Exhibit 225

Association Between Kidney Cancer and Occupational Exposure to Trichloroethylene

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Objective: This study investigates the association between occupational exposure to trichloroethylene (TCE) and kidney cancer, as this correlation has been questioned. **Methods:** The incidence of cancers was studied in a dynamic cohort of 997 male workers who for many years had been occupationally exposed to TCE. **Results:** During a 50-year observation period, 13 cases of kidney cancer were observed (7.5 expected) with a standardized incidence ratio of 1.7 and a 95% confidence interval of 1.0 to 3.0. Four other cases, not included in the SIR analysis, were also observed. Long-term TCE exposure was positively confirmed for 14 of the 17 incident cases. There is reason to assume that the remaining cases also had been exposed to TCE. **Conclusions:** The present study supports the view that TCE is a kidney carcinogen.

In 2012, the International Agency for Research on Cancer classified trichloroethylene (TCE) as carcinogenic to humans on the basis of sufficient evidence for kidney cancer.[1,2] One year later, a large cohort with long-term follow-up based on workers from Denmark, Finland, and Sweden observed no increased risk of kidney cancer based on 32 cases.[3] In that study, the TCE exposure was confirmed by measurement of a TCE metabolite in the urine. The present study of cancer risk is based on a cohort of 997 male potential TCE-exposed workers from Norway. During follow-up from 1960 to 2010, 215 cancer cases occurred versus 214.9 expected cases. Concerning kidney cancer, the relative risk was 1.7 (1.0 to 3.0). TCE-exposure was by interview confirmed in 14 of 17 kidney cancers.

METHODS

The train repair and maintenance workshop at Marienborg in the city of Trondheim in Central Norway was established in the early 1920s. Eventually, all kind of repair and maintenance on rolling railroad equipment was carried out there. In the early decades, all kinds of handcraft were performed next to the mechanical work. From the 1950s, the work was gradually more specialized toward mechanical repair and the maintenance of heavy diesel equipment.

The Norwegian State Railroad Company (NSB) that owned the workshop did not have a complete track of all the workers' employment periods or their various departmental affiliations. For the formation of the cohort, a list of employees who had been employed after 1954 was obtained from the trade union that organized all the workers. By multiple cross checking of other paper archives and electronic lists, 1077 male candidates were identified and included in the cohort. Of these, 35 were excluded from further analysis because they had worked for less than one year, and 45 others were excluded because of lacking or wrong employment information. Consequently, the final cohort consisted of 997 male workers who, at some time from 1954 on, had been employed as blue collar workers for more than one year.

The cleaning, painting, maintenance, testing, and repair of heavy diesel engines and spare parts involves exposure to welding fumes, paints, cleaning fluids, diesel exhaust, and organic solvents. Owing to its degreasing and nonflammable properties, TCE was used extensively for various operations, but mainly in the machinery workshop. In general, the exposure to toxic chemicals decreased with time, and in the mid-1990s, the use of TCE was terminated.

The average employment period in the cohort was as long as 26 years. Most of the employees worked in various departments and under differing exposure conditions during their employment period. As the exposure information was sparse, it has not been possible to undertake individual exposure assessments for the workers. In order to look into specific exposures for some of the workers, interviews were performed with a number of both former and current employees.

Statistical Analysis

The individual calculation of person years started on the date of first registered employment. Follow-up ended on the date of death, date of cancer diagnosis, or on December 31, 2010, whichever came first. Date of death or emigration was obtained by linkage to Statistics Norway (SSB).

The incidence of cancer in the cohort during the follow-up was ascertained by linkage to the Norwegian Cancer Registry. The linkage was done using the unique social security number that has been assigned to all Norwegian citizens since 1964.

National site-specific cancer rates for men by 5-year age groups, and 5-year calendar periods were applied to the person years under observation. Standardized incidence ratios (SIRs), the ratio between observed, and expected number of cancers and corresponding 95% confidence intervals (95% CIs) were calculated for cancer overall and for all of each cancer site.

Analyses were performed using STATA version 13.1 (StataCorp LP, College Station, TX).

The study was approved by the Ethical Committee for Medical Research (Approval No. 2012/1235).

RESULTS

Table 1 summarizes the incidence of all cancer types with three or more incident cases during the observation period from 1960 to 2010. The figures were close to unity for all cancers together and for most specific types of cancer, except for kidney cancer with 13 cases observed and 7.5 expected (SIR 1.7 with 95% CI 1.0 to 3.0) and lung cancer with 32 cases observed and 26.6 expected (SIR 1.2 with 95% CI 0.9 to 1.7).

In addition to the 13 cases of kidney cancer included in the primary SIR analysis, four other cases were observed. Two of these were among those excluded from the original list of 1077 workers. The other two were diagnosed after 2010.

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TABLE 1. Incidence of Cancers With More Than Three Observed Cases and the Standardized Incidence Ratios (SIRs) for These Sites in a Dynamic Cohort of 997 Workers at a Train Repair Workshop Observed in the Period From 1960 to 2010

Location	Observed	Expected	SIR	95% CI
Total cancer	215	214.9	1.0	0.8–1.2
Esophagus	3	2.5	1.2	0.4–3.8
Stomach	11	11.7	0.9	0.5–1.7
Colon	17	18.3	0.9	0.6–1.5
Rectum	13	11	1.2	0.7–2.0
Pancreas	6	6.6	0.9	0.4–2.0
Larynx	3	2.4	1.3	0.4–3.9
Lung and bronchus	32	26.6	1.2	0.9–1.7
Kidney	13	7.5	1.7	1.0–3.0
Urinary bladder	11	15.5	0.7	0.4–1.3
Skin (malignant melanoma)	6	7.7	0.8	0.4–1.7
Skin (other)	12	9.4	1.3	0.7–2.3
Brain	4	5.6	0.7	0.3–1.9
Lymphatic tissue	5	7	0.7	0.3–1.7
Bone marrow	8	9.7	0.8	0.4–1.7
Prostate	46	49.9	0.9	0.7–1.2

95% CI, 95% confidence interval.

As exposure to TCE had occurred at several workshop locations, all the 17 cases were examined closely with respect to occupational exposure to TCE.

Table 2 gives an overview of the altogether 17 cases of kidney cancer that had occurred in the original group of 1077 workers. The two with unconfirmed end of exposure are numbers 12 and 13, and the two diagnosed after 2010 are numbers 16 and 17. By interviews and cross-checking, it was confirmed that in 14 of the 17 incident cases of kidney cancer, the workers had been occupationally exposed to TCE at the workshop, and that there is reason to assume that in the remaining three cases, the workers had also been exposed to TCE.

DISCUSSION

A total of 17 cases of kidney cancer were identified in a cohort of former train repair workshop workers. Among them, 14 had a confirmed occupational exposure to TCE. On the basis of extensive interviews, there is reason to assume that the remaining four workers had also been occupationally exposed to TCE.

In the Nordic study of TCE workers published in 2013, the authors did not find an increased risk of kidney cancer except for a nonstatistically significant increase for workers with measured values of trichloroacetic acid in urine (U-TCA) of more than 50 mg/L (adjusted hazard rate ratio 2.04, 95 % CI 0.81 to 5.17).[3] This was contradictory to the conclusions in other epidemiological studies.[4–10] The anticipated explanation for the generally negative findings in regard to kidney cancer was that the levels and/or time of exposure to TCE had been relatively low in all three countries. Exposure levels in the current cohort are not known, but the employment time with exposure to TCE was certainly longer with a median of 19 years up to 1995. The exposure indicators given in

TABLE 2. Occupational TCE Exposure and Diagnosis in 17 Train Repair Workshop Workers With Kidney Cancer Diagnosed From 1960 to 2012

No.	Workplace and/or Occupation	Confirmed Exposure to TCE*	Year of Birth	Year of First TCE Exposure†	Year of Last TCE Exposure	Year of Kidney Cancer Diagnosis
1	Machinery workshop	1	1931	1947	1992	2006
2	Foreman, electricians	_	1904	1925	1963	1968
3	Machinery workshop	1	1933	1949	1993	1996
4	Machinery workshop/ Blacksmith	1	1923	1941	1986	1979
5	Machinery workshop	2	1933	1950	1993	2005
6	Train maintenance	1	1938	1982	1995	2008
7	Machinery workshop	1	1927	1945	1992	1981
8	Machinery workshop	1	1917	1940	1978	1993
9	Machinery workshop/ Lathe operator	1	1908	1942	1972	1978
10	Machinery workshop/ Plate smith	1	1920	1945	1980	1999
11	Administration	1	1936	1964	1995	1999
12	Carpenter, painter	_	1902	1955	_	2008
13	Machinery workshop/ Lathe operator	_	1925	1943	_	1989
14	Machinery workshop/ Painter	2	1954	1986	1995	1972
15	Machinery workshop and engine shed	1	1932	1950	1989	1970
16	Machinery workshop	1	1958	1980	1994	2011
17	Machinery workshop/ Plumber	2	1927	1945	1987	2012

*1, Light, but daily; 2, Moderate and daily; _, no information available.
†Same as year of employment.

Table 2 are for the greater part based on working conditions as they were in the seventies and eighties. Because there is reason to assume that working conditions have improved over the decades, the exposure data given for the earliest years are more likely to be underestimated than overestimated.

A slight increase in lung cancer was observed in the cohort. Exposure to asbestos, which was commonly used until the 1980s, is probably the main contributor to this. The two cases of malignant mesothelioma of the pleura that were observed in the cohort, against 0.9 expected, are also indicators of asbestos exposure. Asbestos exposure has been considered a risk factor for kidney cancer, but in a meta-analysis published in 2000, it was considered unlikely that asbestos exposure was responsible for an important increase in kidney cancer risk.[11]

Tobacco smoking is a well-documented cause of kidney cancer, but no information on smoking habits was available for this cohort. As the observed SIRs for other tobacco-related cancers such as cancer of the esophagus, stomach, colon, rectum, pancreas, larynx, urinary bladder, or lymphatic tissue are all close to unity, an overall assessment indicates that smoking habits do not affect the risk estimates.

As in other studies of TCE exposure and cancer, we cannot exclude possible confounding from other occupational exposures that have been in some way associated with kidney cancer, such as arsenic and cadmium compounds, coke-oven emissions, petroleum products, or tetrachloroethylene, but we have no information indicating that the workers in the current cohort have experienced such exposures. The workers have certainly been exposed to carcinogens from diesel engine exhaust, chromium, and nickel, but such exposures have not been associated with kidney cancer.[12]

It can be noted that the age of the cohort members when kidney cancer was diagnosed was relatively high, that is, between 54 and 84 years. Also, the latency from first exposure to diagnosis was long, between 17 and 59 years. Some previous studies have taken lag/latency into account with little specific information given. A Danish study has shown that the relative risk for kidney cancer increases with increasing lag time ($\geq$20 years), as well as with the duration of employment ($\geq$5 years), and with the year of first employment (before 1970).[13] Thus, there seems to be no contradiction between exposure to TCE and the development of kidney cancer and long latency or high age at the time of diagnosis.

CONCLUSIONS

In the present study of 997 train repair workshop workers with long employment and follow-up time, we were able to show an increased risk of kidney cancer of borderline statistical significance. We have also shown that most workers who acquired kidney cancer had been exposed to TCE for many years. Together with other evidence, this supports the view that TCE is a kidney carcinogen, and that an association can also be found in workers from the Nordic countries.

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