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American Journal of Epidemiology

Vol. 158, No. 12
Printed in U.S.A.
DOI: 10.1093/aje/kwg282

Cancer Risk among Workers at Danish Companies using Trichloroethylene: A Cohort Study

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Received for publication March 24, 2003; accepted for publication June 24, 2003.

Trichloroethylene is an animal carcinogen with limited evidence of carcinogenicity in humans. Cancer incidence between 1968 and 1997 was evaluated in a cohort of 40,049 blue-collar workers in 347 Danish companies with documented trichloroethylene use. Standardized incidence ratios for total cancer were 1.1 (95% confidence interval (CI): 1.04, 1.12) in men and 1.2 (95% CI: 1.14, 1.33) in women. For non-Hodgkin's lymphoma and renal cell carcinoma, the overall standardized incidence ratios were 1.2 (95% CI: 1.0, 1.5) and 1.2 (95% CI: 0.9, 1.5), respectively; standardized incidence ratios increased with duration of employment, and elevated standardized incidence ratios were limited to workers first employed before 1980 for non-Hodgkin's lymphoma and before 1970 for renal cell carcinoma. The standardized incidence ratio for esophageal adenocarcinoma was 1.8 (95% CI: 1.2, 2.7); the standardized incidence ratio was higher in companies with the highest probability of trichloroethylene exposure. In a subcohort of 14,360 presumably highly exposed workers, the standardized incidence ratios for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma were 1.5 (95% CI: 1.2, 2.0), 1.4 (95% CI: 1.0, 1.8), and 1.7 (95% CI: 0.9, 2.9), respectively. The present results and those of previous studies suggest that occupational exposure to trichloroethylene at past higher levels may be associated with elevated risk for non-Hodgkin's lymphoma. Associations between trichloroethylene exposure and other cancers are less consistent.

adenocarcinoma; biliary tract neoplasms; esophageal neoplasms; kidney neoplasms; liver neoplasms; lymphoma, non-Hodgkin; occupations; trichloroethylene

Abbreviation: CI, confidence interval.

Since the Second World War, trichloroethylene has been widely used in many industries, mainly because of its degreasing properties and nonflammable character. The risk of acute intoxication of workers exposed to high trichloroethylene concentrations has been known for decades (1), and exposure to trichloroethylene has been shown to induce cancer of the kidney, liver, lung, testis, and lymph nodes of experimental animals (2, 3). On the basis of experimental data and limited evidence from epidemiologic studies (primarily related to cancer of the liver and biliary tract and non-Hodgkin's lymphoma), the International Agency for Research on Cancer in 1995 classified trichloroethylene as a probable human carcinogen (2). A more recent review reported the strongest epidemiologic evidence for cancer of the kidney and liver (4), but others have found the data for these cancers inconsistent, and the carcinogenicity of trichloroethylene in humans remains a matter of controversy (3, 5–9).

Previously, we reported a significantly increased risk of non-Hodgkin's lymphoma and esophageal adenocarcinoma among men and cervical cancer among women, nonsignificantly increased risk for cancer of the liver and biliary tract,

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but no increased risk for kidney cancer in a relatively small cohort of Danish workers with confirmed individual exposure to trichloroethylene (10). In the present study, we report on the cancer morbidity of a much larger cohort of workers employed at 347 Danish trichloroethylene-using companies.

MATERIALS AND METHODS

Identification and selection of companies

We obtained information on trichloroethylene-using companies from historical measurement files in the archives of the Danish National Institute for Occupational Health (11, 12), the Danish Product Registry (13), the files of a dry cleaning survey (14), and the archives of the company that for decades has been the dominant supplier of trichloroethylene to enterprises in Denmark. These sources provided a total of 457 companies with confirmed use of trichloroethylene; these companies could be identified by name and a unique company number, which is applied to all companies in Denmark for tax reasons.

Only a relatively small proportion of workers employed at these companies were likely to be exposed to trichloroethylene. On the basis of information collected at 93 trichloroethylene-using companies, we observed an inverse relation between the number of employees at a company and the proportion of trichloroethylene-exposed workers; in companies with 1–50, 51–100, 101–200, and more than 200 employees, the proportions of exposed workers were, respectively, 48, 30, 11, and 2 percent (12). Therefore, to increase the likelihood of trichloroethylene exposure in the present study, we excluded 110 companies with more than 200 employees.

The main industries represented by the remaining 347 and the excluded 110 companies, respectively, were iron and metal (48 and 48 percent), electronics (11 and 12 percent), painting (11 and 0 percent), printing (8 and 3 percent), chemical (5 and 6 percent), dry cleaning (5 and 2 percent), and other industries (13 and 30 percent).

Employees at the companies

By use of the unique company number, each of the 347 companies was linked to the computerized records of the national Supplementary Pension Fund, which includes information on the type of industry of the company and the identity and employment history of all employees (15). Membership in the Pension Fund has been mandatory for all employees in Denmark since its establishment in 1964. Altogether, 152,726 workers at these companies were identified by the unique 10-digit personal identification number assigned to each resident in Denmark since the Central Population Registry began on April 1, 1968. Thus, all workers who were employed by the companies since this date were identified. By use of the personal identification number, these employees were linked to the files of the Central Population Registry, which provides information on job title and dates of death, emigration, or disappearance. By use of the job title, each employee was characterized as a blue-collar worker, white-collar worker, or unknown. The Central Population Registry shows only the most recently reported job title for each individual; although the relevance of this job title to periods of employment in trichloroethylene-using companies is uncertain, the classification using blue collar versus white collar would be expected to be very stable over time in Denmark.

We excluded four workers with a personal identification number that could not be verified by the Central Population Registry. In addition, to increase the proportion of trichloroethylene-exposed workers in the cohort, we excluded 39,074 presumably unexposed white-collar workers and 56,970 workers for whom blue- or white-collar status was unknown. Among the remaining 56,678 blue-collar workers, we excluded 16,629 workers with a duration of employment of

TABLE 1. Characteristics of the cohort of 40,049 blue-collar workers employed at Danish trichloroethylene-using companies, 1964–1997

Characteristics	%
Year of birth	
1890–1919	5.3
1920–1939	24.0
1940–1959	55.5
1960–1979	15.2
First year of employment in a TCE*-using company	
Before 1970	21.2
1970–1979	34.9
1980 and later	43.8
Years of follow-up for cancer	
<10	22.4
10–19.9	35.0
20–30	42.6
No. of different TCE-using companies where each worker was employed	
1	88.9
2	9.6
3 or more	1.5
Average no. of employees in the company(-ies) where employed	
<50	21.3
50–99.9	24.4
100–200	54.3
Industry of the company(-ies) where employed	
Iron and metal	54.2
Electronics	10.9
Chemical	5.6
Printing	1.4
Dry cleaning	0.8
Other	16.9
Two or more of the above	5.2

* TCE, trichloroethylene.

TABLE 2. Cancer incidence among 40,049 Danish blue-collar workers employed for at least 3 months at trichloroethylene-using companies, 1964–1997

Cancer site (ICD-7*)	Men (588,047 person-years)				Women (118,270 person-years)			
	Observed no. of cancers	Expected no. of cancers	SIR*	95% CI*	Observed no. of cancers	Expected no. of cancers	SIR	95% CI
Total (codes 140–205)	2,620	2,434	1.08	1.04, 1.12	624	507	1.23	1.14, 1.33
Buccal cavity and pharynx (codes 140–148)	95	85.5	1.1	0.90, 1.36	10	5.7	1.8	0.84, 3.24
Esophagus (code 150)	40	35.5	1.1	0.81, 1.53	4	2.0	2.0	0.54, 5.16
Adenocarcinomas	23	12.7	1.8	1.15, 2.73	0	0.4	0.0	0.00, 8.32
Others (mainly squamous cell carcinomas)	17	22.8	0.7	0.43, 1.19	4	1.6	2.4	0.67, 6.24
Stomach (code 151)	77	75.8	1.0	0.80, 1.27	9	7.0	1.3	0.59, 2.46
Colon (code 153)	142	155.0	0.9	0.77, 1.08	35	28.6	1.2	0.85, 1.70
Rectum (code 154)	128	112.6	1.1	0.95, 1.35	15	13.5	1.1	0.62, 1.84
Liver, primary (code 155.0)	27	24.0	1.1	0.74, 1.64	7	2.5	2.8	1.13, 5.80
Gallbladder, biliary passages (code 155.1)	14	12.5	1.1	0.61, 1.87	9	3.2	2.8	1.28, 5.34
Liver, not specified (code 156)	22	18.9	1.2	0.73, 1.77	3	2.7	1.1	0.22, 3.23
Pancreas (code 157)	66	60.4	1.1	0.85, 1.39	9	8.7	1.0	0.47, 1.96
Larynx (code 161)	53	45.8	1.2	0.87, 1.52	3	1.8	1.7	0.33, 4.82
Lung (code 162)	559	401.7	1.4	1.28, 1.51	73	39.0	1.9	1.48, 2.35
Breast (code 170)	2	3.8	0.5	0.06, 1.90	145	137.7	1.1	0.89, 1.24
Cervix uteri (code 171)					62	33.5	1.9	1.42, 2.37
Corpus uteri (code 172)					24	23.4	1.0	0.66, 1.53
Ovary (code 175)					22	25.2	0.9	0.55, 1.32
Prostate (code 177)	163	176.5	0.9	0.79, 1.08				
Testis (code 178)	93	81.3	1.1	0.92, 1.40				
Kidney (code 180)	93	77.1	1.2	0.97, 1.48	10	8.7	1.2	0.55, 2.11
Renal parenchyma	68	57.1	1.2	0.93, 1.51	8	6.5	1.2	0.53, 2.44
Renal pelvis, ureter	25	20.1	1.2	0.81, 1.84	2	2.2	0.9	0.10, 3.27
Bladder (code 181)	203	197.6	1.0	0.89, 1.18	17	10.6	1.6	0.93, 2.57
Skin melanomas (code 190)	56	77.5	0.7	0.55, 0.94	16	20.9	0.8	0.44, 1.24
Other skin (code 191)	350	386.5	0.9	0.81, 1.01	69	65.8	1.1	0.82, 1.33
Brain and nervous system (code 193)	85	89.0	1.0	0.76, 1.18	19	17.1	1.1	0.67, 1.74
Non-Hodgkin's lymphoma (codes 200 and 202)	83	67.6	1.2	0.98, 1.52	13	9.5	1.4	0.73, 2.34
Hodgkin's disease (code 201)	18	20.8	0.9	0.51, 1.37	2	2.4	0.8	0.09, 3.00
Multiple myeloma (code 203)	28	26.6	1.1	0.70, 1.52	3	3.4	0.9	0.18, 2.56
Leukemia (code 204)	69	63.8	1.1	0.84, 1.37	13	7.8	1.7	0.89, 2.86
Other and unspecified	154	138.2	1.1	0.95, 1.31	32	26.3	1.2	0.83, 1.72

* ICD-7, *International Classification of Diseases*, Seventh Revision; SIR, standardized incidence ratio; CI, confidence interval.

less than 3 months. Thus, our study cohort consisted of 40,049 blue-collar workers who were followed for cancer incidence.

Exposure assessment

We previously addressed trichloroethylene exposure patterns of Danish workers (11, 12). On the basis of these studies and the characteristics of the cohort of this study, three variables seem most reliable as predictors of trichloroethylene exposure, namely, duration of employment, year of first employment at a trichloroethylene-using company, and number of employees in the company.

Duration of employment is often a useful surrogate for cumulative exposure to occupational agents. Measurements of trichloroacetic acid (a metabolite of trichloroethylene) in the urine of Danish workers showed arithmetic mean concentrations of 58 mg/liter for measurements taken between 1960 and 1964 and 14 mg/liter for measurements taken between 1980 and 1985 (11). Similarly, the arithmetic

mean concentration of trichloroethylene in Danish work environments was 318 mg/m^3 for measurements taken in the 1960s and 75 mg/m^3 for measurements taken in the 1980s (12). Thus, calendar year is a strong predictor of trichloroethylene exposure of Danish workers, and we would expect 4–5 times higher exposures in the 1960s than in the 1980s.

In each of the three strata of company size, 59 percent were blue-collar and 41 percent were white-collar workers (calculated using the 63 percent of workers for whom status was known). The exclusion of white-collar workers, who were assumed to be unexposed, would increase the proportion of trichloroethylene-exposed workers from 48, 30, and 11 percent among all workers to 81, 51, and 19 percent among the remaining blue-collar workers in companies with 1–50, 51–100, and 101–200 employees, respectively. Thus, the proportion of exposed workers is expected to be about four times higher in smaller than in larger companies, and 41 percent of the entire cohort would be expected to be exposed to trichloroethylene. Trichloroethylene exposure levels were also found to increase as the company size decreased (12).

Follow-up for cancer

Each person in the cohort was linked to the files of the nationwide Danish Cancer Registry by use of the personal identification number (16). Data on the type of cancer and the date of diagnosis were retrieved for all recorded cancers among cohort members. Tumors were classified according to a Danish modified version of the *International Classification of Diseases*, Seventh Revision (17), which allowed us to subdivide kidney cancers into renal cell carcinomas and renal pelvis/ureter cancers (18) and to identify esophageal adenocarcinomas. The period of follow-up for cancer occurrence began on April 1, 1968, or the date of first employment at a trichloroethylene-using company, whichever occurred later. Follow-up ended on the date of death, emigration, disappearance, or December 31, 1997, whichever occurred first. We calculated the expected numbers of cancers based on Danish national incidence rates of site-specific cancers by sex, 5-year age group, and calendar year.

Analyses

We calculated standardized incidence ratios, the ratios of observed-to-expected cancers, and 95 percent confidence intervals, assuming that the observed number of cancers followed a Poisson distribution (19). We allowed for latency by calculating standardized incidence ratios after inclusion of a lag period from the date of first employment to the start of follow-up for cancer. Moreover, standardized incidence ratios were calculated within different strata of duration of employment (<1 year, 1–4.9 years, ≥5 years), first year of employment (before 1970, 1970–1979, 1980 and later), and number of employees in the company or companies where the worker had been employed (<50, 50–99.9, 100–200). The latter variable was calculated as a time-weighted average over the actual follow-up period of each worker.

For non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma, standardized incidence ratios were further explored in a subcohort with presumably higher exposure levels, including only workers with first employment before 1980 and with employment for at least 1 year. In addition, we calculated standardized incidence ratios for those workers employed for at least 3 months in the trichloroethylene-using companies who were excluded from the blue-collar cohort (i.e., white-collar workers and workers with unknown blue- or white-collar status). We would expect the lowest trichloroethylene exposure among white-collar workers, intermediate trichloroethylene exposure among those with unknown status, and highest trichloroethylene exposure among the blue-collar workers.

RESULTS

Almost 80 percent of the 40,049 blue-collar workers were followed up for cancer for more than 10 years (table 1). During the follow-up period (average: 17.6 years; range: 0.1–29.7 years), men and women contributed 588,047 and 118,270 person-years, respectively. Overall, 3,244 primary cancers were identified among 3,016 workers.

The standardized incidence ratio for cancer overall was significantly increased by 8 percent for men and 23 percent for women. Men had significantly elevated standardized incidence ratios for lung cancer and esophageal adenocarcinoma (table 2). Women had significantly elevated standardized incidence ratios for cancer of the liver, gallbladder/biliary passages, lung, and cervix uteri (table 2). Men and women combined had significant standardized incidence ratios of 1.43 (95 percent confidence interval (CI): 1.32, 1.55) for lung cancer, 1.24 (95 percent CI: 1.01, 1.52) for non-Hodgkin's lymphoma, 1.77 (95 percent CI: 1.12, 2.65) for esophageal adenocarcinoma, and 0.73 (95 percent CI: 0.57, 0.92) for melanoma; the combined standardized incidence ratio for renal cell carcinoma was 1.20 (95 percent CI: 0.94, 1.50). Of the cancers with significantly elevated standardized incidence ratios, only non-Hodgkin's lymphoma is not known to be associated with cigarette smoking or alcohol consumption.

For cancers of a priori interest or with significant standardized incidence ratios in table 2, we evaluated the effects of a 20-year lag and of three variables related to trichloroethylene exposure, namely, duration of employment, year of first employment, and company size (table 3). For non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma, standardized incidence ratios showed little change with lag time. Among men and women, standardized incidence ratios for non-Hodgkin's lymphoma increased with increasing duration of employment and with earlier first year of employment, but significance was achieved only for the latter variable among men. No increased risk of non-Hodgkin's lymphoma was seen for workers with first employment after 1980. Among men, significantly elevated standardized incidence ratios for renal cell carcinoma were observed for workers employed for 5 years or more and for workers with first employment before 1970. The standardized incidence ratios for renal cell carcinoma among women increased with increasing duration of employment, but no clear pattern was evident for year of first employment. For non-Hodgkin's lymphoma and renal cell carcinoma, no clear pattern was evident for company size, with the lowest stan-

TABLE 3. Influence of lag time, duration of employment, year of first employment, and number of employees in the company on the risk for cancer among workers in Danish trichloroethylene-using companies, 1964–1997

	Men			Women			Men			Women		
	Observed no. of cancers	SIR*	95% CI*	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI
	Non-Hodgkin's lymphoma						*Renal cell carcinoma*					
Lag time												
None	83	1.2	1.0, 1.5	13	1.4	0.7, 2.3	68	1.2	0.9, 1.5	8	1.2	0.5, 2.4
20 years	31	1.3	0.9, 1.9	7	1.9	0.8, 3.9	25	1.3	0.8, 1.9	3	1.3	0.3, 3.7
Duration of employment (years)												
<1	23	1.1	0.7, 1.6	2	0.7	0.1, 2.4	14	0.8	0.5, 1.4	2	1.1	0.1, 3.8
1–4.9	33	1.3	0.9, 1.8	6	1.6	0.6, 3.5	25	1.2	0.8, 1.7	3	1.2	0.2, 3.4
≥5	27	1.4	0.9, 2.0	5	1.8	0.6, 4.3	29	1.6	1.1, 2.3	3	1.5	0.3, 4.3
Year of first employment												
Before 1970	38	1.4	1.0, 2.0	6	1.5	0.6, 3.4	44	1.7	1.2, 2.3	6	1.9	0.7, 4.1
1970–1979	35	1.3	0.9, 1.8	6	1.6	0.6, 3.5	16	0.7	0.4, 1.2	0	0.0	0.0, 1.2
1980 and later	10	0.7	0.3, 1.3	1	0.5	0.0, 3.0	8	0.9	0.4, 1.7	2	2.4	0.3, 8.5
No. of employees in the company												
<50	13	0.9	0.5, 1.6	2	1.1	0.1, 4.1	8	0.7	0.3, 1.4	0	0.0	0.0, 2.6
50–99	23	1.3	0.9, 2.0	3	1.6	0.3, 4.6	23	1.6	1.0, 2.4	2	1.7	0.2, 6.1
100–200	47	1.3	0.9, 1.7	8	1.4	0.6, 2.7	37	1.2	0.8, 1.6	6	1.5	0.5, 3.2
	Esophagus, adenocarcinoma						*Liver, primary*					
Lag time												
None	23	1.8	1.2, 2.7				27	1.1	0.7, 1.6	7	2.8	1.1, 5.8
20 years	10	1.7	0.8, 3.0				8	0.9	0.4, 1.7	2	2.1	0.2, 7.5
Duration of employment (years)												
<1	6	1.7	0.6, 3.6				9	1.3	0.6, 2.5	2	2.8	0.3, 10.0
1–4.9	9	1.9	0.9, 3.6				9	1.0	0.5, 1.9	4	4.1	1.1, 10.5
≥5	8	1.9	0.8, 3.7				9	1.1	0.5, 2.1	1	1.3	0.0, 7.1
Year of first employment												
Before 1970	8	1.5	0.6, 2.9				17	1.5	0.9, 2.4	3	2.5	0.5, 7.3
1970–1979	10	2.0	1.0, 3.7				7	0.8	0.3, 1.6	2	2.1	0.2, 7.7
1980 and later	5	2.2	0.7, 5.1				3	0.9	0.2, 2.6	2	5.9	0.7, 21.2
No. of employees in the company												
<50	7	2.7	1.1, 5.6				6	1.3	0.5, 2.7	1	2.2	0.0, 12.3
50–99	5	1.6	0.5, 3.6				7	1.2	0.5, 2.4	2	4.4	0.5, 15.8
100–200	11	1.6	0.8, 2.9				14	1.1	0.6, 1.8	4	2.5	0.7, 6.5
	Gallbladder, biliary passages						*Lung*					
Lag time												
None	14	1.1	0.6, 1.9	9	2.8	1.3, 5.3	559	1.4	1.3, 1.5	73	1.9	1.5, 2.4
20 years	3	0.7	0.1, 1.9	1	0.8	0.0, 4.4	202	1.4	1.2, 1.6	26	1.6	1.0, 2.3
Duration of employment (years)												
<1	4	1.1	0.3, 2.9	2	2.3	0.3, 8.4	181	1.6	1.4, 1.9	28	2.5	1.6, 3.6
1–4.9	4	0.8	0.2, 2.1	6	4.8	1.7, 10.4	193	1.3	1.1, 1.5	25	1.6	1.1, 2.4
≥5	6	1.4	0.5, 3.1	1	0.9	0.0, 5.2	185	1.4	1.2, 1.6	20	1.6	1.0, 2.5

Table continues

TABLE 3. Continued

	Men			Women			Men			Women		
	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI
Year of first employment												
Before 1970	7	1.1	0.5, 2.3	3	1.7	0.3, 4.9	276	1.4	1.3, 1.6	37	2.2	1.5, 3.0
1970–1979	4	0.9	0.2, 2.2	5	4.5	1.4, 10.4	200	1.3	1.1, 1.5	25	1.6	1.0, 2.4
1980 and later	3	1.9	0.4, 5.4	1	3.4	0.0, 18.6	83	1.5	1.2, 1.9	11	1.8	0.9, 3.1
No. of employees in the company												
<50	3	1.2	0.2, 3.5	1	1.8	0.0, 9.8	110	1.4	1.1, 1.7	15	2.1	1.2, 3.5
50–99	3	1.0	0.2, 2.9	4	7.4	2.0, 19.0	130	1.3	1.1, 1.6	17	2.2	1.3, 3.6
100–200	8	1.2	0.5, 2.3	4	1.9	0.5, 4.9	319	1.4	1.3, 1.6	41	1.7	1.2, 2.3
	Renal pelvis, ureter						*Skin melanoma*					
Lag time												
None	25	1.2	0.8, 1.8	2	0.9	0.1, 3.3	56	0.7	0.6, 0.9	16	0.8	0.4, 1.2
20 years	11	1.4	0.7, 2.5	1	1.1	0.0, 6.0	16	0.7	0.4, 1.1	2	0.4	0.0, 1.3
Duration of employment (years)												
<1	7	1.2	0.5, 2.5	1	1.7	0.0, 9.2	17	0.6	0.4, 1.0	9	1.2	0.6, 2.3
1–4.9	11	1.5	0.7, 2.6	1	1.2	0.0, 6.5	26	0.9	0.6, 1.3	3	0.4	0.1, 1.0
≥5	7	1.0	0.4, 2.1	0	0.0	0.0, 4.1	13	0.6	0.3, 1.0	4	0.8	0.2, 2.1
Year of first employment												
Before 1970	10	1.1	0.5, 2.0	1	0.9	0.0, 5.0	24	0.9	0.6, 1.3	6	0.9	0.3, 1.9
1970–1979	10	1.3	0.6, 2.4	1	1.2	0.0, 6.6	22	0.7	0.4, 1.1	7	0.8	0.3, 1.6
1980 and later	5	1.7	0.6, 4.0	0	0.0	0.0, 12.0	10	0.6	0.3, 1.0	3	0.6	0.1, 1.7
No. of employees in the company												
<50	2	0.5	0.1, 1.8	1	2.5	0.0, 14.0	14	0.9	0.5, 1.5	4	1.0	0.3, 2.5
50–99	9	1.8	0.8, 3.4	0	0.0	0.0, 7.5	13	0.7	0.4, 1.1	3	0.7	0.1, 1.9
100–200	14	1.3	0.7, 2.1	1	0.7	0.0, 3.9	29	0.7	0.5, 1.0	9	0.7	0.3, 1.4
				Cervix uteri								
Lag time												
None				62	1.9	1.4, 2.4						
20 years				9	1.5	0.7, 2.9						
Duration of employment (years)												
<1				30	2.5	1.7, 3.5						
1–4.9				22	1.6	1.0, 2.4						
≥5				10	1.3	0.6, 2.4						
Year of first employment												
Before 1970				31	2.4	1.6, 3.4						
1970–1979				26	1.9	1.2, 2.7						
1980 and later				5	0.7	0.2, 1.7						
No. of employees in the company												
<50				15	2.4	1.3, 3.9						
50–99				10	1.4	0.7, 2.6						
100–200				37	1.8	1.3, 2.5						

* SIR, standardized incidence ratio; CI, confidence interval.

TABLE 4. Risk of non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma (both sexes combined) in the cohort of workers in Danish trichloroethylene-using companies (1964–1997) and in a subcohort with expected higher exposure levels (at least a 1-year duration of employment and year of first employment before 1980)

	Non-Hodgkin's lymphoma			Renal cell carcinoma			Esophagus, adenocarcinoma		
	Observed no. of cancers	SIR*	95% CI*	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI
Cohort	96	1.2	1.0, 1.5	76	1.2	0.9, 1.5	23	1.8	1.2, 2.7
Subcohort	65	1.5	1.2, 2.0	53	1.4	1.0, 1.8	13	1.7	0.9, 2.9
Lag time (years)									
0–9	12	1.8	0.9, 3.1	6	0.9	0.3, 1.8	0	0.0	0.0, 5.1
10–19	22	1.3	0.8, 2.0	22	1.5	0.9, 2.2	6	2.3	0.9, 5.0
≥20	31	1.7	1.1, 2.4	25	1.6	1.0, 2.3	7	1.6	0.6, 3.2
Duration of employment (years)									
1–4.9	35	1.5	1.1, 2.1	23	1.1	0.7, 1.7	6	1.6	0.6, 3.4
≥5	30	1.6	1.1, 2.2	30	1.7	1.1, 2.4	7	1.9	0.8, 3.8
Year of first employment									
Before 1970	35	1.6	1.1, 2.3	41	1.9	1.4, 2.6	6	1.5	0.5, 3.2
1970–1979	30	1.5	1.0, 2.1	12	0.7	0.4, 1.2	7	2.0	0.8, 4.1
No. of employees in the company									
<50	11	1.4	0.7, 2.5	6	0.9	0.3, 1.9	3	2.1	0.4, 6.2
50–99	18	1.7	1.0, 2.8	18	2.0	1.2, 3.1	2	1.0	0.1, 3.8
100–200	36	1.5	1.1, 2.1	29	1.3	0.9, 1.9	8	1.9	0.8, 3.7

* SIR, standardized incidence ratio; CI, confidence interval.

dardized incidence ratios observed among the smallest companies presumed to have the highest potential for exposure. For esophageal adenocarcinoma, a significantly elevated standardized incidence ratio was observed for the smallest companies. No patterns suggesting an association with exposure to trichloroethylene were evident in table 3 for the other cancers, including lung, cervical, liver, and biliary tract cancer.

In the subcohort with presumably higher exposure levels, including 14,360 workers contributing 339,486 person-years at risk, the standardized incidence ratios for non-Hodgkin's lymphoma and renal cell carcinoma, but not for esophageal adenocarcinoma, were higher than those in the entire cohort, and they were significantly elevated (table 4). For renal cell carcinoma, the standardized incidence ratios increased with increasing lag time, increasing duration of employment, and earlier year of first employment; no evidence of increased risk was seen for first employment in 1970 or later. The renal cell carcinoma standardized incidence ratio was less than one for companies with the fewest employees (table 4). For non-Hodgkin's lymphoma and esophageal adenocarcinoma, no consistent lag-time pattern was seen, and the risk differed little between strata of duration of employment, year of first employment, or company size (table 4). Except for non-Hodgkin's lymphoma and renal cell carcinoma, few standardized incidence ratios (both sexes combined) differed by more than 10 percent between the cohort and the subcohort. These included standardized incidence ratios for cancer of the buccal cavity and pharynx, decreasing from 1.15 to 0.94 (95 percent CI: 0.70, 1.25); pancreatic cancer, increasing from 1.09 to 1.28 (95 percent CI: 0.97, 1.66); ovarian cancer, decreasing from 0.87 to 0.68 (95 percent CI: 0.32, 1.24); renal pelvis and ureter cancer, decreasing from 1.21 to 1.08 (95 percent CI: 0.60, 1.78); Hodgkin's disease, increasing from 0.86 to 1.06 (95 percent CI: 0.55, 1.85); and leukemia, decreasing from 1.15 to 0.96 (95 percent CI: 0.69, 1.30) (data not shown).

Table 5 shows that the standardized incidence ratios for non-Hodgkin's lymphoma and esophageal adenocarcinoma were about twice as high for blue-collar workers as for the white-collar workers presumed to have little or no exposure to trichloroethylene; intermediate standardized incidence ratios were observed for workers for whom the blue- or white-collar status was unknown. Standardized incidence ratios for renal cell carcinoma differed little among the three categories of workers.

DISCUSSION

We found significantly elevated standardized incidence ratios for non-Hodgkin's lymphoma, esophageal adenocarcinoma, and lung cancer in the entire cohort of Danish blue-collar workers with employment at trichloroethylene-using companies. Additional significantly elevated standardized incidence ratios were observed among women for cancer of the liver, biliary tract, and cervix uteri. For non-Hodgkin's lymphoma and renal cell carcinoma, the standardized incidence ratios increased with two of three markers of increasing exposure (i.e., duration of employment and early year of first employment). For esophageal adenocarcinoma,

TABLE 5. Risk of non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma (both sexes combined) in cohorts of 40,049 blue-collar workers (676,317 person-years), 28,047 white-collar workers (493,444 person-years), and 36,881 workers of unknown blue- or white-collar status (413,057 person-years) employed for at least 3 months at Danish trichloroethylene-using companies, 1964–1997

Cohort	Non-Hodgkin's lymphoma			Renal cell carcinoma			Esophagus, adenocarcinoma		
	Observed no. of cancers	SIR*	95% CI*	Observed no. of cancers	SIR	95% CI	Observed no. of cancers	SIR	95% CI
White collar	26	0.6	0.4, 0.9	38	1.1	0.8, 1.6	5	0.8	0.3, 1.9
Unknown collar	32	0.9	0.6, 1.3	30	1.0	0.7, 1.5	4	1.0	0.3, 2.7
Blue collar	96	1.2	1.0, 1.5	76	1.2	0.9, 1.5	23	1.8	1.1, 2.6

* SIR, standardized incidence ratio; CI, confidence interval.

a significantly increased standardized incidence ratio was observed in smaller companies with greater likelihood of trichloroethylene exposure. No consistent exposure-related trends were observed for other cancers with elevated standardized incidence ratios. In a subcohort with presumed greater exposure to trichloroethylene, standardized incidence ratios were higher for non-Hodgkin's lymphoma and renal cell carcinoma than in the entire blue-collar cohort. Finally, standardized incidence ratios for non-Hodgkin's lymphoma and esophageal adenocarcinoma were twice as high for blue-collar than for presumably unexposed white-collar workers.

In this study, follow-up was virtually complete, and reliable nationwide registries provided information on the employment history, cancer morbidity, and vital status of cohort members. The expected numbers of cancers were calculated on the basis of cancer rates for the Danish population, but lower social classes were probably overrepresented in the cohort of blue-collar workers; this would lead to underestimation of standardized incidence ratios for cancers associated with higher social classes and overestimation of standardized incidence ratios for cancers associated with lower social classes. Such selection bias may partly explain the general pattern of slightly elevated standardized incidence ratios for the majority of cancer sites, particularly those associated with cigarette smoking and alcohol consumption. Selection bias may also arise because of the healthy worker effect, which would tend to produce underestimated standardized incidence ratios, but this effect is likely small in cancer studies (20).

Employment as a blue-collar worker at trichloroethylene-using companies was used as a marker of exposure, but only an estimated 41 percent of workers in the cohort had likely exposure to trichloroethylene, defined as working *in the same room* where trichloroethylene was used (12). An unknown proportion of workers in the cohort who were not considered to have likely trichloroethylene exposure may have been exposed to trichloroethylene at levels 30–50 percent of the exposure levels of actual trichloroethylene workers (11). Some of the workers in the cohort, however, probably received little or no trichloroethylene exposure, which would introduce a nondifferential misclassification likely to bias standardized incidence ratios toward the null value and decrease somewhat the statistical power of this large study.

We included lag time and evaluated risk patterns according to three exposure-related variables (i.e., duration of employment, year of first employment, and number of employees in the company) to help assess whether the observed associations were likely to be causal. Because the Pension Fund provided information on employment only from 1964, earlier employment was not included when duration of employment was calculated. For workers with employment in a trichloroethylene-using company earlier than 1964, this could lead to misclassification of cohort members from higher to lower categories of duration of employment (e.g., if they left employment prior to 1969). Such misclassification of duration could lead to attenuation of an apparent dose-response relation. No other studies have examined the relation between trichloroethylene exposure potential and company size. The inverse relation between the number of employees in the company and the proportion of exposed workers was established from data collected in 1989 and 1998, and the degree to which the finding can be generalized to preceding decades is uncertain (12). Our previous study also indicated that exposure levels between 1964 and 1989 were higher in small companies, although we would expect the differences in exposure levels among the categories of company size to be much less than exposure differences among the categories of calendar time and duration of employment (12).

As in previous trichloroethylene and cancer studies, confounding by exposure to chemicals other than trichloroethylene cannot be excluded, although no such chemical is apparent. Since many of the standardized incidence ratios were only slightly elevated (table 2), even weak confounding by factors possibly relating to the socioeconomic status of the cohort (e.g., diet, smoking, alcohol consumption, and sexual behavior) is a concern. Cigarette smoking is a possible confounding factor, since smoking prevalence tends to be higher in the least educated groups in Denmark (21, 22) and therefore probably also among blue-collar workers. Indeed, among women, standardized incidence ratios for tobacco-related cancers were substantially elevated, whereas among men, standardized incidence ratios for lung and laryngeal cancers were only slightly elevated, and standard-

ized incidence ratios for bladder cancer and squamous cell carcinoma of esophagus were not elevated (table 2).

The finding of increased risk of non-Hodgkin's lymphoma in this study is unlikely to be explained by the lower social class of the cohort, because non-Hodgkin's lymphoma risk appears to increase somewhat with increasing social class (23, 24). Because the etiology of non-Hodgkin's lymphoma is largely unknown (24), confounding cannot be ruled out. We found, in both sexes, elevated standardized incidence ratios for variables related to exposure. Three Nordic cohort studies of workers monitored for a urinary metabolite of trichloroethylene because of occupational exposure to trichloroethylene all reported elevated standardized incidence ratios for non-Hodgkin's lymphoma; the combined standardized incidence ratio from all three studies is 2.1 (95 percent CI: 1.3, 3.1; number of cases (n) = 21) (10, 25, 26). Three other cohort studies with individual assessment of trichloroethylene exposure found a standardized mortality ratio of 1.2 (n = 14) with indication of an exposure-response pattern (5), a rate ratio of 2.0 (n = 28) and no indication of exposure response (27), and a standardized mortality ratio of 1.0 (n = 3) (28). A number of case-control studies have provided mixed results (29–34). The association between trichloroethylene exposure and non-Hodgkin's lymphoma found in this study is consistent with the results of the most reliable cohort studies, and it can be considered as independent of the similar finding of our previous study (10) because the overlap between cases was negligible; only two non-Hodgkin's lymphoma cases were included in both studies.

The present study indicated an association between trichloroethylene exposure and renal cell carcinoma, which is unlikely to be explained by the lower socioeconomic status of the cohort (23, 35–42). The results for lung and other smoking-related cancers indicate that smoking was more prevalent in the cohort than in the background population and may have contributed to the elevated standardized incidence ratio for renal cell carcinoma. However, since current smokers tend to have only about a 40 percent increased risk of renal cell carcinoma (43), the percentage of smokers would have to be extraordinarily high among cohort members to account for the 20 percent and 40 percent excesses observed in the cohort and subcohort, respectively (table 2 and 4). Such a high smoking rate would be expected to generate a much higher excess risk of lung cancer than was observed in this study (standardized incidence ratio = 1.4, 95 percent CI: 1.3, 1.6). Most previous cohort and case-control studies have found little or no relation between trichloroethylene and renal cell carcinoma (39). For the three Nordic cohort studies of workers monitored for trichloroethylene exposure, the combined standardized incidence ratio for kidney cancer is 1.0 (95 percent CI: 0.6, 1.6; n = 16) (10, 25, 26). The three cohort studies assessing trichloroethylene exposure at the individual level found a standardized mortality ratio for kidney cancer of 1.0 (n = 7) and no indication of a dose-response pattern (5), a rate ratio of 1.6 (n = 15) with indication of an inverse dose-response relation (27), and a standardized mortality ratio of 1.3 (n = 8) (28). Other cohort studies where trichloroethylene was only one of many potential exposures (44–48) and most but not all of the case-control studies of renal cell carcinoma and kidney cancer reported relative risk estimates close to unity (31, 34, 41, 49, 50). An odds ratio of 11 found in another case-control study (51) strikingly contrasts with other findings, and the study methods have been criticized (52–54). Two cluster-motivated studies reported substantially elevated relative risks for renal cell carcinoma associated with trichloroethylene exposure (55, 56), but confirmation of such clusters is suitable for generating—not testing—hypotheses. Thus, although research into the metabolism and toxicology of trichloroethylene has identified a possible nephrocarcinogenic mechanism (57), the most reliable cohort studies provide no support for a causal link between exposure to trichloroethylene and renal cell carcinoma. The previously reported higher relative risk of renal cell carcinoma for women than for men exposed to trichloroethylene (50) was not apparent in the present study.

We observed an elevated standardized incidence ratio for esophageal adenocarcinoma, one of the most rapidly rising cancers in Europe and the United States (58). The result for esophageal adenocarcinoma represents an independent confirmation of our earlier finding (10), because only two esophageal adenocarcinoma cases were included in both studies, and yet the highest standardized incidence ratios were observed for esophageal adenocarcinoma in both investigations. The other two Nordic studies of workers monitored for trichloroethylene exposure did not report on esophageal cancer (25, 26). Risk factors for esophageal adenocarcinoma include gastroesophageal reflux disease, obesity, and, to a lesser extent, cigarette smoking (58). The association with smoking is much weaker than that between smoking and esophageal squamous cell carcinomas (59, 60). Just as was the case for renal cell carcinoma, the association between smoking and esophageal adenocarcinoma would be expected to account for little of the increased standardized incidence ratio for esophageal adenocarcinoma in our cohort. Except for our previous study, we are aware of no epidemiologic reports on occupational hazards for esophageal adenocarcinoma, although metal dust has been reported to increase the risk of tumors of the lower third of the esophagus where adenocarcinomas usually occur (61), and perchloroethylene exposure has been associated with esophageal cancer (although primarily with squamous cell carcinoma) among dry cleaners (62).

We challenged our findings for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma in different ways. If the cases clustered mainly among workers in a single or a few companies, which were not the same for the three types of cancer, then it would be less likely that trichloroethylene was the common causal factor. No such clustering was observed. Similarly, if the distribution of industries where cases had worked differed markedly for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma, it would be less likely that trichloroethylene was the common causal factor; we detected no significant difference in the distribution of industries for non-Hodgkin's lymphoma, renal cell carcinoma, and esophageal adenocarcinoma cases.

We found substantially elevated standardized incidence ratios for cancer of the liver and gallbladder/biliary passages among women but not among men. Evidence of elevated risk

of cancer of the liver and biliary tract played an important role in the classification of trichloroethylene by the International Agency for Research on Cancer as a probable human carcinogen (2). For the three Nordic studies of workers monitored for trichloroethylene exposure, the standardized incidence ratio for cancer of the liver or biliary tract is 1.8 (95% CI: 1.1, 2.9; $n = 18$) (10, 25, 26). The three other cohort studies with trichloroethylene exposure assessment reported standardized mortality ratios of 0.5, 1.2, and 1.0 for liver cancer (5, 27, 28). In the current cohort study, the lower standardized incidence ratios when including lag time and the inverse relation of standardized incidence ratios with duration of employment and first year of employment argue against a causal relation between trichloroethylene exposure and cancer of the liver and gallbladder/biliary passages. Alcohol is a major risk factor for primary liver cancer in Denmark (63), and standardized incidence ratios for other alcohol-related cancers (i.e., laryngeal, esophageal squamous cell, and buccal cavity and pharyngeal cancer) were also found in the current study for women but not for men. However, despite a stronger association with alcohol for these cancers (63), the standardized incidence ratios were less increased than those for liver and biliary tract cancer and moreover, in general, Danish women from lower social classes have a lower alcohol intake (64). Thus, neither trichloroethylene exposure nor alcohol consumption alone provides a likely explanation for our finding.

The results of this study showed an increased risk of cervical cancer, which was also found in some (10, 25, 27) but not all (5, 28) previous studies of trichloroethylene-exposed cohorts. Two Nordic studies reported a twofold increased risk of cervical cancer among women of lower social classes (23, 65), and confounding by social class is, therefore, the likely explanation for the increased risk of cervical cancer in our study. Moreover, the lower risk when including lag time and in association with long duration of employment argues against trichloroethylene as the causal agent for cervical cancer.

Finally, the lower risk for skin melanoma in the cohort is probably caused by the social selection, as two Nordic studies have consistently shown a similar decreased risk among the lower social classes (23, 65).

In conclusion, the results of our cohort study provide support for an association between trichloroethylene exposure and non-Hodgkin's lymphoma, which is consistent with several earlier studies. The study also found evidence for an association with renal cell carcinoma, which, however, is less consistent with the epidemiologic evidence. Our increased standardized incidence ratio for liver and biliary tract cancer in women did not follow a dose-response pattern; however, in view of past findings the possibility of an association between trichloroethylene and liver/biliary passage cancer cannot be excluded. We confirmed our previous observation of an increased standardized incidence ratio for esophageal adenocarcinoma among Danish workers exposed to trichloroethylene; such an association has not been reported by others but warrants further research, given the rapid increase in esophageal adenocarcinoma incidence rates in industrial countries.

ACKNOWLEDGMENTS

The authors received funding for their research by way of an unrestricted grant from the International Epidemiology Institute.

The authors thank Andrea Meersohn and Visti Birk Larsen for data processing.

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