

Exhibit 259

ARTICLE

Risk of Cancer Among Workers Exposed to Trichloroethylene: Analysis of Three Nordic Cohort Studies

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Background Trichloroethylene (TCE) is a widely used chlorinated solvent with demonstrated carcinogenicity in animal assays. Some epidemiologic studies have reported increased risk of cancer of the kidney, cervix, liver and biliary passages, non-Hodgkin lymphoma, and esophageal adenocarcinoma.

Methods We established a pooled cohort, including 5553 workers with individual documented exposure to TCE in Finland, Sweden, and Denmark. Study participants were monitored for the urinary TCE metabolite trichloroacetic acid from 1947 to 1989 and followed for cancer. Standardized incidence ratios (SIRs) were calculated based on cancer incidence rates in the three national populations. Cox proportionate hazard analyses were used for internal comparisons. Tests of statistical significance are two-sided.

Results Overall, 997 cases of cancer ($n = 683$ in men; $n = 314$ in women) were identified during 154 778 person-years of follow-up. We observed statistically significant elevated standardized incidence ratios for primary liver cancer (1.93; 95% confidence interval [CI] = 1.19 to 2.95) and cervical cancer (2.31; 95% CI = 1.32 to 3.75). The standardized incidence ratio for kidney cancer was 1.01 (95% CI = 0.70 to 1.42) based on 32 cases; we did not observe a statistically significant increased risk of non-Hodgkin's lymphoma (SIR = 1.26; 95% CI = 0.89 to 1.73) or esophageal adenocarcinoma (SIR = 1.84; 95% CI = 0.65 to 4.65). Tobacco- and alcohol-associated cancers were not statistically significantly increased.

Conclusions Our results suggest TCE exposure is possibly associated with an increased risk for liver cancer. The relationship between TCE exposure and risks of cancers of low incidence and those with confounding by lifestyle and other factors not known in our cohort require further study.

J Natl Cancer Inst

Trichloroethylene (TCE) is a nonflammable, volatile, chlorinated organic solvent that has been used industrially for about 100 years. Since World War II, TCE has been used primarily as a cleaner and degreaser for metal parts (1–3). Because of the widespread occupational use of TCE, traces have been detected in the drinking water and food in certain areas (4), and TCE is now among the most frequently detected xenobiotics in groundwater (5,6).

It has for decades been established that very high doses of TCE given to certain strains of both sexes of experimental rats and mice can cause a variety of cancers, including tumors of the liver, kidney, lung, and testis as well as lymphoma (7). Further, epigenetic factors in cancer risk have recently been associated with TCE exposure (8,9). In October 2012, a working group convened by the International Agency for Research on Cancer reclassified TCE as carcinogenic to humans (group 1). This evaluation was built on sufficient epidemiologic and animal evidence for kidney cancer and qualitative mechanistic

similarities between humans and rodents (10). Limited epidemiologic evidence of human carcinogenicity was found for cancer of the liver and non-Hodgkin lymphoma. Thus, questions surrounding the human carcinogenicity of TCE remain (7,11). Inconsistencies in results between studies may be due in part to differences in follow-up time, study design (cohort vs case-control), studied outcome (mortality vs incidence), and, in particular, exposure assessment methods. Therefore, cohort studies of cancer incidence with reliable evidence of TCE exposure and long-term follow-up may be particularly useful to further clarify the issue of carcinogenicity of TCE in humans.

TCE accumulates in the body, and measurements of the main urinary TCE metabolite trichloroacetic acid (U-TCA) provide a reliable measure of exposure to TCE during the preceding week (12) and have, in some countries, been used to survey occupational exposure levels. Results from three independent cohort studies in Finland, Sweden, and Denmark, based on both male and female

workers routinely monitored for U-TCA, have previously been reported (13–15). This study is a pooled and updated analysis of these three Nordic studies, including a 10- to 15-year extension of follow-up for cancer incidence in all three cohorts. In addition to evaluating associations between TCE and cancer sites reported to be elevated in previous studies (kidney, liver and biliary passages, and non-Hodgkin lymphoma), we have also examined the risk of esophageal adenocarcinoma previously reported to be increased in two independent Danish cohort studies (14,16).

Methods

Description of National Cohorts

Detailed descriptions of the individual cohorts included in this pooled analysis have been published previously (13–15,17,18). In brief, all three cohorts are based on workers who have been exposed to TCE at specific workplaces and, because of national legislation on worker protection, have been monitored to evaluate individual biologic uptake of TCE. U-TCA was measured by the alkali-pyridine two-phase method based on the Fujiwara reaction. Ethical approval for Finland (ETR 04/2005) and Sweden (Uppsala 2005:132) and permission from the Danish Data Protection Agency (2010-41-5260) were obtained. Participants are not required to give written informed consent in this type of study conducted in the Nordic countries. Further details are given in the [Supplementary Methods](#) (available online).

Table 1 gives an overview of each of the three Nordic studies, including information on measured U-TCA samples, subjects, and levels during the period from 1947 to 1989, intervals for birth year and age, and years of follow-up for cancer.

Case Ascertainment

Since 1947 in Sweden, 1967 in Finland, and 1968 in Denmark, all residents in the three countries are assigned a unique personal identification number at birth or immigration (19). Using this number, the uniquely identified 5553 TCE-exposed workers ($n = 3776$ men; $n = 1777$ women) were linked to the respective Central Person Registers to retrieve individual information on vital status and date of death, emigration, or disappearance using well-described procedures (19). Similarly, information on cancer incidence, including date of diagnosis, was obtained by computerized linkages to the three nationwide cancer registries that have been in operation since 1943, 1953, and 1958 in Denmark, Finland, and Sweden, respectively. Modified versions of the International Classification of Diseases, Seventh Revision were used for cancer site classification (19).

Statistical Analysis

The individual calculation of person-years started on January 1, 1958, in Sweden, on January 1, 1967, in Finland, and on April 1, 1968, in Denmark or on the date of first registered U-TCA measurement, whichever came later. Follow-up ended on the date of death, emigration, or disappearance or on December 31, 2003, in Sweden, on December 31, 2004, in Finland, and on December 31, 2008, in Denmark, whichever came first.

National site-specific cancer incidence rates by sex, 5-year age groups, and 5-year calendar periods were applied to the person-years under observation for the cohort members to obtain the number of cancers expected had the cohort members experienced the same rate of cancers as that observed in the respective general populations.

Standardized incidence ratios (SIRs), the ratio between observed and expected number of cancers, and corresponding 95% confidence intervals (CIs), assuming that the observed number follows a Poisson distribution, were calculated for cancer overall and for each cancer site by sex and by country as well as pooled across cohorts (20). We used a modified version of the PYRS software (International Agency for Research on Cancer, Lyon, France) for these calculations (21). To include latency periods, exposure follow-up was delayed by 10 and 20 years from date of first known measurement of U-TCA (22). We also assessed heterogeneity between countries for the overall results of the a priori selected cancers by use of the software *Episheet* by Rothman (Kenneth.Rothman@gmail.com) (23).

Dates of start and end of TCE exposure were not available from our cohorts. Therefore, analyses by duration of exposure or cumulative exposure were not feasible. However, incomplete information was available concerning employment period, not necessarily equal to exposure period, from subjects from Sweden and Denmark. Based on this information, median duration of employment in the company with TCE exposure were 5.5 and 6.3 years in the Sweden and Denmark, respectively. To evaluate indicators for exposure–response relationships, we calculated standardized incidence ratios for cancers of a priori interest by age at first registered U-TCA measurement (<35 , $35–47$, ≥ 48 years) based on the observed cut points in the Danish measurements (2) and, similarly, by period of first U-TCA measurement (<1965 , $1965–1979$, ≥ 1980). Finally, we classified individuals according to average measured U-TCA level (<5 [referent], $5–24$, $25–49$, and ≥ 50 mg/L). Based on U-TCA level groups, we performed internal analyses by use of Cox regression with the Breslow method for ties to estimate hazard rate ratios (HRRs) for cancers of primary interest. Age was used as the underlying timescale (delayed entry) to ensure that estimates were based on individuals of the same age. We adjusted for the effects of sex, country, and 5-years calendar time periods. The proportional hazard assumption for the analyses was tested by Kaplan–Meier plots and by the Schoenfeld test by use of the Stata Statistical Software version 11.2 (Statacorp, Texas, USA).

All tests of statistical significance are two-sided. *P* values less than .05 and relative risk estimates with 95% confidence intervals that exclude one were considered statistically significant.

Because we have no information on tobacco smoking and alcohol drinking, and because some of the cancer sites (liver, esophagus, cervix, and kidney) of interest are causally associated with these exposures, we indirectly evaluated potential confounding by calculation of combined standardized incidence ratios for other cancers that are generally accepted to be causally associated with smoking and alcohol drinking. These were cancers of the oral cavity, pharynx, stomach, colo-rectum, pancreas, nasal cavity, larynx, lung, ovary, and urinary bladder, as well as leukemia for tobacco (24) and cancers of the oral cavity, pharynx, larynx, colo-rectum, and female breast for alcohol drinking (24). Observed increased standardized incidence ratios for these two groups would suggest confounding by smoking and alcohol drinking, respectively.

Results

This cohort of TCE-exposed workers contributed a total of 154 778 person-years of observation (102 011 for men; 52 767 for women)

Table 1. Descriptive characteristics of the urinary trichloroethylene (TCE) metabolite trichloroacetic acid (U-TCA) measurements and the cohorts of Finnish, Swedish, and Danish TCE-monitored workers*

Characteristic	Finland	Sweden	Denmark
U-TCA measurements	7300	1668†	1826‡
Individual range of measurements	1–25	1–NA	1–35
Subjects with 2 measurements, No. (%)	1126 (36)	NA	272 (34)
Subjects with ≥3 measurements, No. (%)	819 (27)	NA	269 (37)
Measurement period	1965–1982	1955–1975	1947–1989
Measurement level, %			
<Detection limit§	3.1	0.5	9.8
<5 mg/L	28.8	32.8	27.5
5–25 mg/L	43.8	32.5	28.0
25–50 mg/L	11.0	16.6	13.9
≥50 mg/L	13.3	17.7	20.7
Mean, mg/L (SD)	30.3 (82.1)	28.2 (39.9)	39.2 (77.7)
Median	9.2	13.0	15.0
Interquartile range	20.3	34.0	36.9
Duration of employment, median years	NA	5.5	6.3
Follow-up for cancer			
Start–end: current (previous report)	1967–2004, (1967–1992)	1958–2003, (1958–1987)	1968–2008, (1968–1996)
Lost to follow-up, No.	4	2	2
Males	1696	1419	661
Females	1389	249	139
Total	3085	1668	800
Birth year, No. (%)			
<1930	906 (29)	844 (51)	367 (46)
1930–39	716 (23)	275 (16)	127 (16)
1940–49	976 (32)	330 (20)	128 (16)
1950–59	456 (15)	219 (13)	135 (17)
≥1960	31 (1)	0 (0)	43 (5)
Age at first known U-TCA measurement, No. (%)			
<25	794 (26)	374 (22)	180 (22)
25–34	914 (30)	332 (20)	196 (25)
35–44	711 (23)	298 (18)	174 (22)
45–54	452 (15)	395 (24)	138 (17)
≥55	214 (7)	269 (16)	112 (14)
Year of first known U-TCA measurement, No. (%)			
<1950	0 (0)	0 (0)	39 (5)
1950–59	0 (0)	172 (10)	114 (14)
1960–69	1083 (35)	388 (23)	122 (15)
1970–79	1832 (59)	1108 (66)	377 (47)
≥1980	170 (6)	0 (0)	148 (18)
Years of follow-up for cancer, No. (%)			
<5	70 (2)	56 (3)	31 (4)
5–9	102 (3)	54 (3)	42 (5)
10–19	230 (7)	219 (13)	134 (17)
20–29	940 (30)	666 (40)	272 (34)
30–39	1743 (56)	583 (35)	266 (33)
≥40	0 (0)	90 (5)	55 (7)

* NA = not available; SD = standard deviation.

† Based on mean measurement for individuals.

‡ One hundred ninety-nine air zone measurements included.

§ Before 1979, 2.5 mg/L; from 1979, 0.5 mg/L.

|| Only period since 1964 is available.

derived from Finland (58%), Sweden (29%), and Denmark (13%). The standardized incidence ratios for specific cancer sites and all sites combined by country and sex and pooled for all U-TCA measured workers in the three countries are shown in Table 2. Overall, 997 cancers (n = 683 in men; n = 314 in women) were observed vs 942.21 expected, yielding a standardized incidence ratio of 1.06 (95% CI = 0.99 to 1.13). The age-standardized incidence rates of

overall cancer were 644.15 per 100 000 person-years in the workers with U-TCA measurements versus 608.74 per 100 000 person years in the general population.

For the sites of a priori interest, a statistically significant increased standardized incidence ratio pooled across country and sex was observed only for liver cancer (SIR = 1.93; 95% CI = 1.19 to 2.95); for the combined site of liver and biliary

Table 2. Relative risk (standardized incidence ratio [SIR]) of cancer among Danish, Swedish, and Finnish workers exposed to trichloroethylene (TCE) by sex and country*

Site (International Classification of Diseases, Seventh Revision)	Men											
	Denmark (1968–2008)			Sweden (1958–2003)			Finland (1967–2004)			Total		
	16 867 person-years			38 221 person years			46 923 person-years			102 011 person-years		
	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)
Total (140–204)	193	167.81	1.15 (0.99 to 1.32)	276	271.40	1.02 (0.90 to 1.14)	214	207.48	1.03 (0.90 to 1.18)	683	646.69	1.06 (0.98 to 1.14)
Pharynx (145–148)	5	1.43	2.04 (1.13 to 8.15)	2	2.00	1.00 (0.11 to 3.62)	1	1.24	0.81 (0.03 to 4.49)	8	4.67	1.71 (0.74 to 3.38)
Esophagus (150)	8	2.45	3.27 (1.41 to 6.44)	1	3.37	0.30 (0 to 1.65)	2	2.67	0.75 (0.08 to 2.70)	11	8.49	1.30 (0.65 to 2.32)
Adenocarcinomas	5	1.01	4.95 (1.61 to 11.60)	0	0.90	— (0 to 4.10)	0	0.64	— (0 to 6.10)	5	2.55	1.96 (0.65 to 4.65)
Stomach (151)	3	4.98	0.60 (0.12 to 1.76)	12	12.83	0.94 (0.48 to 1.63)	14	11.57	1.21 (0.66 to 2.03)	29	29.38	0.99 (0.66 to 1.42)
Colon (153)	8	11.99	0.67 (0.29 to 1.31)	26	19.36	1.34 (0.88 to 1.97)	11	10.15	1.08 (0.54 to 1.94)	45	41.50	1.08 (0.79 to 1.45)
Rectum (154)	8	8.30	0.96 (0.41 to 1.90)	11	13.16	0.84 (0.42 to 1.50)	14	8.32	1.68 (0.92 to 2.82)	33	29.78	1.11 (0.76 to 1.56)
Liver and biliary passages (155)	8	2.83	2.83 (1.22 to 5.57)	6	5.98	1.00 (0.37 to 2.18)	11	4.38	2.51 (1.25 to 4.49)	25	13.19	1.90 (1.23 to 2.81)
Liver, primary (155.0)	5	1.93	2.59 (0.84 to 6.05)	3	3.54	0.85 (0.17 to 2.48)	8	2.87	2.79 (1.20 to 5.50)	16	8.34	1.92 (1.10 to 3.12)
Biliary passages (155.1)	3	0.90	3.33 (0.19 to 2.63)	3	2.44	1.23 (0.25 to 3.59)	3	1.51	1.99 (0.41 to 5.81)	9	4.85	1.86 (0.85 to 3.52)
Pancreas (157)	6	4.34	1.38 (0.51 to 3.01)	3	7.77	0.39 (0.08 to 1.13)	8	7.23	1.11 (0.58 to 2.18)	17	19.34	0.88 (0.51 to 1.41)
Larynx (161)	3	2.58	1.16 (0.23 to 3.40)	4	2.66	1.50 (0.40 to 3.85)	4	2.29	1.75 (0.47 to 4.48)	11	7.53	1.46 (0.72 to 2.61)
Lung (162)	33	27.87	1.18 (0.82 to 1.66)	28	27.01	1.04 (0.69 to 1.50)	39	40.41	0.97 (0.69 to 1.32)	100	95.29	1.05 (0.85 to 1.28)
Breast (170)	1	0.25	4.00 (0.05 to 21.9)	1	0.44	2.27 (0.03 to 12.60)	0	0.26	— (0 to 14.20)	2	0.95	2.11 (0.26 to 7.60)
Cervix (171)												
Corpus uteri (172)												
Ovary (175)												
Prostate (177)	15	20.98	0.79 (0.40 to 1.18)	67	68.38	0.98 (0.80 to 1.20)	46	44.43	1.04 (0.76 to 1.38)	128	133.79	0.96 (0.80 to 1.14)
Testis (178)	2	1.60	1.25 (0.14 to 4.51)	2	1.54	1.30 (0.15 to 4.69)	3	1.20	2.50 (0.50 to 7.32)	7	4.34	1.61 (0.65 to 3.32)
Kidney (180)	4	4.86	0.82 (0.22 to 2.11)	10	9.82	1.02 (0.49 to 1.87)	10	8.72	1.15 (0.55 to 2.11)	24	23.40	1.03 (0.66 to 1.53)
Bladder (181)	22	14.22	1.55 (0.97 to 2.34)	22	19.51	1.13 (0.71 to 1.71)	10	10.74	0.93 (0.45 to 1.71)	54	44.47	1.21 (0.91 to 1.58)
Melanomas of skin (190)	2	3.79	0.53 (0.06 to 1.90)	6	8.43	0.71 (0.26 to 1.55)	2	6.51	0.31 (0.03 to 1.11)	10	18.73	0.53 (0.26 to 0.98)
Other skin (191)	28	27.30	1.03 (0.70 to 1.48)	19	13.95	1.36 (0.82 to 2.12)	4	5.34	0.75 (0.20 to 1.90)	51	46.59	1.09 (0.72 to 1.44)
Brain and nervous system (193)	6	5.35	1.12 (0.41 to 2.44)	2	7.25	0.28 (0.03 to 1.00)	8	6.82	1.17 (0.51 to 2.31)	16	19.42	0.82 (0.47 to 1.34)
Thyroid gland (194)	0	0.37	— (0 to 9.97)	2	1.22	1.64 (0.18 to 5.90)	2	1.56	1.28 (0.14 to 4.63)	4	3.15	1.27 (0.35 to 3.25)
Connective tissue, other (197)	0	0.71	— (0 to 5.20)	3	1.86	1.61 (0.32 to 4.72)	1	1.46	0.68 (0.01 to 3.83)	4	4.03	0.99 (0.27 to 2.54)
Non-Hodgkin lymphoma (200–202)	9	3.83	2.35 (1.07 to 4.46)	15	8.88	1.69 (0.94 to 2.79)	8	7.87	1.02 (0.44 to 2.00)	32	20.58	1.55 (1.06 to 2.20)
Multiple myeloma (203)	1	1.98	0.26 (0.01 to 2.81)	2	4.07	0.49 (0.06 to 1.77)	1	2.52	0.40 (0.01 to 2.21)	4	8.57	0.47 (0.13 to 1.20)
Leukemia (204)	10	4.20	2.61 (1.14 to 4.38)	4	6.81	0.59 (0.16 to 1.50)	5	4.91	1.02 (0.32 to 2.38)	19	15.92	1.19 (0.72 to 1.86)
Other	11	11.60	0.95 (0.47 to 1.70)	28	25.10	1.12 (0.75 to 1.62)	10	16.88	0.59 (0.28 to 1.09)	49	53.58	0.91 (0.68 to 1.21)

* All statistical tests were two-sided and based on Byar's approximation. CI = confidence interval; Exp = expected number of cases; Obs = observed number of cases.

passages cancer, the standardized incidence ratio was 1.77 (95% CI = 1.24 to 2.45).

The only other statistically significant elevated site-specific standardized incidence ratio in the pooled analysis was that for cervical cancer (SIR = 2.31; 95% CI = 1.32 to 3.75) based on 16 cases.

No increased risk of kidney cancer was observed in any country either among men or women; the pooled standardized incidence ratio was 1.01 (95% CI = 0.70 to 1.42) based on 32 cases.

For non-Hodgkin lymphoma, 38 cases were observed vs 30.14 expected, yielding a non-statistically significant increased pooled standardized incidence ratio of 1.26 (95% CI = 0.89 to 1.73). When men and women were considered separately, a statistically significant increased standardized incidence ratio was observed among men (SIR = 1.55; 95% CI = 1.06 to 2.20), whereas six cases vs 9.56 expected were observed in women.

The pooled relative risks of esophagus cancer (SIR = 1.12; 95% CI = 0.58 to 1.96) and of adenocarcinoma of the esophagus in particular (SIR = 1.84; 95% CI = 0.65 to 4.65) were not statistically significantly elevated.

For the remaining cancers, the patterns of standardized incidence ratios for men and women were virtually identical. The only notable exception was a statistically significant elevated

standardized incidence ratio for pancreas cancer among women (SIR = 2.18; 95% CI = 1.35 to 3.34).

Table 3 shows standardized incidence ratios for both sexes combined total cancer and for the a priori selected cancer sites by 10 and 20 years of lag of follow-up from date of first known U-TCA measurement. Overall, the changes are small when results including lag time are compared with results with no lag time. Table 3 also shows P values for test of heterogeneity between countries in overall results; only heterogeneity for standardized incidence ratios of esophageal cancer appears statistically significant ($P_{\text{trend}} = .01$).

Table 4 displays estimates for the internal analyses of the a priori interest sites based on individual average U-TCA measurement categories. Increasing hazard rate ratio by monotonic increasing U-TCA level (<5 [referent], 5–25, 25–50, 50 mg/L) was indicated only for cervical cancer where the hazard rate ratio in the highest category was 3.28 (95% CI = 0.73 to 14.91) ($P_{\text{trend}} = .08$). For kidney cancer, we observed a hazard rate ratio of 2.04 (95% CI = 0.81 to 5.17) in the highest category and hazard rate ratios roughly about 1 for levels below. In contrast, there was a decreasing trend of hazard rate ratios with increasing U-TCA level for esophagus cancer and liver and biliary passage cancer and no apparent trend for non-Hodgkin lymphoma. Further, we found no consistent pattern in

Table 2 (Continued).

Women													Men and women		
Denmark (1968–2008)			Sweden (1958–2003)			Finland (1967–2004)			Total			Total			
3651 person-years			6904 person-years			42 212 person-years			52 767 person-years			154 778 person-years			
Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	Obs	Exp	SIR (95 % CI)	
27	30.62	0.88 (0.58 to 1.28)	64	43.57	1.47 (1.13 to 1.88)	223	221.33	1.01 (0.88 to 1.15)	314	295.52	1.06 (0.95 to 1.19)	997	942.21	1.06 (0.99 to 1.13)	
0	0.10	— (0 to 36.90)	1	0.12	8.33 (0.11 to 46.80)	1	0.46	2.17 (0.03 to 12.08)	2	0.68	2.94 (0.36 to 10.6)	10	5.35	1.87 (0.90 to 3.44)	
0	0.17	— (0 to 2.17)	0	0.19	— (0 to 19.40)	1	1.86	0.54 (0.01 to 2.98)	1	2.22	0.45 (0.01 to 2.51)	12	10.71	1.12 (0.58 to 1.96)	
0	0.00	—	0	0.00	—	0	0.17	— (0 to 21.70)	0	0.17	— (0 to 53.00)	5	2.72	1.84 (0.65 to 4.65)	
1	0.48	2.08 (0.03 to 11.53)	2	1.03	1.94 (0.22 to 7.02)	13	9.43	1.38 (0.73 to 2.36)	16	10.94	1.46 (0.84 to 2.38)	45	40.32	1.12 (0.81 to 1.49)	
0	2.34	— (0 to 1.58)	4	3.15	1.27 (0.34 to 3.25)	15	12.97	1.16 (0.65 to 1.91)	19	18.46	1.03 (0.62 to 1.61)	64	59.96	1.07 (0.82 to 1.36)	
0	1.10	— (0 to 3.35)	4	1.64	2.44 (0.66 to 6.24)	6	7.89	0.76 (0.28 to 1.66)	10	10.63	0.94 (0.45 to 1.73)	43	40.41	1.06 (0.78 to 1.43)	
0	0.45	— (0 to 8.20)	3	0.94	3.19 (0.66 to 9.33)	8	5.74	1.39 (0.61 to 2.76)	11	7.13	1.54 (0.77 to 2.76)	36	20.32	1.77 (1.24 to 2.45)	
0	0.20	— (0 to 18.40)	0	0.31	— (0 to 11.90)	5	2.05	2.44 (0.78 to 5.68)	5	2.56	1.90 (0.63 to 4.56)	21	10.90	1.93 (1.19 to 2.95)	
0	0.25	— (0 to 14.80)	3	0.63	4.76 (0.96 to 13.97)	3	3.69	0.81 (0.16 to 2.38)	6	4.57	1.31 (0.48 to 2.86)	15	9.42	1.59 (0.89 to 2.63)	
3	0.75	4.00 (0.81 to 11.73)	3	1.08	2.78 (0.56 to 8.13)	15	7.79	1.93 (1.08 to 3.19)	21	9.62	2.18 (1.35 to 3.34)	38	28.96	1.31 (0.93 to 1.80)	
0	0.10	— (0 to 36.90)	0	0.07	— (0 to 52.70)	0	0.31	— (0 to 11.90)	0	0.48	— (0 to 7.69)	11	8.01	1.37 (0.69 to 2.46)	
2	2.77	0.72 (0.08 to 2.61)	1	2.21	0.45 (0.01 to 2.52)	16	9.87	1.62 (0.93 to 2.63)	19	14.85	1.28 (0.77 to 2.00)	119	110.14	1.08 (0.90 to 1.29)	
5	6.85	0.73 (0.24 to 1.70)	20	12.27	1.63 (1.00 to 2.52)	61	66.51	0.92 (0.70 to 1.18)	86	85.63	1.00 (0.80 to 1.24)	88	86.58	1.02 (0.82 to 1.25)	
4	1.14	3.51 (0.90 to 9.00)	1	1.28	0.78 (0.01 to 4.35)	11	4.50	2.44 (1.22 to 4.38)	16	6.92	2.31 (1.32 to 3.75)	16	6.92	2.31 (1.32 to 3.75)	
2	1.52	1.32 (0.20 to 4.80)	6	2.88	2.08 (0.76 to 4.54)	10	15.67	0.64 (0.31 to 1.17)	18	20.07	0.90 (0.53 to 1.42)	18	20.07	0.90 (0.53 to 1.42)	
2	1.32	1.52 (0.17 to 5.48)	6	2.46	2.44 (0.89 to 5.30)	9	11.19	0.80 (0.37 to 1.53)	17	14.97	1.14 (0.66 to 1.82)	17	14.97	1.14 (0.66 to 1.82)	
												128	133.79	0.96 (0.80 to 1.14)	
												7	4.34	1.61 (0.65 to 3.32)	
1	0.61	1.64 (0.04 to 9.13)	1	1.08	0.93 (0.01 to 5.13)	6	6.68	0.90 (0.33 to 1.96)	8	8.37	0.96 (0.41 to 1.88)	32	31.77	1.01 (0.70 to 1.42)	
0	0.60	— (0 to 6.15)	2	1.03	1.94 (0.22 to 6.98)	2	3.59	0.56 (0.06 to 2.01)	4	5.22	0.77 (0.21 to 1.96)	58	49.69	1.17 (0.75 to 1.26)	
0	0.90	— (0 to 4.11)	1	1.45	0.69 (0.01 to 3.83)	6	5.82	1.03 (0.38 to 2.25)	7	8.17	0.86 (0.34 to 1.77)	17	26.90	0.63 (0.37 to 1.01)	
1	4.60	0.22 (0.01 to 1.21)	1	1.19	0.84 (0.01 to 4.67)	8	5.72	1.40 (0.60 to 2.75)	10	11.51	0.87 (0.42 to 1.60)	61	58.10	1.05 (0.80 to 1.35)	
1	0.96	1.04 (0.03 to 5.80)	0	1.41	— (0 to 2.62)	7	8.65	0.81 (0.32 to 1.66)	8	11.02	0.73 (0.31 to 1.43)	24	30.44	0.79 (0.51 to 1.17)	
0	0.16	— (0 to 23.10)	1	0.48	2.08 (0.03 to 11.56)	5	4.61	1.08 (0.35 to 2.53)	6	5.25	1.14 (0.42 to 2.49)	10	8.40	1.19 (0.57 to 2.19)	
0	0.11	— (0 to 33.50)	0	0.27	— (0 to 13.70)	3	1.45	2.07 (0.41 to 6.03)	3	1.83	1.64 (0.34 to 4.79)	7	5.86	1.19 (0.40 to 2.46)	
0	0.62	— (0 to 0.95)	2	1.18	1.69 (0.19 to 6.10)	4	7.76	0.52 (0.14 to 1.32)	6	9.56	0.63 (0.23 to 1.37)	38	30.14	1.26 (0.89 to 1.73)	
0	0.28	— (0 to 13.20)	0	0.52	— (0 to 7.09)	4	3.03	1.32 (0.36 to 3.38)	4	3.83	1.04 (0.29 to 2.67)	8	12.40	0.65 (0.28 to 1.27)	
1	0.52	1.92 (0.05 to 10.70)	1	0.79	1.27 (0.02 to 7.05)	2	4.40	0.45 (0.05 to 1.64)	4	5.71	0.70 (0.19 to 1.79)	23	21.63	1.06 (0.67 to 1.60)	
4	2.17	1.84 (0.50 to 4.72)	4	4.85	0.82 (0.20 to 2.20)	10	15.43	0.65 (0.31 to 1.19)	18	22.45	0.80 (0.45 to 1.27)	67	76.03	0.88 (0.68 to 1.12)	

standardized incidence ratios by age at first TCA measurement (Supplementary Table 1, available online) or by calendar period of first TCA-measurement (Supplementary Table 2, available online) for any of the a priori selected cancer sites.

The standardized incidence ratio for tobacco-associated cancers combined, excluding those of interest for TCE exposure (esophagus, liver, kidney, and cervix), was slightly elevated among men (SIR = 1.08; 95% CI = 0.99 to 1.22) and women (SIR = 1.23; 95% CI = 1.00 to 1.51). For cancers associated with alcoholic beverage drinking, the standardized incidence ratios were 1.10 (95% CI = 0.92 to 1.38) and 0.97 (95% CI = 0.82 to 1.24) among men and women, respectively.

Discussion

Positive associations between occupational TCE exposure and risk of kidney cancer have been reported in other epidemiologic studies, most recently with high TCE exposure levels in a community-based case-control study from France (25,26). This and another study from eastern Europe provided evidence for exposure-response relationships after adjustment for confounders (27). The association between occupational TCE exposure and kidney

cancer risk has recently been quantitatively reviewed based on virtually all existing studies in three independent reports with roughly similar conclusions (28–30). Thus, Kelsh et al. calculated a summary relative risk of 1.34 (95% CI = 1.07 to 1.67) for cohort studies that had complete enumeration of the exposed workforce and that specifically identified TCE as a workplace exposure and 1.33 (95% CI = 1.02 to 1.73) for case-control studies (30). A summary relative risk of 1.58 (95% CI = 1.28 to 1.96) was calculated by Scott and Jinot for the highest exposure group (28). An association with kidney cancer has also been observed in experimental animals (31), and biological mechanisms and pathways for renal carcinogenicity have been conjectured (27,32–34). Despite long-term follow-up of workers with documented exposure to TCE in this study, we did not observe an overall increased risk of kidney cancer in any of the three subcohorts, in either men or women, based on 32 cases. We did, however, observe a twofold non-statistically significant increase (HRR = 2.04; 95% CI = 0.81 to 5.17) based on nine cases of kidney cancer in workers categorized with highest U-TCA measurements. Duration of exposure, as well as exposure levels of TCE, have in general been relatively low in Finland, Sweden, and Denmark (13–15,35,36), and if TCE is a risk factor for kidney cancer only at extremely high levels of TCE-exposure (7,25), this may

Table 3. Relative risk (standardized incidence ratio [SIR]) of selected cancers among Danish, Swedish, and Finnish workers exposed to trichloroethylene by lag time*

Site	Lagtime†	Denmark				Sweden				Finland				Total				Test for heterogeneity between countries P‡
		Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI	
Total	No	220	198.43	1.11	0.97 to 1.27	340	314.97	1.08	0.97 to 1.20	437	428.81	1.02	0.93 to 1.12	997	942.21	1.06	0.99 to 1.13	.54
	10 years	196	172.91	1.13	0.98 to 1.30	291	261.44	1.11	0.99 to 1.25	373	369.11	1.01	0.91 to 1.12	860	803.46	1.07	1.00 to 1.14	
	20 years	143	122.89	1.16	0.98 to 1.37	178	161.12	1.10	0.95 to 1.28	276	254.29	1.09	0.96 to 1.22	597	538.30	1.11	1.02 to 1.20	
Esophagus	No	8	2.62	3.05	1.32 to 6.02	1	3.56	0.28	0.01 to 1.57	3	4.53	0.66	0.14 to 1.94	12	10.71	1.12	0.58 to 1.96	.01
	10 years	8	2.35	3.40	1.47 to 6.71	1	2.92	0.34	0.01 to 1.91	2	3.93	0.51	0.08 to 2.47	11	9.20	1.20	0.60 to 2.14	
	20 years	7	1.70	4.12	1.66 to 8.48	0	1.76	0.00	0 to 2.10	2	2.69	0.74	0.09 to 2.69	9	6.15	1.46	0.67 to 2.78	
Liver and biliary passages	No	8	3.30	2.40	1.05 to 4.78	9	7.10	1.30	0.60 to 2.47	19	10.12	1.88	1.13 to 2.93	36	20.32	1.77	1.24 to 2.45	.08
	10 years	7	2.87	2.44	0.99 to 5.06	8	5.84	1.37	0.59 to 2.70	17	8.96	1.90	1.11 to 3.04	32	17.47	1.83	1.24 to 2.56	
	20 years	6	2.02	2.97	1.09 to 6.47	5	3.35	1.49	0.49 to 3.48	13	6.10	2.13	1.13 to 3.64	24	11.47	2.09	1.34 to 3.11	
Cervix	No	4	1.14	3.51	0.96 to 8.98	1	1.28	0.78	0.02 to 4.35	11	4.50	2.44	1.22 to 4.37	16	6.92	2.31	1.32 to 3.75	.33
	10 years	3	0.86	3.49	0.72 to 10.2	0	0.76	0.00	0 to 4.85	5	2.75	1.82	0.50 to 4.24	8	4.37	1.83	0.80 to 3.61	
	20 years	1	0.47	2.13	0.05 to 11.9	0	0.34	0.00	0 to 10.8	4	1.44	2.78	0.76 to 7.11	5	2.25	2.22	0.72 to 5.19	
Kidney	No	5	5.49	0.91	0.30 to 2.13	11	10.83	1.02	0.51 to 1.82	16	15.40	1.04	0.59 to 1.69	32	31.77	1.01	0.70 to 1.42	.98
	10 years	4	4.69	0.86	0.23 to 2.19	11	10.43	1.05	0.52 to 1.87	15	13.62	1.10	0.62 to 1.82	30	28.79	1.04	0.71 to 1.50	
	20 years	2	3.24	0.62	0.07 to 2.23	7	4.61	1.52	0.61 to 3.13	10	9.31	1.07	0.52 to 1.98	19	17.16	1.11	0.67 to 1.73	
Non-Hodgkin lymphoma	No	9	4.45	2.02	0.93 to 3.84	17	10.06	1.69	0.98 to 2.71	12	15.63	0.77	0.40 to 1.34	38	30.14	1.26	0.89 to 1.73	.06
	10 years	6	3.88	1.55	0.57 to 3.37	16	8.52	1.88	1.07 to 3.05	10	13.97	0.72	0.34 to 1.32	32	26.37	1.21	0.83 to 1.71	
	20 years	4	2.72	1.47	0.40 to 3.77	10	5.31	1.88	0.90 to 3.46	6	9.94	0.60	0.22 to 1.31	20	17.97	1.11	0.68 to 1.72	

* CI = confidence interval; Exp = expected number of cases; Obs = observed number of cases.

† Lag of years for start of follow-up after first known measurement.

‡ P values for between subcohort heterogeneity are calculated using the *I*² statistic. All statistical tests were two-sided and based on Byar's approximation. No lag time included.

Table 4. Adjusted hazard rate ratios (HRR) for selected cancers sites among workers exposed to trichloroethylene (TCE) by mean levels of the measured urinary TCE metabolite trichloroacetic acid (U-TCA)*

Site	U-TCA (mg/L)	Observations	Cases	HRR* (95% CI)	<i>P</i> _{trend} †
Esophagus	<5	1921	8	1.00 (referent)	.02
	5–25	2054	4	0.48 (0.14 to 1.60)	
	25–50	757	0	—	
	>50	821	0	—	
Liver and biliary passages	<5	1921	16	1.00 (referent)	.20
	5–25	2054	12	0.66 (0.31 to 1.42)	
	25–50	757	5	0.45 (0.13 to 1.54)	
	>50	821	3	0.63 (0.22 to 1.68)	
Cervix	<5	551	3	1.00 (referent)	.08
	5–25	745	6	1.54 (0.38 to 6.26)	
	25–50	227	3	2.41 (0.49 to 11.98)	
	>50	250	4	3.28 (0.73 to 14.91)	
Kidney	<5	1921	9	1.00 (referent)	.19
	5–25	2054	11	1.12 (0.46 to 2.70)	
	25–50	757	3	0.81 (0.21 to 2.97)	
	>50	821	9	2.04 (0.81 to 5.17)	
Non-Hodgkin lymphoma	<5	1921	12	1.00 (referent)	.79
	5–25	2054	14	1.16 (0.53 to 3.09)	
	25–50	757	8	1.56 (0.63 to 3.81)	
	>50	821	4	0.66 (0.21 to 2.03)	

* Adjusted for sex, country, age, and calendar time (5-years groups). No lag time included. CI = confidence interval.

† Test for trend was calculated using the Wald test statistic.

explain in part our overall null finding for this cancer. Alternative explanations may be lower statistical power in our study to examine moderately increased risks for rare tumors such as kidney cancer or simply no true association.

For non-Hodgkin lymphoma, we observed a statistically significant increased relative risk in male (RR = 1.55; 95% CI = 1.06 to 2.20) but not in female (RR = 0.63; 95% CI = 0.23 to 1.37) workers, with no apparent trend of increasing risk with increasing U-TCA levels. An excess for non-Hodgkin lymphoma has been reported in previous studies (37–39), including each of the three earlier reports from the subcohorts (13–15). Further, an independent large Danish cohort showed increased risks for non-Hodgkin lymphoma with indicators of increasing TCE exposure (16). However, a European case-control study of exposure to organic solvents reported no increase for any type of non-Hodgkin lymphoma after exposure to TCE (40). The recent meta-analysis by Scott and Jinot (28) based on nine cohorts and eight case-control studies reported an overall random effect meta-relative risk of 1.23 (95% CI = 1.07 to 1.42). The causes of non-Hodgkin lymphoma remain virtually unknown, apart from exposure to certain viruses and immunosuppression (41,42). TCE may have immunotoxic effects (43) and may, through this pathway, be linked to non-Hodgkin lymphoma, which is associated with immune dysregulation (44). Further, a recent study showed that modest TCE exposure was associated with a decrease in all major lymphocyte subsets and a decline in markers of lymphocyte activation, thus providing possible biologic plausibility of TCE as a potential lymphomagen (45). However, to date the epidemiologic evidence remains somewhat inconsistent.

We observed a significantly increased standardized incidence ratio for liver cancer (SIR = 1.93; 95% CI = 1.19 to 2.95). A recent meta-analysis found a modest increased overall relative risk of 1.29

(95% CI = 1.07 to 1.56) based on nine cohort studies (28). Increased occurrence of liver cancer has been observed in experimental rodent studies, as has TCE-induced peroxisome proliferation in the liver (31). Alcohol drinking and tobacco smoking are both established causes of liver cancer (24). The observed standardized incidence ratio pattern for other alcohol and tobacco associated cancers in our study of TCE-exposed workers, not exceeding 10% in men and 23% in women compared with the general population, does not suggest a major risk contribution from tobacco and alcohol habits in this cohort. Therefore, a possible contribution may exist from other exposures, such as occupational exposure to TCE or other solvents, to the observed increased risk for liver cancer (46).

The statistically significant positive association between TCE exposure and cervical cancer risk in this study, including a monotonic increasing trend by increasing U-TCA level, has been observed in an independent Danish study (16). Results from the few other cohorts that have examined this cancer are inconsistent and based on mortality of relative few cases (47–49). One recent case-control study that included control for major confounders did not find an association (50). Infection with certain types of human papilloma viruses (HPVs) is the major cause of cervical cancer (51), although there is also an influence of tobacco smoking (52), both of which are related to socioeconomic factors (53). Therefore, additional epidemiologic studies, including information on HPV infections, tobacco smoking habits, and screening behavior, are warranted.

A previously reported increased relative risk for esophageal adenocarcinomas in the Danish cohort was not confirmed in the Finnish or Swedish cohorts; the updated Danish standardized incidence ratio remained statistically significantly elevated, but there were no additional cases observed during the extended follow-up

period, including an additional 3788 person-years. Therefore, the observation from Denmark may likely be associated with other exposures than TCE or may simply be due to chance.

The major strengths of this study are the similar sampling strategies, which enabled pooling of workers across the subcohorts, and the prospective design, in which cohort members were selected because of documented metabolic evidence of exposure to TCE before diagnosis. Moreover, the study has a long follow-up period (49% of monitored workers have been followed for more than 30 years). Further, reliable nationwide registers provided virtually complete information on vital status and cancer incidence. Finally, the subcohorts were, compared with studies from other countries, derived from populations with relatively homogeneous ethnicity and socioeconomic conditions, which likely limits confounding by these factors.

Although this pooled study provides the largest cohort with individual TCE exposure documented by biological measurements, including almost 1000 cancers, the study has limited statistical power to detect associations of specific cancers of modest magnitude (eg, a relative risk of 1.3 for kidney cancer), as calculated in the three independent meta-analyses of TCE exposure and kidney cancer risk (28–30). Other limitations of this study include lack of information on potential confounders and the absence of information on duration of TCE exposure, which hinders calculation of cumulative dose–response estimates.

In conclusion, our pooled study of documented TCE-exposed workers provides some evidence for an increased risk of liver cancer, although confounding by other exposures cannot be ruled out. Evaluation of a possible modest risk for kidney cancer and non-Hodgkin lymphoma requires studies with greater statistical power. Finally, our observation of increased cervical cancer risk warrants further investigation by inclusion of data on potential socioeconomic confounders and participation in organized screening.

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Supplementary Materials

Supplementary Methods

The cohort from Finland is based on a database of workers who were monitored by the Finnish Institute of Occupational Health for U-TCA after exposure to TCE during the period from 1965 through 1982 (1;2). In total, 3,085 subjects (1,696 men, 1,389 women) with 2.4 measurements per subject on average were included in the study and followed-up for cancer. A temporal decline in measurement levels was observed during the period. Before 1970 the median U-TCA level was slightly higher for men (13-15 mg/L) than for women (10-13 mg/L), afterwards the opposite situation occurred (1).

The Swedish cohort is based on historical laboratory files from workers enrolled in a monitoring program for U-TCA, offered to customer companies by the Swedish producer of TCE (3-5). In total, 1,668 exposed workers (1,419 men, 249 women) from 115 different companies, which had used the surveillance service at least once between 1955 and 1975, were identified from the laboratory files and included in the study. The level of U-TCA was below 50 mg/L (corresponding to an eight hours' time-weighted average exposure concentration of 110 mg/m²) in 81% of the workers during the about 20 year period with measurements (3). For each study participant, there was only computerized information about the calculated individual average U-TCA measurement level rather than information on each measurement. Information about first and last registered year of measurement was also available (4).

The Danish cohort was primarily established from paper files of 2,397 U-TCA measurements performed by the Danish Institute of Occupational Health in the period from 1947 to 1985 (6). The measurements were performed in workers at 275 companies, and on average 2.2 U-TCA measurements were available per worker. In addition, files for a total of 472 measurements of the individual concentration of TCE in the breathing zone were available for the period 1974 to 1989 (7). It was possible to identify in total 661 men and 139 women from in total 1826 measurement files (1627 U-TCA; 199 air measurements) based on name, residence, date of birth or personal identification number (8). These 800 exposed subjects were included in the study. The median concentration of U-TCA decreased during the almost 40 years period with measurements from about 30 mg/L before 1960, to about 5 mg/L in the 1980s (9). The

breathing zone measurements, collected in the period 1974 to 1989, correspond to a median U-TCA level of 12 mg/L (6).

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Supplementary Table 1. Relative risk (SIR) of selected cancers among Danish, Swedish and Finnish workers exposed to trichloroethylene (TCE), by age at first known urinary TCA-measurement.*

Cancer	Age at first known urinary TCA-measurement (years)	Men				Women				Total			
		Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
Esophagus	< 35	1	1.94	0.52	0.01 to 2.87	0	0.27	-	0 to 13.7	1	2.21	0.91	0.11 to 3.27
	35-47	3	2.37	1.27	0.26 to 3.70	0	0.75	-	0 to 4.92	3	3.12	0.96	0.20 to 2.81
	≥ 48	7	4.17	1.68	0.68 to 3.46	1	1.22	0.82	0.02 to 4.57	8	5.39	1.48	0.64 to 2.92
Liver & billiary passages	< 35	5	2.48	2.02	0.66 to 4.70	2	0.96	2.08	0.25 to 7.53	7	3.44	2.03	0.82 to 4.19
	35-47	4	3.74	1.07	0.29 to 2.74	5	2.67	1.87	0.61 to 4.37	9	6.41	1.40	0.64 to 2.67
	≥ 48	16	6.97	2.30	1.31 to 2.70	4	3.49	1.15	0.31 to 2.93	20	10.46	1.91	1.17 to 2.95
Cervix	< 35			-		3	1.90	1.58	0.33 to 4.61	3	1.90	1.58	0.33 to 4.61
	35-47			-		7	2.37	2.95	1.19 to 6.09	7	2.37	2.95	1.19 to 6.09
	≥ 48			-		6	2.64	2.27	0.83 to 4.95	6	2.64	2.27	0.83 to 4.95
Kidney	< 35	4	5.91	0.68	0.78 to 1.73	1	1.63	0.61	0.02 to 3.42	5	7.54	0.66	0.22 to 1.55
	35-47	10	7.20	1.39	0.67 to 2.55	3	3.46	0.87	0.18 to 2.53	13	10.66	1.22	0.65 to 2.09
	≥ 48	10	10.29	0.97	0.47 to 1.79	4	3.29	1.22	0.33 to 3.11	14	13.58	1.03	0.56 to 1.73
Non-Hodgkin lymphoma	< 35	10	6.17	1.62	0.78 to 2.98	2	2.29	0.87	0.11 to 3.15	12	8.46	1.42	0.73 to 2.48
	35-47	8	5.99	1.34	0.58 to 2.63	1	3.72	0.25	0.01 to 1.50	9	9.71	0.93	0.42 to 1.76
	≥ 48	14	8.42	1.66	0.91 to 2.79	3	3.55	0.85	0.17 to 2.47	17	11.97	1.42	0.83 to 2.27

*All statistical tests were two-sided and based on Byar's approximation. SIR = Standardized Incidence Ratio; Obs: number of cases; Exp: expected number of cases; CI = confidence interval.

Supplementary Table 2. Relative risk (SIR) of selected cancers among Danish, Swedish and Finnish workers exposed to trichloroethylene (TCE), by calendar period at first known urinary TCA-measurement*

Cancer	Period of first known urinary TCA-measurement	Men				Women				Total			
		Obs	Exp	SIR	95%CI	Obs	Exp	SIR	95%CI	Obs	Exp	SIR	95%CI
Oesophagus	< 1965	2	1.53	1.31	0.16 to 4.72	1	0.10	10.0	0.25 to 55.7	3	1.63	1.84	0.38 to 5.38
	1965-1979	8	6.63	1.21	0.52 to 2.38	0	2.07	-	0 to 1.78	8	8.70	0.92	0.40 to 1.81
	≥ 1980	1	0.32	3.13	0.08 to 17.4	0	0.06	-	0 to 61.5	1	0.38	2.63	0.07 to 14.7
Liver & biliary passages	< 1965	3	2.42	1.24	0.26 to 3.63	0	0.31	-	0 to 11.9	3	2.73	1.10	0.23 to 3.21
	1965-1979	22	10.40	2.12	1.33 to 3.20	11	6.61	1.66	0.82 to 2.98	33	17.01	1.94	1.34 to 2.72
	≥ 1980	0	0.36	-	0 to 10.20	0	0.18	-	0 to 20.5	0	0.54	-	0 to 6.83
Cervix	< 1965			-		3	0.63	4.78	0.98 to 13.9	3	0.63	4.78	0.98 to 13.9
	1965-1979			-		11	5.95	1.85	0.93 to 3.31	11	5.95	1.85	0.93 to 3.31
	≥ 1980			-		2	0.34	5.88	0.71 to 21.2	2	0.34	5.88	0.71 to 21.2
Kidney	< 1965	4	3.92	1.02	0.28 to 2.61	1	0.39	2.56	0.06 to 14.3	5	4.31	1.26	0.38 to 2.71
	1965-1979	19	18.75	1.01	0.61 to 1.58	7	7.70	0.91	0.37 to 1.87	26	26.45	0.98	0.64 to 1.44
	≥ 1980	1	0.73	1.37	0.03 to 7.63	0	0.27	-	0 to 13.7	1	1.00	1.00	0.03 to 5.57
Non-Hodgkin lymphoma	< 1965	7	2.98	2.35	0.94 to 4.84	0	0.37	-	0 to 9.97	7	3.35	2.09	0.84 to 4.31

	1965-1979	23	16.90	1.36	0.86 to 2.04	6	8.86	0.68	0.25 to 1.47	29	25.76	1.13	0.75 to 1.62
	≥ 1980	2	0.71	2.82	0.34 to 10.2	0	0.36	-	0 to 10.2	2	1.07	1.87	0.23 to 6.75

* All statistical tests were two-sided and based on Byar's approximation. SIR = Standardized Incidence Ratio; Obs: number of cases; Exp: expected number of cases; CI = confidence interval.