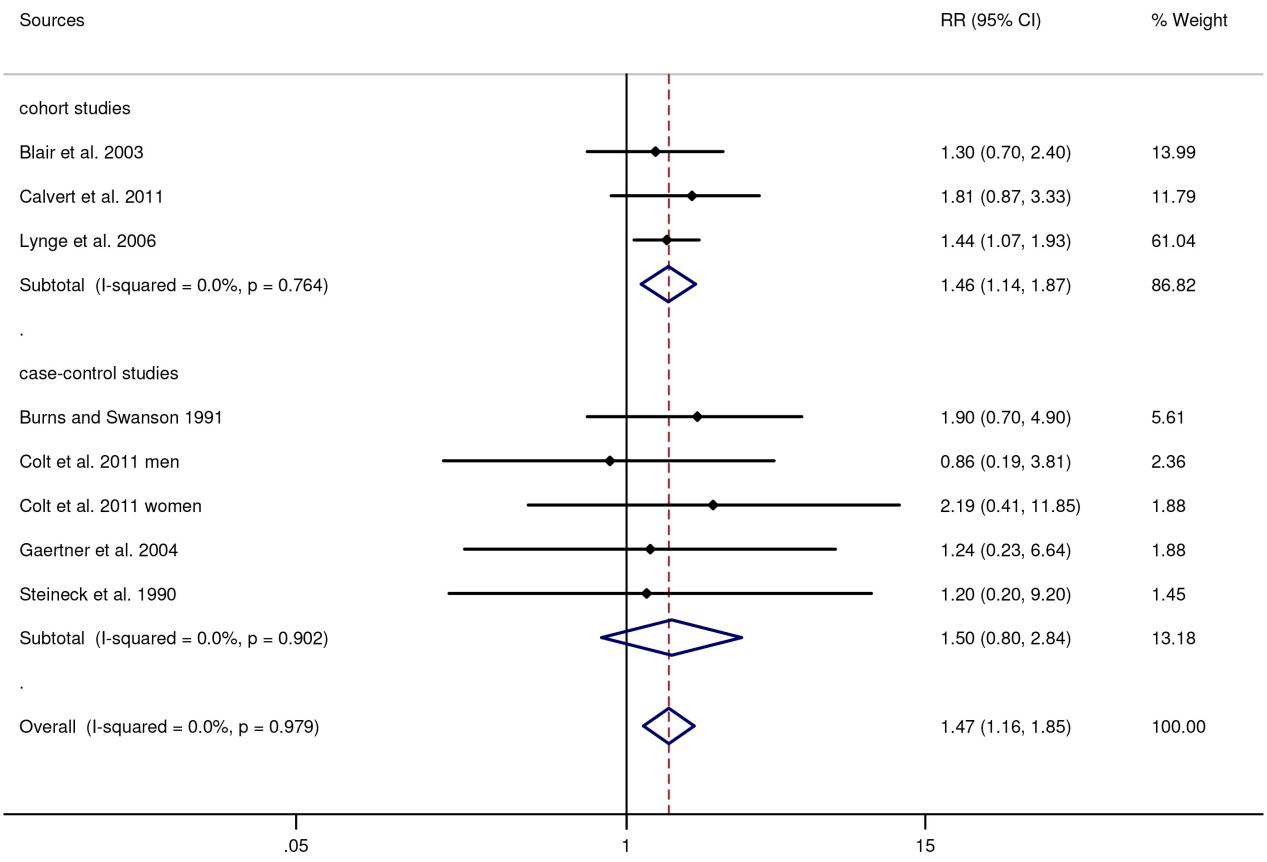
Study and Exposure	Association	No. cases
Pesch et al. 2000, Tetrachloroethylene exposure index[a]		
Men[b]		
Medium	OR = 1.1; 95% CI: 0.9, 1.3	162
High	OR = 1.2; 95% CI: 1.0, 1.5	172
Substantial	OR = 1.4; 95% CI: 1.0, 1.9	71
Men[c]		
Medium	OR = 1.0; 95% CI: 0.7, 1.5	37
High	OR = 1.2; 95% CI: 0.8, 1.7	47
Substantial	OR = 1.8; 95% CI: 1.1, 3.1	22
Women[b]		
Medium	OR = 1.8; 95% CI: 1.0, 3.0	21
High	OR = 1.0; 95% CI: 0.6, 1.9	16
Substantial	OR = 0.7; 95% CI: 0.2, 2.5	3
Christensen et al. 2012, Exposure to tetrachloroethylene		
Any exposure	OR = 0.5; 95% CI: 0.1, 3.0	2
Substantial exposure[d]	OR = 0.9; 95% CI: 0.1, 7.3	2
Blair et al. 2013, Duration in the union		
<4.4 years	SMR = 1.4	Not reported
> 4.4 years	SMR = 1.5	Not reported
Blair et al. 2013, Level of exposure to dry cleaning solvents		
Little/no	SMR = 1.4, 95% CI: 0.4, 3.2	5
Medium/high	SMR = 1.5, 95% CI: 0.6, 3.1	7
Lynge et al. 2006, Duration of employment as dry cleaner		
>0-1 year[e]	RR = 1.50, 95% CI: 0.57, 3.96	6
2-4 years	RR = 2.39, 95% CI: 1.09, 5.22	10
5-9 years	RR = 0.91, 95% CI: 0.52, 1.59	17
≥ 10 years	RR = 1.57, 95% CI: 1.07, 2.29	53
Calvert et al. 2011, Duration of exposure among workers for which time since exposure > 20 years[f]		
< 5 years	SMR = 0.53, 95% CI: 0.03, 2.52	1
> 5 years	SMR = 4.08, 95% CI: 2.13, 7.12	9

[a]Product of duration, probability, and intensity of exposure to tetrachloroethylene. [b]Based on JEM exposure estimates. [c]Based on JTEM exposure estimates. [d]In order to be classified as exposed at the substantial level, a subject had to have been exposed at confidence of probable or definite, concentration and frequency of medium or high, and for duration greater than 5 years. [e]In the original publication the lowest exposure category was defined as 0-1 year. As only exposed cases and controls were categorized by length of employment in the shop where they worked in 1970, we changed the lower bound of this category to >0. [f]No bladder cancer deaths were observed among any of the workers with time since exposure less than twenty years.

Figure legend

Figure 1. Forest plot of cohort and case-control studies included in the meta-analysis that assessed the risk of bladder cancer in relation to occupation as dry cleaner. See Table 1 for details on included studies.

Figure 1.


Sources
RR (95% CI)
% Weight
cohort studies
Blair et al. 2003
1.30 (0.70, 2.40)
13.99
Calvert et al. 2011
1.81 (0.87, 3.33)
11.79
Lynge et al. 2006
1.44 (1.07, 1.93)
61.04
Subtotal (I-squared = 0.0%, p = 0.764)
1.46 (1.14, 1.87)
86.82
.
case-control studies
Burns and Swanson 1991
1.90 (0.70, 4.90)
5.61
Colt et al. 2011 men
0.86 (0.19, 3.81)
2.36
Colt et al. 2011 women
2.19 (0.41, 11.85)
1.88
Gaertner et al. 2004
1.24 (0.23, 6.64)
1.88
Steineck et al. 1990
1.20 (0.20, 9.20)
1.45
Subtotal (I-squared = 0.0%, p = 0.902)
1.50 (0.80, 2.84)
13.18
.
Overall (I-squared = 0.0%, p = 0.979)
1.47 (1.16, 1.85)
100.00
.05
1
15