Renal cell carcinoma and occupational exposure to chemicals in Canada

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This study assesses the effect of occupational exposure to specific chemicals on the risk of renal cell carcinoma in Canada. Mailed questionnaires were used to obtain data on 1279 (691 male and 588 female) newly diagnosed, histologically confirmed renal cell carcinoma cases and 5370 population controls in eight Canadian provinces, between 1994 and 1997. Data were collected on socio-economic status, smoking habit, alcohol use, diet, residential and occupational histories, and years of exposure to any of 17 chemicals. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived using unconditional logistic regression. The study found an increased risk of renal cell carcinoma in males only, which was associated with occupational exposure to benzene; benzidine; coal tar, soot, pitch, creosote or asphalt; herbicides; mineral, cutting or lubricating oil; mustard gas; pesticides; and vinyl chloride. Compared with no exposure to the specific chemical, the adjusted ORs were 1.8 (95% CI = 1.2–2.6), 2.1 (1.3–3.6), 1.4 (1.1–1.8), 1.6 (1.3–2.0), 1.3 (1.1–1.7), 4.6 (1.7–12.5), 1.8 (1.4–2.3) and 2.0 (1.2–3.3), respectively; an elevated risk was also associated with exposure to cadmium salts and isopropyl oil. The risk of renal cell carcinoma increased with duration of exposure to benzene, benzidine, cadmium, herbicides and vinyl chloride. Very few females were exposed to specific chemicals in this study; further research is needed to clarify the association between occupational exposure to chemicals and renal cell carcinoma in females.

Key words: Chemicals; logistic regression; occupational exposure; odds ratio; renal cell carcinoma.

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Introduction

The relationship between occupational exposure to chemicals and renal cell carcinoma (RCC), which constitutes 70% of all kidney cancers, is poorly understood [1]. A number of studies have reported an association with asbestos [2–6]; gasoline [6–10]; dinitrotoluene [11]; polycyclic aromatic hydrocarbons [12]; chlorinated solvents, including trichloroethene [13, 14], perchloroethylene [15] and tetrachlorocarbonate [15]; cadmium [6, 16, 17]; inorganic lead compounds [17–20]; solder fumes [17]; and benzene [17]. However, other studies [21–28] found no relationship for these occupational exposures.

The objective of this study was to evaluate the aetio-

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logical role for RCC of occupational exposure to specific chemicals.

Subjects and methods

This study is part of the National Enhanced Cancer Surveillance System (NECSS), which collected individual data from a population-based sample, including 18 types of cancer, and 5380 population controls between 1994 and 1997, in the Canadian provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Nova Scotia and Newfoundland. The overall methodology for the NECSS has been explained in Johnson *et al.* [29].

Cases

All histologically confirmed incident cases of kidney cancer between 1994 and 1997 were identified by participating provincial cancer registries. Approximately 7% of those diagnosed with kidney cancer were not contacted because the attending physician did not provide consent. Of 1873 questionnaires sent to kidney cancer patients, 1479 were returned, a response rate for patient contact of 79.0%. Of these, 1279 (691 male and 588 female) cases of RCC as defined by ICDO-2 [30] were included in this study.

Controls

In the NECSS, population controls were frequency-matched to the expected distribution of cancer cases by 5 year age group, sex and province. A total of 5380 (2704 males and 2676 females) people without cancer were selected from a random sample of individuals within a province, with an age/sex distribution similar to that of all the cancer cases in the NECSS (i.e. 18 cancer types: liver, testis, pancreas, brain, stomach, bladder, kidney, colon, rectum, prostate, breast, lung, bone, salivary, leukaemia, multiple myeloma, non-Hodgkin's lymphoma and mesothelioma). Provincial cancer registries collected information from controls using the same protocol as for the cases. The strategies for population controls varied by province, depending on data availability and accessibility. In Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan and British Columbia, an age group- and sex-stratified random sample of the province's population was obtained through the Provincial Health Insurance Plans. In Ontario, Ministry of Finance data were used to obtain a stratified random sample. Newfoundland and Alberta used random digit dialling to obtain a population sample.

Of 8105 questionnaires sent to selected potential controls, 573 were returned because of a wrong address. A total of 5380 questionnaires (2704 for males and 2676 for females) were completed, representing 66.4% of controls ascertained and 71.4% (5380/7532) of controls contacted. For the present analyses, 10 controls (eight males and two females) were excluded because their age was missing.

Data collection

The cancer registries identified most cases within 1–3 months of diagnosis through pathology reports. After obtaining physician consent for cases, questionnaires were mailed to the cancer cases and controls by the cancer registries. If the questionnaire was not completed and returned, a reminder postcard was sent out after 14 days and, if necessary, a second copy of the questionnaire at 4 weeks; if there was still no response after 6 weeks, individuals were contacted by telephone in order to complete the questionnaire. Information was collected on socio-economic status, employment history, residential history, height, weight, smoking history, alcohol use, dietary history, physical activity, and use of vitamin or mineral supplements. Data concerning family history of cancer were collected in the province of Ontario only. In addition, the NECSS collected histories of lifetime residential and occupational exposure to environmental tobacco smoke.

The dietary portion of the questionnaire, which examined eating habits over the two previous years, was based on the Block–National Cancer Institute Health Habits and History Questionnaire [31], modified to reflect the Canadian diet in collaboration with Bureau of Biostatistics and Computer Applications, Food Directorate, Health Canada. A 70-question food frequency questionnaire provided data on Canadian eating patterns and the major sources of nutrients in the Canadian diet.

Each subject was also asked about exposure at work (or home) to any of the following 17 specified chemicals: asbestos; arsenic salts; benzene; benzidine; cadmium salts; chromium salts; coal tar, soot, pitch, creosote or asphalt; dyestuffs; mineral, cutting or lubricating oil; herbicides; isopropyl oil; mustard gas; pesticides; radiation sources; vinyl chloride; welding; and wood dust. Exposure was defined as exposed for ≥1 year; subjects reported ever or never exposed, and duration of exposure in years.

Information concerning occupational history was coded to the 1980 Standard Occupation Classification [32]. The codes were converted to social class, defined according to the British Registrar General's Classification [33]: social class I (professional), II (intermediate), III N (skilled non-manual), III M (skilled manual), IV (partly skilled) and V (unskilled). For each person, the total occupational years and the years within each social class were calculated according to lifetime occupational history. The social class with most years reported was selected as the person's social class; where the numbers of years in different social classes were identical, the lowest social class was chosen. In this analysis, social

class was categorized as high (I and II), intermediate (III N and III M) or low (IV and V).

Odds ratios (ORs) and 95% confidence intervals (CIs) were computed as a measure of the relative risk. Unconditional logistic regression analysis was used for multivariate analyses using SAS software [34].

Results

The age distribution of cases and controls by sex is presented in Table 1. About 95% of the cases were >40 years old. Table 2 compares selected demographic characteristics and body mass index (BMI) for cases and controls. For both males and females, cases of RCC reported a lower education level. BMI was associated with increased risk of RCC for both genders. For females, cases were more likely to report low family income and low social class. Income adequacy was not reported for 20.3 and 23.3% of male and 29.6 and 28.6% of female cases and controls, respectively.

The ORs for never/ever occupationally exposed to chemicals are shown in Table 3. After adjusting for 10 year age group, province, education, BMI, pack-years of smoking, alcohol use and total consumption of meat, significantly elevated ORs were observed in males for exposure to benzene; benzidine; coal tar, soot, pitch, creosote or asphalt; herbicides; mineral, cutting or lubricating oil; mustard gas; pesticides; and vinyl chloride. Compared with those not exposed to each specific chemical,

Table 1. Frequency distribution of cases and controls by age and sex

	Cases				*Controls*			
	Males		*Females*		*Males*		*Females*	
Age (years)	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
20–29	2	0.3	3	0.5	164	6.1	64	2.4
30–39	16	2.3	30	5.1	276	10.2	196	7.3
40–49	113	16.4	92	15.6	231	8.5	259	22.3
50–59	185	26.8	149	25.3	400	14.8	585	21.9
60–69	253	36.6	209	35.5	969	35.8	813	30.4
≥70	122	17.6	105	17.8	656	24.2	419	15.6
Total	691	100.0	588	100.0	2696	100.0	2674	100.0

Table 2. Odds ratios for RCC by demographic characteristics and body mass index, NECSS, Canada, 1994–1997

	Men				*Women*			
	Cases (n)	*Controls (n)*	*Age and province adjusted OR (95% CI)*	*P value for trend*	*Cases (n)*	*Controls (n)*	*Age and province adjusted OR (95% CI)*	*P value for trend*
Family income								
Low	78	412	1.0 (ref.)	0.56	122	439	1.0 (ref.)	0.0001
Lower middle	129	459	1.4 (1.0–1.9)		107	449	0.8 (0.6–1.1)	
Upper middle	204	718	1.2 (0.9–1.7)		124	636	0.7 (0.5–0.9)	
High	140	478	1.2 (0.8–1.7)		61	386	0.5 (0.3–0.7)	
Not reported	140	629			174	764		
Education								
1–8 years	136	511	1.0 (ref.)	0.004	124	352	1.0 (ref.)	0.0001
9–13 years	349	1246	0.9 (0.7–1.2)		317	1455	0.6 (0.5–0.8)	
≥14 years	196	898	0.7 (0.5–0.9)		138	831	0.5 (0.4–0.7)	
Not reported	10	41			9	36		
Social class								
High (I and II)	221	814	1.0 (ref.)	0.68	133	778	1.0 (ref.)	0.002
Intermediate (III)	336	1248	1.0 (0.8–1.3)		235	1174	1.1 (0.9–1.4)	
Low (IV and V)	116	485	1.0 (0.8–1.4)		106	390	1.6 (1.2–2.2)	
Not reported	18	149			114	332		
Body mass index (kg/m^2)								
20–27	374	1828	1.0 (ref.)	0.0001	326	1813	1.0 (ref.)	0.0001
<20	13	108	0.8 (0.4–1.4)		32	248	0.8 (0.5–1.2)	
>27	304	760	2.2 (1.8–2.6)		230	613	1.9 (1.6–2.3)	

Table 3. Odds ratios for RCC by occupational exposure, NECSS study, Canada, 1994–1997

	Men				*Women*			
Exposure	*Cases (n)*	*Controls (n)*	*Age and province adjusted OR (95% CI)*	*OR[a] (95% CI)*	*Cases (n)*	*Controls (n)*	*Age and province adjusted OR (95% CI)*	*OR[a] (95% CI)*
Total subjects	691	2696			588	2676		
Asbestos	76	288	1.0 (0.7–1.3)	0.9 (0.7–1.2)	5	40	0.5 (0.2–1.4)	0.6 (0.2–1.5)
Arsenic salts	15	32	1.7 (0.9–3.2)	1.5 (0.8–2.8)	0	8		
Benzene	53	104	1.8 (1.3–2.6)	1.8 (1.2–2.6)	7	29	1.1 (0.5–2.5)	1.3 (0.6–3.2)
Benzidine	28	44	2.4 (1.4–4.0)	2.1 (1.3–3.6)	4	22	0.7 (0.2–2.0)	1.0 (0.3–3.1)
Chromium salts	18	44	1.3 (0.7–2.2)	1.1 (0.6–2.0)	3	15	0.9 (0.2–3.1)	1.1 (0.3–3.9)
Cadmium salts	19	32	1.9 (1.1–3.5)	1.7 (1.0–3.2)	2	14	0.6 (0.1–2.5)	0.7 (0.2–3.1)
Coal tar, soot, pitch, creosote, asphalt	125	350	1.5 (1.2–1.9)	1.4 (1.1–1.8)	18	54	1.4 (0.8–2.4)	1.3 (0.7–2.3)
Dyestuffs	28	68	1.5 (1.0–2.5)	1.5 (0.9–2.4)	13	48	1.2 (0.7–2.3)	1.3 (0.7–2.6)
Herbicides	131	318	1.6 (1.3–2.0)	1.6 (1.3–2.0)	20	112	0.8 (0.5–1.3)	0.8 (0.5–1.3)
Isopropyl oil	30	63	1.7 (1.1–2.7)	1.6 (1.0–2.6)	5	18	1.1 (0.4–3.0)	1.2 (0.4–3.5)
Mineral, cutting or lubricating oil	176	489	1.5 (1.2–1.8)	1.3 (1.1–1.7)	17	67	1.1 (0.6–1.9)	1.1 (0.6–1.9)
Mustard gas	11	10	4.0 (1.6–9.9)	4.6 (1.7–12.5)	0	2		
Pesticides	157	368	1.8 (1.4–2.2)	1.8 (1.4–2.3)	41	147	1.3 (0.9–1.9)	1.3 (0.9–1.8)
Radiation sources	55	160	1.2 (0.9–1.7)	1.3 (0.9–1.8)	17	77	1.1 (0.6–1.9)	1.3 (0.8–2.4)
Vinyl chloride	29	49	2.0 (1.2–3.2)	2.0 (1.2–3.3)	2	7	1.1 (0.2–5.3)	1.6 (0.3–9.0)
Welding	159	536	1.1 (0.9–1.4)	1.1 (0.9–1.3)	12	46	1.1 (0.6–2.1)	1.0 (0.5–2.0)
Wood dust	212	738	1.1 (0.9–1.4)	1.1 (0.9–1.3)	44	155	1.4 (1.0–2.0)	1.2 (0.8–1.7)

[a]Adjusted for 10 year age groups, province, education, BMI (<20, 20–27, >27), pack-years of smoking, alcohol use and total consumption of meat.

the adjusted ORs were 1.8 (95% CI = 1.2–2.6), 2.1 (1.3–3.6), 1.4 (1.1–1.8), 1.6 (1.3–2.0), 1.3 (1.1–1.7), 4.6 (1.7–12.5), 1.8 (1.4–2.3) and 2.0 (1.2–3.3), respectively. Although a high OR was found for mustard gas, it was based on few observations. Borderline significant risks of RCC were also seen for exposure to cadmium salts and isopropyl oil. No excess risk was found in females.

Increased risks with duration were found for a number of exposures (Table 4); the adjusted ORs (95% CI) for exposure to vinyl chloride (compared with no exposure to vinyl chloride) were 0.7 (95% CI = 0.2–2.3) for 1–4 years, 1.7 (95% CI = 0.8–3.8) for 5–19 years and 4.5 (95% CI = 1.9–10.6) for ≥20 years, and the test for trend was significant ($P = 0.0006$). Increased risks and significant tests for trend ($P < 0.05$) were also observed for increasing years of exposure to benzene, benzidine, cadmium and herbicides.

Discussion

This study assessed the relationship between RCC and exposure to 17 chemicals. The findings indicated increased risks of RCC in males associated with occupational exposure to benzene; benzidine; cadmium salts; coal tar, soot, pitch, creosote or asphalt; herbicides; isopropyl oil; mineral, cutting or lubricating oil; mustard gas; pesticides; and vinyl chloride. The excess risk was significantly associated with duration of exposure to benzene, benzidine, cadmium, herbicides or vinyl chloride. These findings suggest that specific chemicals might play an important role in the aetiology of RCC.

In the last 20 years, there has been growing evidence indicating occupational causes of RCC. This association has been reported in particular in chemical and petrochemical industry workers [7, 9, 35–38], metal-related industry workers [6, 15], coke-oven workers [6, 39], cardboard workers [13, 40], laundry and dry-cleaning workers [5, 41, 42], health care workers [43, 44] and truck drivers [10], although other studies [21, 23–25, 45] found no association related to these occupations.

We found a significantly increased risk of RCC associated with benzidine in a dose–response manner. Benzidine is carcinogenic in experimental animals, producing bladder cancer in dogs [46]. Moreover, occupational exposure to benzidine is associated with an increased risk of bladder cancer in humans [46, 47]; an increased risk of upper urinary tract tumours has also been reported [47]. Further research on workers exposed to benzidine is needed to demonstrate a causal association, such as cohort studies of workers in a specific occupation or from work histories of those exposed to this specific agent.

The present study showed a significant association with a dose–response relationship between RCC and benzene exposure; the results provide further evidence that occupational exposure to benzene may be related to RCC risk. Bertazzi *et al.* [35] reported an elevated kidney

Table 4. Odds ratios for RCC by years of exposure to selected chemicals in males, NECSS, Canada, 1994–1997

Agent	*Cases (n)*	*Controls (n)*	*Age and province adjusted OR (95% CI)*	*P value for trend*	*Adjusted OR[a] (95% CI)*	*P value for trend*
Benzene						
Never exposed	635	2582	1.0 (ref.)	0.0002	1.0 (ref.)	0.001
1–5	11	39	1.1 (0.5–2.2)		1.1 (0.6–2.4)	
≥6	42	65	2.3 (1.5–3.4)		2.1 (1.3–3.2)	
Benzidine						
Never exposed	661	2647	1.0 (ref.)	0.0005	1.0 (ref.)	0.004
1–10	12	24	1.9 (0.9–4.0)		1.8 (0.8–3.9)	
≥11	16	20	3.0 (1.5–5.9)		2.5 (1.2–5.0)	
Cadmium						
Never exposed	671	2660	1.0 (ref.)	0.01	1.0 (ref.)	0.03
1–5	5	14	1.0 (0.4–3.0)		0.9 (0.3–2.7)	
≥6	14	18	2.7 (1.3–5.5)		2.4 (1.2–5.0)	
Herbicides						
Never exposed	551	2355	1.0 (ref.)	0.0001	1.0 (ref.)	0.0001
1–15	61	171	1.4 (1.0–1.9)		1.3 (0.9–1.8)	
≥16	70	147	1.9 (1.4–2.6)		2.0 (1.4–2.7)	
Vinyl chloride						
Never exposed	661	2640	1.0 (ref.)	0.0004	1.0 (ref.)	0.0006
1–4	4	20	0.8 (0.2–2.3)		0.7 (0.2–2.3)	
5–19	11	19	1.7 (0.8–3.7)		1.7 (0.8–3.8)	
≥20	14	10	4.7 (2.0–11.0)		4.5 (1.9–10.6)	

[a]Adjusted for 10 year age groups, province, education, BMI (<20, 20–27, >27), pack-years of smoking, alcohol use and total consumption of meat.

cancer mortality in male oil refinery workers. A Finnish cohort study indicated a significant excess of kidney cancer in males, which was highest in men with at least 5 years of employment in oil refineries (SIR 2.8; 95% CI = 1.6–4.7) [38]. Exposure to petroleum products, especially gasoline [48] or aviation gasoline [8], has been suggested as a risk factor associated with kidney cancer in males in two Canadian studies. A significant association was also found with exposure to gasoline and RCC in males in an international multi-centre population-based case–control study [6]. A cohort study followed up 19 000 service station workers in the Nordic countries for 15–20 years [49]; for males, those exposed to gasoline vapours with benzene levels estimated at 0.5–1 mg/m^3 showed a 30% elevated risk of kidney cancer. In a Finnish case-referent study, an elevated RCC risk in males with an exposure–response relationship was observed for gasoline exposure as approximated by the benzene-equivalent concentration [9]. Recently, a case–control study in Germany showed that exposure to benzene was also associated with RCC development in both males and females [17]. Other studies, however, have found no association with gasoline or for petroleum workers [23, 25, 50, 51].

Our findings provide support for the link in males between vinyl chloride and RCC, demonstrating a dose–response relationship. Vinyl chloride is carcinogenic to mice, rats and hamsters, producing tumours at different sites. Vinyl chloride is also a human carcinogen; epidemiological studies report an association of occupational exposure to vinyl chloride with cancers in humans, including cancers of the digestive system, liver, lung, brain and lymphatic organs in both males and females [46, 52], and of the urinary system and breast in women [52]. Tabershaw and Gaffey [53] reported associations with some but not all of these cancers (digestive system, respiratory system, brain, lymphomas, but not urinary organs) in a mortality study of males working in the manufacture of vinyl chloride and its polymers. More research is needed to clarify whether vinyl chloride causes kidney cancer.

Similarly, our results indicated a significant association with exposure to cadmium, consistent with some studies on males [16, 17] and females [17], including an international multicentre population-based case–control study of RCC in males [6], although other case–control and cohort studies found no association [9, 54–57]. Further research on this agent should be pursued.

Our study supports the hypothesis that exposure to herbicides and pesticides increases the risk of RCC, showing, in particular, a dose–response relationship for herbicides. Our data on herbicide and pesticide use were not limited to those exposed at work (e.g. the agricultural population), as the general population uses these chemicals at home. In this study, ~50% of males reported using herbicides and pesticides at home only. Thus, strategies to reduce the impact of exposure to herbicides and pesticides should consider both the general population

and occupational groups in Canada. An increased risk associated with long-term exposure to herbicides and insecticides in males was reported by Mellemgaard *et al.* [10], but not others [6, 15].

Our results did not substantiate the associations between asbestos and RCC reported in some studies [2–6], supporting instead those studies that failed to find an association [9, 15], including two recent meta-analyses of cohort studies of workers predominantly exposed to asbestos that found no association between asbestos exposure and kidney cancer risk [28], and no clear association with other cancers except lung cancer and laryngeal carcinoma [27].

Although epidemiological studies have so far not shown uniform associations of RCC risk with occupational exposure, one of the criteria of causality is a dose–response relationship. In the present study, such a relationship has been shown with certain chemicals, including benzidine, benzene, cadmium, herbicides and vinyl chloride; our agent-specific results add further evidence that occupational exposures may play a large role in the aetiology of RCC.

In our study, we found associations between occupational exposure to specific chemicals and RCC in males only. Although there is evidence for a high susceptibility of kidneys to heavy metals in females [17], we could not examine this issue, because very few females were exposed. Fewer women than men reported occupational exposure to each chemical, specifically benzidine, benzene, cadmium and vinyl chloride; thus, the resulting sample sizes in women limited the power of the study, and we could not examine risks by duration. Further research is needed to clarify the association between occupational exposure to specific chemicals and RCC in females.

The NECSS study was conducted on a large population-based sample from eight Canadian provinces. The analysis of the effect of 17 chemicals is based on self-reported exposure; misclassification may bias the effects, including any dose–response trends. However, non-differential misclassification between cases and controls would bias the OR estimates towards unity in most instances [58]. Furthermore, in this study, the potential confounding effects of medication and medical history could not be considered; in particular, we did not have data on hypertension or use of anti-hypertensive medication, or on the use of analgesics, for which associations are reported in some studies [59–64], but not others [65–67].

In conclusion, we observed a number of associations between occupational exposure and RCC in males, most of them consistent with previous reports. In particular, a dose–response relationship was shown for agent-specific exposure to some of the chemicals. These findings support the hypothesis that specific chemicals play an important role in the development of RCC; however, further research is needed to clarify these findings, in particular, in females.

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