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Active and passive smoking and risk of renal cell carcinoma in Canada

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Abstract

This study aimed to assess the role of active and passive smoking in the development of renal cell carcinoma (RCC). Mailed questionnaires were completed by 1279 incident RCC cases and 5370 population controls between 1994 and 1997 in eight Canadian provinces. Data were collected on socio-economic status, smoking habits, diet and passive smoking status, as well as residential and occupational history. The study found an increased risk of RCC associated with active smoking. Elevated risk of RCC was also observed with passive smoking; compared with those never exposed to either passive or active smoking, men and women with 43 or more years of passive residential and/or occupational exposure had respective adjusted Odds Ratios (ORs) of 3.9 (95% Confidence Interval (CI) 1.4–10.6) and 1.8 (95% CI 1.0–3.3) ($P = 0.001$ and $P = 0.09$, respectively). Both active and passive smoking might play a role in the aetiology of RCC.

Keywords: Carcinoma; Renal cell; Environmental tobacco smoke; Logistic models; Smoking

1. Introduction

The incidence of kidney cancer has increased substantially in all areas around the world [1]. Renal cell carcinoma (RCC) represents 80–85% of all kidney cancers [2]. A number of epidemiological studies, particularly case-control studies, indicated that cigarette smoking is an important risk factor [3–9]. A recent study reported that cessation of smoking was indeed associated with a linear decrease in RCC risk [10]. Cigarette smoking has been causally associated with RCC [11]. Passive smoking has been linked with a variety of health consequences in humans, including cancer. Elevated risks have been seen for several specific cancer sites, and are not limited to lung cancer [12]. They have been observed also for stomach [13] and breast cancers [14]. However, certain details of the association

Abbreviations: BMI, body mass index; CI, Confidence Interval; ETS, environmental tobacco smoke; NECSS, National Enhanced Cancer Surveillance System; OR, Odds Ratio; RCC, renal cell carcinoma.

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between passive smoking and RCC have not been well established.

Data from the National Enhanced Cancer Surveillance System (NECSS) have been used here to examine the role of active and passive smoking on the risk of RCC in Canada.

2. Patients and methods

The NECSS collected individual data from a population-based sample between 1994 and 1997, including 18 types of cancer and 5380 population controls in eight of 10 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Nova Scotia and Newfoundland).

2.1. Cases

A total of 2199 (995 female and 1204 male) histologically confirmed incident cases of kidney cancer were ascertained by participating provincial cancer registries between 1994 and 1997. Of these, 174 patients (7.9%; 70 female and 104 male) had died at the time of physician contact and 152 (6.9%; 79 female and 73 male) were not contacted because consent was refused by the attending physician (generally because the patient was too ill). Of 1873 questionnaires sent, 1497 questionnaires were completed; the response rate was 68.1% (95% CI = 66.2–70.0) of cases ascertained and 79.9% (95% CI = 78.1–81.7) of patients contacted. This study involved 1279 (691 male and 588 female) histologically confirmed cases of RCC (as defined by the International Classification of Diseases (ICDO-2) [15]).

2.2. Controls

In the NECSS, population controls were frequency matched to the overall collection of cases for 18 types of cases. Individuals without cancer were selected from a random sample of individuals within a province, with an age and gender distribution similar to that of all 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 selecting population controls varied by province, depending on data availability and accessibility. In Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan and British Columbia, age group- and gender-stratified random samples of the province's population were obtained through the provincial health insurance plans. In Ontario, the 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 8117 questionnaires sent to potential controls, 573 questionnaires were returned because they were wrongly addressed; of the remainder, 5380 were completed, representing 66.3% (95% CI = 65.3–67.3) of controls ascertained and 71.3% (95% CI = 70.3–72.3) of controls contacted. For the present analyses, 10 controls (eight male and two female) were excluded because information on their age was missing.

2.3. Data collection

The cancer registries identified most cases within 1–3 months of diagnosis through pathology reports. After obtaining physician consent, questionnaires were mailed to 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 a second copy of the questionnaire at 4 weeks; after 6 weeks telephone follow-up was used to complete the questionnaire, if required. Information was collected on socio-economic status, employment history, residential history, height, weight, smoking history, physical activity, alcohol use, dietary history and use of vitamin or mineral supplements. Data concerning family history of cancer were collected only in the province of Ontario.

For weight, information was gathered on how much each subject weighed "about two years ago" (in pounds or kilograms) and the most that the subject had ever weighed. The body mass index (BMI), calculated as weight (kg)/height squared (m^2), was used to assess overweight and obesity. BMI (kg/m^2) was classified according to the World Health Organization standards for adults [16] as follows: underweight (BMI < 18.50), normal weight (BMI 18.50–24.99) and overweight (BMI $\geqslant 25.00$), which includes pre-obesity (BMI 25.00–29.99) and obesity (BMI $\geqslant 30.00$).

The diet portion of the questionnaire, which examined eating habits from two years before, was based on the short version of the Block [17] questionnaire. Block and colleagues [17] showed that, when validated against the full version, the shorter 60-item version documents 90–95% of the nutrients captured using the full version. A 70-item food frequency questionnaire provided data on Canadian eating patterns and the major sources of nutrients in the Canadian diet, as well as general changes in the individual's diet compared with 20 years ago (Bureau of Biostatistics and Computer Applications, Food Directorate, Health Canada). For each food item, cases and controls were asked to describe how often (per day, per week, per month), on average, they ate the serving size specified for the item. Information on alcohol consumption included beer, wine and liquor.

Employment history included each job or occupation at which the subject had worked for at least 12 months in Canada or elsewhere; time period; type of industry, business or service and company name; main job duties; job location(s); job title; and status (full-time, part-time, seasonal, other). In addition, each subject was also asked about exposure at work (or home) to any of 17 specified chemicals (for at least one year) and the duration of exposure in years.

Residential history included a list of each place in Canada where the subject had lived for at least one year. The first and last year of residence, address, main source of drinking water and primary types of home heating were indicated for each place where the subject lived, starting with the most recent residence and continuing back to childhood. The questionnaire collected information on lifetime exposure to environmental tobacco smoke (ETS) through the residential and occupational histories: it assessed exposure by source (household or workplace), intensity (number of smokers) and duration of exposure in each residence (as child or adult) or workplace. The questionnaire on residential history asked each subject to indicate how many regular smokers usually lived in the home with him/her (none, 1, 2, 3 or more, do not know) while living at each residence. In the questionnaire on occupational history, each subject was asked to indicate how many people smoked regularly in his/her immediate work area (none, 1 or 2, 3 to 5, 6 or more, do not know) during each employment time period (i.e., from first year to last year). Calculations were made for total number of years exposed to ETS at the residence and work area and for total smoker-years of residential and occupational exposure to ETS (i.e., number of regular smokers living in the subject's home multiplied by the number of years in that home; number of employees who smoked regularly in the subject's immediate work area multiplied by the number of years at that job).

Four hundred forty cases (157 male and 283 female) and 2037 controls (704 male and 1333 female) reported not having smoked more than 100 cigarettes in their lives. In order to minimise passive smoke exposure status misclassification, the data analysed were only subjects who had reported a relatively complete history of residential passive smoke exposure. From reported never-smokers, the data analyses were restricted to the 260 cases (89 male and 171 female) and 1214 controls (411 male and 803 female) who reported their residential passive smoking exposure history for at least 90% of their lifetimes. These were essentially those who reported living in Canada at least 90% of their lives.

Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were computed as a measure of the relative risk. Unconditional logistic regression was used for multivariate analyses using SAS software [18]. Using the likelihood ratio test [19], the potential confounding variables were selected: education, BMI, total alcohol use, total consumption of meat and total consumption of vegetables and fruit. Tests for trends were assessed for each study variable by substituting the variable in the model in continuous form.

3. Results

The demographic characteristics of RCC cases and controls are presented by gender in Table 1. Approximately 96% of the cases were older than 40 years. For both genders, cases reported a lower education level than did controls. Among males, income adequacy was not reported by 20.3% of cases and 23.3% of controls, and among females, by 29.6% of cases and 28.6% of controls. Female cases were more likely to report lower family income than were female controls.

Table 2 shows the ORs for RCC according to selected factors among men and women. Significantly elevated ORs were observed with increased BMI. Compared with those with normal BMI, obese people (BMI $\geqslant$ 30) had the highest risk of RCC: the adjusted ORs were 2.7 (95% CI 2.1–3.6) among men and 3.2 (95% CI 2.5–4.1) among women (test for trend, $P = 0.0001$ for both). The total consumption of vegetables and fruit showed a statistically significant inverse association with RCC for both genders. An inverse association between alcohol use and RCC risk was also observed in both genders.

Tables 3 and 4 portray the relationship between active smoking history and risk of RCC among males and females, respectively. Compared with those who had never smoked, only ex-smokers showed a slight association between cigarette smoking and RCC risk, with an adjusted OR of 1.2 (95% CI 1.0–1.5) for males and 1.3 (95% CI 1.0–1.6) for females. For males, the risk rose with increasing smoking pack-years; the adjusted OR was 1.4 (95% CI 1.0–1.9) for more than 40 smoking pack-years ($P = 0.05$). For females, the risk increased with increasing average number of cigarettes per day, with a statistically significant dose-response relationship; the adjusted OR was 1.4 (95% CI 1.1–1.8) for 20 or more cigarettes per day ($P = 0.03$). The risk of RCC decreased for both genders with increased years since quitting smoking; however, after adjusted for smoking pack-years, the risk decreased for males in particular.

For subjects who were never active smokers and at least 90% lifetime residential passive smoking history was reported, we assessed their risk of RCC by gender in relation to their lifetime exposure to ETS (i.e., passive smoking) at home or at work (Tables 5 and 6). Compared with those never exposed to either passive or active smoking, men and women with 43 or more years of passive residential and/or occupational exposure had respective adjusted ORs of 3.9 (95% CI 1.4–10.6)

Table 1
Demographic characteristics of cases and controls for renal cell carcinoma, by gender, NECSS, Canada, 1994–1997

	Males				Females			
	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
Age								
20–29	2	164			3	64		
30–39	16	276			30	196		
40–49	113	231			92	597		
50–59	185	400			149	585		
60–69	253	969			209	813		
⩾70	122	656			105	419		
Total	691	2696			588	2674		
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 (years)								
1–8	136	511	1.0 Ref.	0.004	124	352	1.0 Ref.	0.0001
9–13	349	1246	0.9 (0.7–1.2)		317	1455	0.6 (0.5–0.8)	
⩾14	196	898	0.7 (0.5–0.9)		138	831	0.5 (0.4–0.7)	
Not reported	10	41			9	36		

95% CI, 95% Confidence Interval; OR, Odds Ratio; NECSS, National Enchanced Cancer Surveillance System; Ref., reference group.

Table 2
Odds Ratios for renal cell carcinoma by selected risk factors, NECSS, Canada, 1994–1997

	Males				Females			
	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
Body mass index[a]								
Normal (<25)	147	1044	1.0 Ref.	0.0001	221	1517	1.0 Ref.	0.0001
Overweight (⩾25 to <30)	369	1225	2.0 (1.6–2.5)		200	795	1.6 (1.3–2.0)	
Obese (⩾30)	173	414	2.7 (2.1–3.6)		164	351	3.2 (2.5–4.1)	
Not reported	2	13			3	11		
Total alcohol (servings/week)[b]								
Never	217	751	1.0 Ref.	0.0006	342	1245	1.0 Ref.	0.0003
1–6	253	994	0.8 (0.6–1.0)		191	1047	0.7 (0.6–0.9)	
7–17	116	509	0.7 (0.5–0.9)		36	264	0.6(0.4–0.8)	
⩾18	104	440	0.7 (0.5–0.9)		19	116	0.6 (0.4–1.1)	
Not reported	1	2			0	2		
Total consumption of meat (servings/week)[c]								
⩽4.9	149	704	1.0 Ref.	0.09	202	1023	1.0 Ref.	0.09
5.0–8.3	167	661	1.2 (0.9–1.6)		163	773	1.2 (0.9–1.5)	
8.4–12.5	180	674	1.1 (0.8–1.5)		140	570	1.3 (1.0–1.7)	
⩾12.6	194	655	1.3 (1.0–1.8)		83	306	1.2 (0.9–1.7)	
Not reported	1	2			0	2		
Total consumption of vegetables and fruit (servings/week)[c]								
⩽25.7	343	1265	1.0 Ref.	0.0002	182	751	1.0 Ref.	0.01
25.8–36.9	205	746	1.0 (0.8–1.2)		253	1199	0.8 (0.6–1.0)	
37–52.9	100	441	0.7 (0.5–0.9)		87	401	0.8 (0.6–1.1)	
⩾53.0	42	242	0.5 (0.3–0.7)		47	254	0.6(0.4–0.9)	
Not reported	1	2			19	69		

[a] Normal weight group also included those with BMI < 18.5: 16 cases (14 males and 2 females) and 119 controls (41 males and 78 females). Adjusted for 10-year age groups, province, education, total consumption of meat and total consumption of vegetables and fruit.

[b] Adjusted for 10-year age groups, province, education, body mass index (<25, 25–29.9, ⩾30), total consumption of meat and total consumption of vegetables and fruit; alcohol included liquor, beer and wine.

[c] Adjusted for 10-year age groups, province, education, body mass index (<25, 25–29.9, ⩾30) and total consumption of energy; for women, cut-off point for total meat: ⩽3.5, 3.6–6.0, 6.1–9.4, ⩾9.5; for total vegetables and fruit: ⩽23.4, 23.5–40.9, 50.0–56.5, ⩾56.6.

Table 3
Odds Ratios for renal cell cancer by active smoking history, males, NECSS study, Canada, 1994–1997

Exposure variable	Cases *N*	Controls *N*	Age and province adjusted OR (95% CI)	*P* value for trend	Multivariable adjusted OR[a] (95% CI)	*P* value for trend
Current smoking status						
Never-smoker	157	704	1.0 Ref.	0.62	1.0 Ref.	0.79
Ex-smoker	386	1354	1.3 (1.0–1.6)		1.2 (1.0–1.5)	
Current smoker	113	558	0.9 (0.7–1.2)		0.9 (0.7–1.2)	
Age of starting to smoke (years)[b]						
⩾20	81	352	1.0 (0.7–1.3)	0.05	1.0 (0.7–1.4)	0.15
16–19	223	786	1.2 (1.0–1.6)		1.3 (1.0–1.6)	
⩽15	224	842	1.2 (1.0–1.5)		1.1 (0.9–1.5)	
Average cigarettes/day while active smoker[b]						
⩽9	76	277	1.3 (0.9–1.8)	0.02	1.4 (1.0–2.0)	0.13
10–19	139	609	1.0 (0.8–1.3)		1.0 (0.8–1.3)	
20–29	227	839	1.2 (1.0–1.5)		1.2 (0.9–1.5)	
⩾30	83	236	1.6 (1.2–2.2)		1.4 (1.0–2.0)	
Total years of smoking[b]						
⩽10	61	310	0.8 (0.6–1.1)	0.04	0.9 (0.6–1.2)	0.05
11–20	114	442	1.1 (0.9–1.5)		1.1 (0.8–1.4)	
21–30	131	384	1.5 (1.2–2.0)		1.5 (1.1–2.0)	
31–40	116	371	1.2 (0.9–1.6)		1.2 (0.9–1.6)	
⩾41	101	447	1.1 (0.8–1.5)		1.1 (0.8–1.5)	
Smoking pack-years[b]						
⩽10	135	584	1.0 (0.8–1.3)	0.01	1.1 (0.8–1.4)	0.05
11–20	133	472	1.2 (1.0–1.6)		1.2 (0.9–1.6)	
21–30	92	324	1.2 (0.9–1.6)		1.2 (0.9–1.6)	
31–40	68	250	1.2 (0.9–1.7)		1.2 (0.9–1.7)	
⩾41	89	304	1.4 (1.1–2.0)		1.4 (1.0–1.9)	
Years since quitting smoking[c]						
⩾31	60	267	1.0 (0.7–1.4)	0.003	1.0 (0.7–1.4)	0.01
21–30	86	323	1.2 (0.8–1.6)		1.2 (0.8–1.6)	
11–20	103	381	1.2 (0.9–1.6)		1.1 (0.8–1.5)	
⩽10	125	357	1.5 (1.2–2.0)		1.5 (1.0–2.3)	

Note: totals may vary due to missing values.

[a] Adjusted for 10-year age groups, province, education, body mass index (<25, 25–29.9, ⩾30), alcohol use, total consumption of meat, and total consumption of vegetables and fruit.

[b] Never-smokers as reference group.

[c] Also adjusted for smoking pack-years.

and 1.8 (95% CI 1.0–3.3); however, the test for trend was statistically significant only for males ($P = 0.001$ and 0.09, respectively). In terms of smoker-years of exposure to passive smoking, we also observed an increase in risk in both genders, with a statistically significant dose-response relationship; the adjusted ORs were 3.6 (95% CI 1.3–9.6) among males for 93 or more smoker-years of exposure and 2.9 (95% CI 1.5–5.6) among females for 126 or more smoker-years.

4. Discussion

Our results support the association between active cigarette smoking and risk of RCC. The risk rose with increasing average number of cigarettes smoked per day for females and with increasing smoking pack-years for males, and the risk decreased with increased years since quitting smoking, particularly for males. In addition, the risk of RCC was elevated among subjects with greater exposure to ETS at home or at work.

A number of studies of RCC indicated that cigarette smoking was associated with a statistically significant increase in the risk of RCC [3–5,20–22]. A review of seven RCC studies found adjusted ORs of 1.3–9.3 in men who smoked; consumption of more than 20 pack-years led to a significant association [3]. Another study showed a decreased risk of RCC with increased years since quitting smoking [5]. These findings are consistent with our results; we found a significant association between cigarette smoking and RCC in males with more than 40 smoking pack-years, and decreased risk of RCC in males who had quit smoking more than 10 years ago. A recent study on cessation of smoking observed an associated linear decrease in RCC risk, particularly among normotensive subjects [10]. The association

Table 4
Odds Ratios for renal cell cancer by active smoking history, females, NECSS Study, Canada, 1994–1997

Exposure variable	Cases *N*	Controls *N*	Age and province adjusted OR (95% CI)	*P* value for trend	Multivariable adjusted OR[a] (95% CI)	*P* value for trend
Current smoking status						
Never-smoker	283	1333	1.0 Ref.	0.63	1.0 Ref.	0.75
Ex-smoker	195	805	1.1 (0.9–1.4)		1.3 (1.0–1.6)	
Current smoker	83	479	0.9 (0.7–1.1)		0.9 (0.7–1.2)	
Age of starting to smoke[b]						
⩾20	96	377	1.1 (0.9–1.5)	0.22	1.2 (0.9–1.6)	0.18
16–19	120	560	1.0 (0.8–1.3)		1.1 (0.9–1.4)	
⩽15	88	389	1.2 (0.9–1.6)		1.2 (0.9–1.6)	
Average cigarettes/day while active smoker[b]						
⩽9	76	370	1.0 (0.8–1.3)	0.03	1.1 (0.8–1.5)	0.03
10–19	89	481	0.9 (0.7–1.2)		1.0 (0.8–1.3)	
⩾20	138	465	1.4 (1.1–1.8)		1.4 (1.1–1.8)	
Total years of smoking[b]						
⩽10	54	307	0.9 (0.7–1.2)	0.12	0.9 (0.7–1.3)	0.05
11–20	67	293	1.2 (0.9–1.6)		1.2 (0.9–1.7)	
21–30	69	302	1.1 (0.9–1.5)		1.2 (0.9–1.6)	
⩾31	110	405	1.2 (0.9–1.5)		1.2 (1.0–1.6)	
Smoking pack-years[b]						
⩽10	104	585	0.9 (0.7–1.2)	0.01	1.0 (0.8–1.3)	0.02
11–20	75	337	1.1 (0.8–1.4)		1.1 (0.8–1.5)	
21–30	68	194	1.6 (1.2–2.2)		1.6 (1.2–2.2)	
⩾30	51	176	1.3 (0.9–1.8)		1.2 (0.9–1.8)	
Years since quitting smoking[c]						
⩾20	76	301	1.1 (0.8–1.5)	0.03	1.1 (0.7–1.6)	0.47
11–20	34	246	0.7 (0.5–1.0)		0.6 (0.4–1.1)	
⩽10	80	247	1.7 (1.3–2.2)		1.5 (0.8–2.6)	

Note: totals may vary due to missing values.

[a] Adjusted for 10-year age groups, province, education, body mass index (<25, 25–29.9, ⩾30), alcohol use, total consumption of meat, and total consumption of vegetables and fruit.

[b] Never-smokers as reference group.

[c] Also adjusted for smoking pack-years.

Table 5
Lifetime residential and occupational exposure to passive smoking and risk of renal cell carcinoma among male never-smokers, NECSS, Canada, 1994–1997

Lifetime exposure to passive smoking (years)	Controls *N*	Cases *N*	Age and province adjusted OR (95% CI)	*P* value for trend	Multivariable adjusted OR[a] (95% CI)	*P* value for trend
Total years of residential plus occupational exposure[b]						
Never regularly exposed	74	7	1.0 Ref.	0.003	1.0 Ref.	0.001
1–22	108	14	1.4 (0.5–3.7)		1.5 (0.5–4.4)	
23–42	116	27	2.1 (0.8–5.3)		2.5 (0.9–6.9)	
⩾43	113	41	3.2 (1.3–7.8)		3.9 (1.4–10.6)	
Total	411	89				
Total smoker-years of exposure (residential plus occupational)[c]						
Never regularly exposed	74	7	1.0 Ref.	0.0008	1.0 Ref.	0.0002
1–39	109	12	1.1 (0.4-3.0)		1.2 (0.4–3.6)	
40–92	111	26	2.4 (1.0–6.2)		3.0 (1.1–8.2)	
⩾93	117	44	3.1 (1.3–7.6)		3.6 (1.3–9.6)	
Total	411	89				

[a] Adjusted for 10-year age group, province, education, body mass index (<25, 25–29.9, ⩾30), alcohol use, total consumption of meat and total consumption of vegetables and fruit.

[b] Sum of years of residential exposure and years of occupational exposure.

[c] Sum of all smoker-years of residential exposure (i.e., number of regular smokers living in the subject's home multiplied by the number of years in that home) plus sum of all smoker-years of occupational exposure (i.e., number of employees who smoked regularly in the subject's immediate work area multiplied by the number of years at that job).

Table 6
Lifetime residential and occupational exposure to passive smoking and risk of renal cell carcinoma among female never-smokers, NECSS, Canada, 1994–1997

Lifetime exposure to passive smoking (years)	Controls *N*	Cases *N*	Age and province adjusted OR (95% CI)	*P* value for trend	Multivariable adjusted OR[a] (95% CI)	*P* value for trend
Total years of residential plus occupational exposure[b]						
Never regularly exposed	140	19	1.0 Ref.	0.02	1.0 Ref.	0.09
1–22	198	35	1.4 (0.8–2.7)		1.7 (0.9–3.4)	
23–42	215	45	1.5 (0.8–2.7)		1.7 (0.9–3.3)	
⩾43	250	72	1.9 (1.1–3.4)		1.8 (1.0–3.3)	
Total	803	171				
Total smoker-years of exposure (residential plus occupational)[c]						
Never regularly exposed	140	19	1.0 Ref.	0.0004	1.0 Ref.	0.01
1–55	326	62	1.5 (0.8–2.6)		1.7 (0.9–3.2)	
56–125	230	40	1.2 (0.7–2.2)		1.3 (0.7–2.4)	
⩾126	107	50	3.2 (1.7–5.8)		2.9 (1.5–5.6)	
Total	803	171				

[a] Adjusted for 10-year age group, province, education, body mass index (<25, 25–29.9, ⩾30), alcohol use, total consumption of meat and total consumption of vegetables and fruit.
[b] Sum of years of residential exposure and years of occupational exposure.
[c] Sum of all smoker-years of residential exposure (i.e., number of regular smokers living in the subject's home multiplied by the number of years in that home) plus sum of all smoker-years of occupational exposure (i.e., number of employees who smoked regularly in the subject's immediate work area multiplied by the number of years at that job).

between cigarette smoking and RCC has been shown to be similar among men and women [5]. Another population-based Canadian study [23] and several other studies [21,22,24] indicated that cigarette smoking increased the risk of RCC in both genders. Our findings also showed an increased risk of RCC among males and females, although the weak association between active cigarette smoking and RCC appeared only in former smokers. Other studies found that cigarette smoking was a risk factor for RCC only in males, but not in females [6,7,20,25,26]. However, a previous study indicated a weak positive association with cigarette smoking [27]. No association was found between smoking and RCC in a study in France [28]. In addition, a multi-site case-control study indicated that cigarette smoking among men in Montreal was not associated with kidney cancer [29].

Although the previous studies showed inconsistent results regarding the association between smoking and RCC, the strength of the association between tobacco, as an independent risk factor [3], and RCC was consistently shown to be weaker than that between tobacco and lung cancer. Tobacco smoking is accepted as a major cause of kidney cancer [30]. Recently, the causal association of active tobacco smoking with kidney cancer has been established by the International Agency for Research on Cancer [31]. Cigarette smoking appears to be the strongest risk factor for renal cancer, accounting for the majority of cases in most areas of the world [32]. In the last decade, cigarette smoking has been established as a causal risk factor in the development of RCC [4]. A 26-year follow-up study of United States (US) veterans supported this association between cigarette smoking and RCC with a strong dose-response relationship; statistically significant risks of RCC were higher in current smokers than in former smokers [33]. An international RCC study has also confirmed that cigarette smoking is a causal factor in the aetiology of RCC [34]. The population attributable risks of RCC have been calculated for the three main risk factors: 20% for hypertension, 21% for excess weight and 18% for smoking (past and current) [21].

A case-control study on passive smoking and cancer risk indicated that cancer risk among individuals married to smokers was 1.6 times higher than the risk among those who were never married to smokers [12]; this elevated risk was not limited to lung cancer or other "smoking-related" tumours. In the present study, our findings showed that exposure to ETS at home or at work increased the risk of RCC in both genders, suggesting that passive smoking plays an important role in the development of RCC. To our knowledge, this is the first study to assess the association between passive smoking and the risk of RCC. More results from other studies are required.

Recently, research on genetic factors has added to our understanding of the role of cigarette smoking in the development of RCC. The genetic effect plays an important role in increasing the risk of RCC, particularly in smokers. *N*-acetyltransferase 2, which codes for a polymorphic enzyme, is involved in tobacco-carcinogen metabolism [35]. A study on gene–environment interactions showed that slow acetylators are at increased risk of RCC, particularly if they are women [36]. Slow acetylators are at increased risk in the case of smokers. The nitrosamines, especially *N*-nitrosodimethylamine, which are carcinogens in cigarette smoke, have been shown to be kidney carcinogens in rodents [37]. An experimental

animal study has reported the presence of von Hippel–Lindau [38] gene mutations in *N*-nitrosodimethylamine-induced rat renal epithelial tumours.

After an average of 16 years of follow-up, a cohort of 332,547 men provided evidence that cigarette smoking is a modifiable risk factor for kidney cancer in men [39]. Cigarette smoking is the most well-known, modifiable risk factor for human health today. Elimination of the smoking habit would contribute to a reduction in the number of RCC cases around the world [32]. Tobacco control by altering lifestyle in the general population is an important strategy for the prevention of RCC. A healthy lifestyle can lower the risk of the development of RCC.

Although this case-control study was large and population-based, some limitations need to be mentioned here. One is that the potential confounding effects of medication or medical history were not considered; 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 [21,40–43] but not in others [44–46]. Those confounding factors, in particular, hypertension is one of main causes for RCC. However, hypertension independently increases the risk of RCC suggesting that this factor acts to increase this risk through different mechanisms [47].

Another limitation is that 14.8% of the kidney cancer cases (who were too ill or had died) were not included in this study. The response rate was 68.1% of cases ascertained, which might lead to selection bias. However, the significant associations between BMI and RCC in our results are consistent with results from other studies [45,48]; thus, we have no reason to believe that these missing data bias our results.

A final limitation is potential misclassification (recall bias) in the data collection; in particular, we collected information on lifetime exposure to passive smoking. Although non-differential misclassification between cases and controls would bias the ORs toward unity in most instances [49]. The possibility of differential misclassification (recall bias) cannot be excluded in retrospective case-control studies. We think it is unlikely that the results obtained on passive smoking and RCC were biased by misclassification. In order to limit the misclassification of ETS exposure status, data analyses on ETS used were only those who had lived and reported their residential passive smoking exposure history for at least 90% of their lifetimes. There is not enough evidence pertaining to recall bias. In addition, during the data collection phase of the study, active campaigns against tobacco were already in place [50,51]. It is possible that the absence of risk among current smokers, in particular, the trend of increasing risk in ex-smokers, that is, the shorter the time period since quitting, could be explained by the information bias.

In conclusion, our findings add to the evidence that cigarette smoking is associated with the risk of RCC in both genders and that passive smoking also plays an important role in the development of RCC.

Conflict of interest statement

None declared.

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