

Occupational risk factors for renal-cell carcinoma in Denmark

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OBJECTIVES — Risk factors for renal-cell carcinoma, the most frequent type of kidney cancer, remains enigmatic. Time trends in incidence and changes in the regional distribution of this cancer are suggestive of environmental risk factors. This study reports on occupational risk factors for renal-cell carcinoma in Denmark.

METHODS — In a population-based study, 365 persons with histologically verified renal-cell carcinoma and 396 referents were interviewed. Information was collected on occupation, education, and occupational exposure to a number of suspected substances, including hydrocarbons, asbestos, and radiation.

RESULTS — Risk of renal-cell carcinoma was found to be associated with employment as a truck driver, exposure to gasoline, other hydrocarbons, and insecticides and herbicides. The risk of renal-cell carcinoma was higher in the lower socioeconomic strata for both the men and the women. Nonsignificantly elevated risks were observed for employment in oil refineries, gasoline stations, and the iron and steel industry. No association was found for exposure to radiation or for employment in industries such as leather manufacturing and health care, which have previously been linked to an increased risk of renal-cell carcinoma.

CONCLUSIONS — The risk of renal-cell carcinoma is increased in lower socioeconomic strata, and previously identified or suspected risk factors do not explain the excess in risk. This study adds additional support to the hypothesis of a link between renal-cell carcinoma and hydrocarbons and also demonstrates the need for further studies on occupational risk factors for renal-cell carcinoma.

KEY TERMS — hydrocarbons.

Renal-cell carcinoma, which constitutes 70–80% of all kidney cancer, is a numerically important cancer with a relatively poor prognosis, and its etiologic factors are largely unknown. High incidence rates are found in Scandinavia, Western Europe, and North America. In Denmark the incidence has been increasing, although more moderately than in other high-incidence areas (1, 2). Known and suspected risk factors include smoking, obesity, certain medications, and several occupational exposures, for example, to hydrocarbons, coke oven fumes, and asbestos (3). As part of an international collaborative study, a Danish case-referent study of incident cases of renal-cell carcinoma was conducted from 1989 to 1992. Herein we present our findings from the analysis of the occupational data collected in this population-based case-referent study.

Subjects

Cases were identified from notifications to the Danish Cancer Registry and from repeated searches in the files of all pathology departments in Denmark. Histologically confirmed cases involving persons between 20 and 79 years of age who were born and living in Denmark were included. Altogether 482 persons with renal-cell carcinoma were identified, but 44 (9.1%) died before they could be contacted, 26 (5.4%) were too ill, 33 (6.8%) refused to be interviewed, and 11 (2.3%) were unavailable for contact. The referents were matched to the cases as to gender and age in five-year intervals; they were drawn from the Central Population Register.

As the initial reference group was skewed with respect to region, the methods used to develop the Central Population Register were examined. This investigation revealed that, in contrast to what was intended, the sequence of persons born on a particular date was related to the region where the individual lived in 1968, when the system was implemented. To correct for this skewness, the number of referents from regions overrepresented was reduced by random sampling, while the number of referents from regions underrepresented was supplemented by an additional random sample. Of the 500 identified ref-

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erents, 72 (14.4%) refused to be interviewed, 20 (4.9%) were too ill, and 12 (2.4%) were unavailable for contact.

Methods

The remaining 368 cases and 396 referents were interviewed by trained interviewers in the subjects' home. Information on education, past and present occupation, exposure to several suspected occupational risk factors, medication use, smoking history, medical history, and diet was elicited.

Both the most recent and the longest held occupation was recorded. Occupation was coded according to the International Standard Classification of Occupation (4), and industry was coded according to the International Standard Industrial Classification (5). From the literature several suspected high-risk occupations and exposures were identified, and information on these occupational exposures was supplemented with information on the subjects' workplace and occupational duties during which the exposure took place. Occupational exposures to various substances were only considered if the job that resulted in exposure lasted one year or more and if the exposure took place 10 years or more before the interview. As a control for the potential confounding effect of cigarette smoking and obesity, terms for these variables were included in the logistic regression models. Body mass index (BMI) was calculated as weight/height² for the men and as weight/height^{1.5} for the women (6) as a measure of relative weight, and quartiles were calculated for each gender on the basis of the distribution among the referents.

Pack-years were calculated as the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked; the subjects were then grouped into 0, 1–19, 20–39, and ≥40 pack-years.

The subjects' socioeconomic status was estimated according to a modification of the definitions developed by the Danish National Institute for Social Research (7). Three strata were defined as managerial or administrative workers and academics; teachers, nurses, clerical workers; and skilled and unskilled workers. Because the socioeconomic status for married women may be better estimated by the socioeconomic status of their husbands for this age group, the socioeconomic status of the husband was used if it ranked higher than the woman's. The measure of association used was the odds ratio estimated in unconditional logistic regression models (8).

Results

Table 1 shows the distribution of the patients and referents by gender, age, and socioeconomic status. As gender and age were matching variables, the distri-

Table 1. Distribution of cases and referents by gender, age, and socio-economic status.

Gender	Cases	Referents	OR ^a	OR ^b
Men				
Age (years)				
≤49	39	45	·	·
50–59	47	47	·	·
60–69	68	78	·	·
70–79	72	67	·	·
Socioeconomic status				
I	41	65	1	1
II	63	68	1.5	1.5 (0.9–2.6)
III	120	103	1.8	1.8 (1.1–3.0)
Women				
Age (years)				
≤49	17	21	·	·
50–59	27	31	·	·
60–69	46	53	·	·
70–79	52	54	·	·
Socioeconomic status				
I	32	60	1	1
II	55	49	2.1	1.9 (1.0–3.5)
III	54	49	2.1	1.7 (0.9–3.2)

^a Odds ratio estimated in model with age.

^b Odds ratio estimated in model with age, body mass index, and smoking (with 95% confidence interval in parentheses).

bution was identical among the cases and referents. A relatively strong effect was found for socioeconomic status in that individuals with mostly manual work histories were at an increased risk. A weaker association was found with short education (data not shown).

Table 2 gives the number of cases and referents employed 10 or more years before the diagnosis in a priori high-risk industries, with the corresponding odds ratios. A nonsignificantly increased risk was found for employment in oil refineries and dry cleaning, the latter for both genders. Furthermore, no excess risk was found for employment in wool spinning, the military, soap manufacturing, or wood processing, or for having worked as a welder or toolmaker (data not shown).

Odds ratios for a priori high-risk occupations are presented in table 3. A significantly elevated odds ratio was observed for truck drivers and plumbers, but no increased risk was seen for health care workers, who included physicians, nurses, veterinarians, and dentists. Very few subjects had been employed in leather manufacturing or as architects. Pressmen, and bricklayers had a nonsignificantly increased risk of renal-cell carcinoma.

The odds ratios for self-reported exposures to various hydrocarbons, asbestos, insecticides, herbicides, and radiation are presented in table 4. Increased risks were seen for exposure to several forms of hydrocarbons, including gasoline, solvents, and cutting oils or mists. An excess of cases involved exposure to asbestos, herbicides, and insecticides, while radiation

Table 2. Employment in a priori high-risk industries 10 or more years before the interview. (95% CI = 95% confidence interval)

Industry of employment	Men				Women			
	Cases	Referents	OR ^a	95% CI	Cases	Referents	OR ^a	95% CI
Oil refinery	4	1	3.9	0.4–37	—	—	0	·
Gasoline station	10	6	1.8	0.6–5.1	—	2	0	·
Blast furnace	10	8	1.2	0.5–3.3	1	—	0	·
Iron and steel industry	31	26	1.4	0.8–2.4	2	2	1.0	0.1–8.2
Dry cleaning	2	1	2.3	0.2–27	2	1	2.9	0.3–33
Printing	8	8	1.1	0.4–3.1	3	4	1.1	0.2–5.2
Dairy industries	6	4	1.5	0.4–5.7	—	3	0	·

^a Odds ratio estimated in model including terms for age, body mass index, and smoking.

Table 3. Employment in a priori high-risk occupations 10 or more years prior to the interview. (95% CI = 95% confidence interval)

Type of employment	Men				Women			
	Cases	Referents	OR ^a	95% CI	Cases	Referents	OR ^a	95% CI
Health care worker	1	7	0.2	0.02–1.4	15	17	1.3	0.6–2.7
Leather good maker	1	—	0	·	—	1	0	·
Architect	3	2	1.9	0.3–12	—	—	0	·
Truck driver	24	7	3.1	1.3–7.7	—	1	0	·
Bricklayer	9	6	1.6	0.5–4.6	—	—	0	·
Pressman	5	1	5.6	0.6–48	1	1	0.9	0.1–17
Plumber	8	1	8.5	1.1–66	—	—	0	·

^a Odds ratio estimated in model including terms for age, body mass index, and smoking.

Table 4. Occupational exposure to a priori high-risk agents 10 or more years before the interview. (95% CI = 95% confidence interval)

Exposure	Men				Women			
	Cases	Referents	OR ^a	95% CI	Cases	Referents	OR ^a	95% CI
Gasoline	28	16	2.1	1.1–4.1	3	3	0.9	0.2–5.0
Solvents	50	39	1.5	0.9–2.4	16	3	6.4	1.8–23
Cutting oils	26	14	2.1	1.0–4.3	2	1	1.8	0.2–21
Asbestos	30	21	1.6	0.9–2.9	2	—	0	·
Insecticides	11	6	2.2	0.8–6.3	3	1	5.7	0.6–58
Herbicides	13	8	1.7	0.7–4.3	3	1	5.7	0.6–58
Radiation	—	4	0	·	1	3	0.5	0.05–5.4

^a Odds ratio estimated in model including terms for age, body mass index, and smoking.

exposure among men was reported only by the referents.

Odds ratios are presented in table 5 for duration of exposure to gasoline, other hydrocarbons, asbestos, insecticides, and herbicides. Uniformly increased risks were found for exposure to hydrocarbons and asbestos (nonsignificant), while the increased risk for insecticides and herbicides was observed only for those with more than 20 years of exposure. Including terms for body mass index and smoking in the regression models did not change the risk estimates. The increased risk for low socioeconomic status remained after adjustment for exposures and employment associated with an increased risk in our study, suggesting the existence of occupational risk factors which were not identified in this study (9).

Discussion

Our study has confirmed previous findings of associations between renal-cell carcinoma and occupational exposure to various hydrocarbons and asbestos. We were, however, unable to confirm reports of increased risk among physicians, dentists, welders, and wood workers. Although recall bias is always a concern when associations with known hazardous substances are being investigated, the finding that radiation, probably the most widely known carcinogen, was reported by referents rather than by the persons with renal-cell carcinoma suggests that recall bias was negligible. Selection bias was limited because of the use of central population registers and a response rate of approximately 80% for the case and reference groups. The distribution of the cases by socioeconomic status matched that of all cases of

Table 5. Role of occupational exposure by duration. (95% CI = 95% confidence interval)

Exposure	Men				Women			
	Cases	Referents	OR ^a	95% CI	Cases	Referents	OR ^a	95% CI
Gasoline								
No exposure	196	221	1	·	138	156	1	·
<20 years	14	8	2.3	0.9–5.7	3	3	1.1 ^b	·
≥20 years	16	8	2.4	1.0–5.8	1	—	0	·
Other hydrocarbons								
No exposure	137	178	1	·	122	153	1	·
<20 years	47	31	2.1	1.2–3.6	13	5	3.8	1.3–11.2
≥20 years	42	28	2.0	1.2–3.5	7	1	7.8	0.9–68
Asbestos								
No exposure	196	215	1	·	133	149	0	·
<20 years	16	10	1.8	0.8–4.2	1	—	0	·
≥20 years	14	11	1.4	0.6–3.2	1	—	0	·
Insecticides/herbicides								
No exposure	209	227	1	·	131	148	1	·
<20 years	7	6	1.3	0.4–4.1	2	—	0	·
≥20 years	10	3	3.9	1.0–15	2	1	2.3 ^b	·

^a Odds ratio estimated in model including terms for age, body mass index, and smoking.

^b Crude odds ratio.

renal-cell carcinoma notified to the Danish Cancer Registry during the ascertainment period.

The fact that several of the associations were present among both the men and the women adds credibility to the findings. The main limitation of our study therefore is the relatively low number of exposed persons in the case and reference groups, a common problem in population-based studies of occupational factors.

Gasoline and other hydrocarbons

An animal study on the inhalation of gasoline vapors in which male rats developed renal-cell carcinoma (10) has prompted several investigators to examine the association in human populations, although the significance of an excess of renal-cell carcinoma among male rats has been called into question in terms of its relevance to humans (11). In general, follow-up studies of refinery workers and other petroleum-exposed workers have found little evidence to support an association with renal-cell carcinoma (12, 13). A case-referent study from Minnesota found a suggestive increase in risk for gasoline station attendants and for individuals who had been exposed to petroleum, tar, and pitch products (14, 15). To date, most epidemiologic studies examining gasoline exposure or gasoline-associated occupations have not found an association with renal-cell carcinoma (16). However, a recent study from Finland has reported a twofold risk for exposure to gasoline on the job (17). Our study, in which only exposure for more than a year and 10 years prior to interview was considered, also provides support for a link between gasoline and renal-cell carcinoma. We also observed increased risk with exposure to other hydrocarbons, such as solvents and cutting oils.

Asbestos

Several cohort and case-referent studies have found increased risks associated with exposure to asbestos (18–20), including a recent case-referent study from Australia (21). Furthermore, animal experiments have demonstrated asbestos deposits in the kidney of exposed mice and rats (22). In autopsy studies, asbestos has been found in several nonrespiratory and nondigestive organs, including the kidney (23). Although nonsignificant, our findings add further evidence that asbestos increases the risk of renal-cell carcinoma.

Insecticides and herbicides

The finding of an increased risk associated with long-term exposure to insecticides and herbicides was surprising, since farmers usually have a decreased risk of renal-cell carcinoma (24, 25). A total of 31 individuals reported exposure to insecticides, herbicides, or both. Farming, work in nurseries, and logging were the usual occupations of 13 cases and referents, while the remainder had different usual occupations, ranging from mail clerks and drivers to secretaries, teachers, and salespersons. These persons were asked to describe the circumstances of their exposure. Spraying with insecticides and herbicides usually takes place under circumstances in which other potential risk factors are present. One such risk factor is toxins produced by molds. Aflatoxin and ochratoxin A have been linked to nephropathy and have been shown to induce renal-cell carcinoma in rodents (26, 27). However, the odds ratio for employment in industries where molds can be present, such as farming, work in nurseries, logging, and grain milling, was not increased (odds ratio = 0.8), this finding is consistent with that of

other studies (15, 24). Additional research is needed to clarify this association.

Dry cleaning

The small number of exposed individuals (4 cases, 2 referents) limits our finding for this industry. Several earlier proportional mortality studies and a case-referent study have found indications of an increased risk (28–31). However, a relatively large cohort study of dry cleaning workers showed no increased risk for kidney cancer (32), while a recent Australian case-referent study has reported a 2.5-fold risk for employment in the dry-cleaning industry (21). Our results cannot clarify the conflicting findings for this occupation.

Other occupations

Increased risks have been observed for several occupations in linkage studies in which the large number of comparisons makes chance a possible explanation for some of the observed associations. A Swedish linkage study found increased risks among health care workers (24). This finding was confirmed neither in the Australian study nor in our study. Likewise, a report of increased incidence among architects (33) was not corroborated by our findings, nor by a linkage study based on Swedish data (34). We did find a significant increased risk for truck drivers. Truck drivers are exposed to hydrocarbon fumes and other agents. Of the 33 exposed men with renal-cell carcinoma and male referents, five were exposed to gasoline, six to other petroleum products, and two indicated that their occupational activities included exposure to asbestos. Adjusting for body mass index or smoking did not materially affect the risk estimate. Our results are consistent with the significant threefold risk reported for truck drivers in Missouri (35).

A significant inverse association was observed for socioeconomic status. The association was the most pronounced for women, and when the status was based on usual occupation (9). Although we have identified several exposures and occupations that carry an increased risk for renal-cell carcinoma, the socioeconomic status finding suggests the presence of other risk factors related to occupation and possibly to life-style factors which remain unidentified. Further research on the association of socioeconomic status with renal-cell carcinoma is warranted, since it may shed light on as yet unknown risk factors.

In summary, the results of our study on occupational risk factors for renal-cell carcinoma indicate that exposure to gasoline and other hydrocarbons increase risk. Exposure to asbestos was also associated with increased risk, but this association did not reach statistical significance. Further research is needed to evaluate the link with gasoline, since it is a widespread exposure. Employment as a truck driver has also been associated with significant excess risk,

although the exposure that this may reflect is unclear. Exposure to insecticides and herbicides should be examined further in other investigations to evaluate whether this association is causal. We also observed a strong inverse association between the risk of renal-cell carcinoma and socioeconomic status that suggests the existence of unidentified occupational risk factors that may be stronger than the ones which have been identified to date.

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