Tobacco Use in Relation to Renal Cell Carcinoma[1]

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Abstract

The modest effect of cigarette smoking on renal cell carcinoma (RCC) requires a study with a large number of subjects to definitively answer the question of whether smoking is causally related to RCC. A population-based case-control study was conducted in Los Angeles, California that involved 1204 RCC patients and an equal number of neighborhood controls who were matched to the index cases by sex, date of birth (within 5 years), and race. Detailed information on tobacco use was collected through in-person interviews. Cigarette smoking was associated with a statistically significant 35% increase in the risk of RCC [odds ratio (OR), 1.35; 95% confidence interval (CI), 1.14–1.60]. The risk increased with increasing number of cigarettes smoked per day (two-sided $P < 0.001$, linear trend test). Former smokers (OR, 1.24; 95% CI, 1.02–1.50) had a lower risk of RCC than current smokers (OR, 1.53; 95% CI, 1.23–1.90). Compared with current smokers, those who quit smoking 10 or more years ago experienced a statistically significant 30% reduction in the risk of RCC. Current smokers who smoked 40 or more cigarettes/day experienced a nearly 2-fold increase in the risk of RCC compared with lifelong nonsmokers. The association between cigarette smoking and RCC was similar in men and women. There were no measurable differences in the risk of RCC between filtered and nonfiltered cigarette smokers or between those who inhaled cigarette smoke deeply and those who inhaled lightly after adjustment for the number of cigarettes smoked per day and current smoking status. After the effect of cigarette smoking was accounted for, heavy cigar smokers (14 or more cigars/week) exhibited a statistically significant 70% increase in the risk of RCC, but no increased risk of RCC was observed for the use of pipes or smokeless tobacco. Seventeen percent of RCC (21% in men and 11% in women) in Los Angeles, California can be attributed to cigarette smoking.

Introduction

The modest effect of cigarette smoking on RCC[3] leads to inconsistent results on the association between smoking and RCC in previous epidemiological studies, particularly in those with small-to-moderate sample sizes. Some of those studies did not find a statistically significant association between smoking and RCC (1–5), whereas others found an association only in men or women (6–10). The IARC concluded in 1986 that cigarette smoking was "perhaps" a cause of RCC (11), and the 1982 and 1990 United States Surgeon General's reports regarded cigarette smoking as a "contributory" factor for RCC (12, 13). Case-control studies that involved a relatively large number of RCC patients have demonstrated a moderately positive association between cigarette smoking and RCC in both men and women (14–17). Those studies found a maximum 2-fold increase in the risk of RCC in ever smokers relative to lifelong nonsmokers and a significantly positive dose-response relationship between smoking and RCC risk. Thus, Doll (18) reached the conclusion that cigarette smoking was causally associated with RCC in a recent review. However, certain details of the association between tobacco use and RCC (*e.g.*, the effect of cigarettes *versus* other tobacco products, the effect of inhalation, the comparability of effects in men and women, and the impact of filters on risk) have not been well established, even by those large studies.

In the present study, which involved more than 1200 RCC patients and an equal number of community controls in Los Angeles, California, we examined in detail the relationship between tobacco use and RCC.

Materials and Methods

The study design, including data collection strategies, has been described previously (19). In brief, the Los Angeles County Cancer Surveillance Program (20), the population-based Surveillance, Epidemiology, and End Results cancer registry of Los Angeles County, identified 1724 non-Asian patients ages 25–74 years with histologically confirmed RCC between April 1986 and December 1994. Among them, 298 patients died before we could contact them or were too ill to be interviewed. Permission to contact 56 patients was denied by the attending physicians. Ninety-one patients refused to be interviewed. Thus, we interviewed a total of 1276 cancer patients. Of 448 patients who were not interviewed, 65% were men, and 92% were non-Hispanic whites. The corresponding figures among interviewed patients were 65 and 84%. The mean age at diagnosis was similar between eligible patients who were interviewed (58.9 years) and those who were not (60.3 years).

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[3] The abbreviations used are: RCC, renal cell carcinoma; BMI, body mass index; OR, odds ratio; CI, confidence interval.

For each recruited patient, we sought to interview a control who was matched to the patient on sex, date of birth (within 5 years), race, and neighborhood of residence at the time of cancer diagnosis. When we failed to find any resident who met our matching criteria after canvassing 150 housing units by a standard algorithm, we excluded race from the matching criteria. If a matched control based on this relaxed criteria could not be found in a maximum of 300 housing units, the case was dropped from the study. Seventy-two RCC patients were excluded from the current study due to lack of matched controls. We completed in-person interviews on 1204 neighborhood control subjects. There were 98 controls who were not matched by race to the index case. Of the 1204 control subjects interviewed, 834 (69%) were the first eligible controls, and 231 (19%) and 139 (12%) were the second and third eligible controls, respectively. There was no significant difference in the distributions of sex, race, BMI [weight in kilograms divided by height in meters squared (kg/m^2)], smoking patterns, and history of hypertension between the first eligible controls and the replacement controls.

In-person, structured interviews were conducted in the subjects' homes. The questionnaire requested information up to 2 years before the diagnosis of cancer for cases and 2 years before the diagnosis of cancer of the index case for matched controls. The questionnaire requested information on demographic characteristics, height and weight, use of tobacco and alcohol, usual dietary habits, lifetime occupational history, prior medical conditions, and use of selected medications. Both patient and control subjects in a given case-control pair were interviewed by the same interviewer. On average, control subjects were interviewed 14 months after their index cases. All interviews were conducted by the same team of interviewers throughout the entire course of data collection.

In terms of tobacco use, we first asked the subject whether he/she had ever smoked at least 1 cigarette/day for 6 months or longer. If the answer was yes (*i.e.*, the subject was defined as a "regular" cigarette smoker), we then asked about the age at which he/she started to smoke on a regular basis, smoking status (continuing or quitting smoking) 2 years before the cancer diagnosis of the index case, the number of years that he/she smoked regularly, and the number of cigarettes smoked/day. For regular cigarette smokers, information on the type of cigarettes (filtered or nonfiltered) and inhalation patterns (deep, moderate, or light) was solicited from respondents. If a subject reported having used a cigar, pipe, chewing tobacco, or snuff at least once a week for 6 months or longer, he/she was defined as a regular user of noncigarette tobacco products, and the age at starting to use the product on a regular basis, the number of years of use, and the amount of each noncigarette tobacco product used per week were similarly asked.

Data were analyzed by standard matched-pair methods (21). Seventy-two RCC patients were excluded from the study due to a lack of matched controls. Thus, a total of 1204 case-control pairs were included in the present study. Conditional logistic regression models were used to examine the associations between tobacco exposure variables and RCC risk. The associations were measured by ORs and their corresponding 95% CIs. A test for linear trend was used to assess the dose-response relationship of RCC with the amount and duration of smoking.

To examine the association between quitting and detailed patterns of smoking and risk of RCC among ever cigarette smokers, unconditional logistic regression models were used. Six age-sex strata (age groups of <50, 50–59, and ≥60 years for each sex) were included in the models to adjust for age and sex.

Table 1 Tobacco use in relation to risk of RCC

	Cases	Controls	OR[a] (95% CI)
Never used tobacco	357	433	1.00
Ever used tobacco[b]	847	771	1.34 (1.11–1.60)
Ever smoked cigarettes	800	713	1.35 (1.13–1.63)
No. of cigarettes/day[c]			
1–19	246	245	1.23 (0.97–1.55)
20–39	370	333	1.32 (1.06–1.64)
≥40	180	134	1.67 (1.26–2.21)
Ever smoked cigars[d]	124	144	0.88 (0.64–1.23)
No. of cigars/week[c,d]			
1–6	36	66	0.59 (0.36–0.94)
7–13	22	36	0.68 (0.38–1.21)
≥14	66	41	1.67 (1.03–2.68)
Ever smoked pipe[d]	174	177	0.99 (0.72–1.36)
No. of pipes/week[c,d]			
1–13	59	71	0.86 (0.57–1.31)
14–27	54	53	1.05 (0.67–1.65)
≥28	58	53	1.04 (0.65–1.68)
Ever chewed tobacco or used snuff[d]	32	27	1.02 (0.56–1.85)
Cigarettes only	604	523	1.37 (1.13–1.66)
Noncigarette tobacco products only	47	58	1.02 (0.66–1.57)
Both cigarettes and noncigarette tobacco products	196	190	1.30 (0.99–1.70)

[a] Adjusted for level of education (high school or less, college or above).
[b] Defined as smoking at least 1 cigarette/day or at least 1 cigar or pipe/week or chewing tobacco or snuff at least once a week for 6 months or longer.
[c] The sum may be slightly less than the total number of smokers, due to the exclusion of subjects with missing values in amount of tobacco used.
[d] Further adjusted for the number of cigarettes smoked per day and current smoking status (no, yes).

Analyses were conducted for males and females separately and for both sexes combined. In the present study, RCC patients were less educated than the control subjects; 48% of patients *versus* 37% of controls did not attend college. Thus, all analyses were adjusted for the level of education with or without other risk factors for RCC including obesity, history of hypertension, and regular use of analgesics and amphetamines (19).[4] All results presented were adjusted for the level of education, because such an adjustment slightly changed the effect of tobacco use on RCC risk. ORs with two-sided *P*s less than 0.05 were considered statistically significant. All *P*s quoted are two-sided.

Results

There were 847 patients (604 men and 243 women) and 771 control subjects (551 men and 220 women) who used any type of tobacco product regularly (cigarettes, cigars, pipes, chewing tobacco, or snuff). Compared with lifelong nonusers, regular users of any tobacco product had a statistically significant 34% increase in the risk of RCC (Table 1). Cigarette smoking showed the strongest association with RCC; the risk increased with increasing number of cigarettes smoked per day ($P < 0.01$, linear trend test). Most individuals who used noncigarette tobacco products had also smoked cigarettes regularly. A total of 243 cases (242 men and 1 woman) used noncigarette tobacco, and 196 of them (81%; all men) also smoked cigarettes regularly. The comparable figures for controls were 248 (244 men

[4] Gago-Dominguez, M., Yuan, J-M., Castelao, J. E., Ross, R. K., and Yu, M. C. Regular use of analgesics is a risk factor for RCC, submitted for publication.

Table 2 Cigarette smoking in relation to risk of RCC

Cigarette smoking	Total		Males		Females	
	Ca/Co[a]	OR[b] (95% CI)	Ca/Co[a]	OR[b] (95% CI)	Ca/Co[a]	OR[b] (95% CI)
Never	404/491	1.00	223/288	1.00	181/203	1.00
Ever[c]	800/713	1.35 (1.14–1.60)	558/493	1.42 (1.14–1.77)	242/220	1.23 (0.93–1.64)
Former smokers	463/450	1.24 (1.02–1.50)	350/331	1.34 (1.05–1.70)	113/119	1.07 (0.77–1.49)
No. of yr since quitting[d]						
≥20	169/177	1.15 (0.89–1.50)	135/145	1.18 (0.86–1.61)	34/32	1.19 (0.70–2.02)
10–19	135/135	1.25 (0.94–1.64)	98/99	1.26 (0.90–1.76)	37/36	1.23 (0.74–2.04)
1–9	159/138	1.33 (1.02–1.74)	117/87	1.64 (1.17–2.29)	42/51	0.88 (0.56–1.40)
Current smokers	337/262	1.53 (1.23–1.90)	208/162	1.58 (1.20–2.08)	129/100	1.46 (1.03–2.08)
No. of cigarettes/day						
1–19	87/73	1.48 (1.04–2.12)	45/38	1.58 (0.96–2.58)	42/35	1.39 (0.83–2.32)
20–39	183/146	1.45 (1.11–1.88)	114/92	1.46 (1.05–2.03)	69/54	1.41 (0.91–2.22)
≥40	67/43	1.90 (1.25–2.90)	49/32	1.92 (1.17–3.17)	18/11	1.93 (0.88–4.23)
Total no. of cigarettes smoked over lifetime (×1000)						
<117	239/237	1.22 (0.97–1.53)	154/152	1.28 (0.96–1.71)	85/85	1.13 (0.79–1.62)
117–283	244/236	1.25 (0.99–1.58)	172/171	1.27 (0.96–1.69)	72/65	1.22 (0.82–1.83)
≥283	316/239	1.60 (1.28–2.01)	231/170	1.69 (1.29–2.22)	85/69	1.43 (0.93–2.18)

[a] Number of cases (Ca)/number of controls (Co). Two subjects (a male case and a female control) had missing values on the total number of cigarettes smoked, and the female control also had a missing value on current smoking status. These two subjects were excluded from the relevant analyses.
[b] Adjusted for level of education (high school or less, college or above).
[c] Defined as smoking at least 1 cigarette/day for 6 months or longer.
[d] Compared with current smokers, the ORs for both sexes combined were 0.79 (95% CI, 0.59–1.06) for those who quit smoking less than 10 years ago, 0.70 (95% CI, 0.52–0.95) for those who quit smoking 10–19 years ago, and 0.72 (95% CI, 0.54–0.96) for those who quit smoking 20 or more years ago after adjustment for age (<50, 50–59, ≥60 years), sex, level of education (high school or less, college or above), BMI (kg/m^2), and the number of cigarettes smoked per day (P = 0.01, linear trend test).

and 4 women) and 190 (77%; 186 men and 4 women), respectively. After the effect of cigarette smoking was accounted for, heavy cigar smokers had a statistically significant 1.7-fold increase in the risk of RCC, but users of pipes or smokeless tobacco (chewing tobacco or snuff) had a risk level comparable to that of lifelong nonusers of tobacco. The risk of RCC among those who used both cigarettes and noncigarette tobacco products was comparable to that among those who used cigarettes only (Table 1). Thus, all analyses below examined the association between cigarette smoking and RCC risk, regardless of the use of noncigarette tobacco products.

Table 2 presents the detailed association between cigarette smoking and the risk of RCC. In both sexes combined, ever smokers had a statistically significant 35% increase in the risk of RCC compared with lifelong nonsmokers. A significant dose-response relationship between the number of cigarettes smoked per day and RCC risk was observed ($P < 0.001$, linear trend test). Individuals who quit smoking experienced a reduced risk of RCC compared with current smokers. For current smokers, those who smoked 40 or more cigarettes/day had a nearly 2-fold increase in the risk of RCC relative to lifelong nonsmokers. When we estimated the lifetime number of cigarettes, a statistically significant trend in RCC risk with increasing lifetime number of cigarettes was observed ($P < 0.001$, linear trend test; Table 2).

For former smokers, the risk decreased with increasing number of years since quitting smoking ($P = 0.01$, linear trend test). After adjustment for age, sex, level of education, BMI, and the number of cigarettes smoked per day, the ORs were 0.79 (95% CI, 0.59–1.06), 0.70 (95% CI, 0.52–0.95), and 0.72 (95% CI, 0.54–0.95) for those who quit smoking less than 10 years ago, 10–19 years ago, and 20 or more years ago, respectively, compared with current smokers.

The association between cigarette smoking and RCC was similar between men and women, except that there were fewer female cases than female controls who quit smoking less than 10 years ago. In both men and women, current smokers had a higher risk of RCC than former smokers, and the risk increased with increasing number of cigarettes smoked per day or over a lifetime (Table 2).

We examined the association between age at starting to smoke and duration of smoking and the risk of RCC. The risk among those who began smoking regularly at less than 15 years of age (OR, 1.35; 95% CI, 1.02–1.81) was identical to that for those who began smoking at age 25 years or older (OR, 1.35; 95% CI, 0.95–1.95). After an adjustment for the number of cigarettes smoked per day, age at starting to smoke had little additional effect on RCC ($P = 0.34$). Long-term smokers experienced a higher risk of RCC than short-term smokers. Compared with lifelong nonsmokers, the OR was 1.21 (95% CI, 0.96–1.53) for those who had smoked for less than 20 years, whereas the OR was 1.53 (95% CI, 1.1–2.01) for those who had smoked for 40 or more years. Adjustment for the number of cigarettes smoked per day substantially reduced the impact of the duration of smoking on RCC risk. Compared to lifelong nonsmokers, the adjusted ORs were 1.06 (95% CI, 0.82–1.38), 1.13 (95% CI, 0.85–1.49), and 1.23 (95% CI, 0.88–1.73) for those who had smoked for less than 20 years, 20–39 years, and 40 or more years, respectively ($P = 0.17$, linear trend test).

We used two analytic approaches to account for the potential confounding effects of other risk factors on RCC risk. We first examined the smoking-RCC association stratified by usual BMI (<24.4 or ≥24.4 kg/m^2, which was the median value in controls), history of hypertension (yes, no), and regular use of analgesics (yes, no) and amphetamines (yes, no). No modifying effect of any one of these factors on the smoking-RCC association was found. We also used a multivariate conditional logistic regression model to examine the smoking-RCC association while controlling for the aforementioned set of other risk factors. The adjustment did not materially change the associations between cigarette smoking and RCC. Compared with lifelong nonsmokers, for example, the adjusted OR was 1.32 (95% CI, 1.09–1.59) in ever smokers, 1.14 (95% CI,

Table 3 Smoking patterns in relation to risk of RCC among cigarette smokers only

Smoking pattern	Cases	Controls	OR[a] (95% CI)
Type of cigarette			
Filtered	546	464	1.00[b]
Nonfiltered	206	211	0.84 (0.65–1.08)
Both types equally	48	38	1.13 (0.72–1.79)
Inhalation pattern			
Light	171	160	1.00[b]
Moderate	412	338	1.09 (0.83–1.42)
Deep	217	215	0.83 (0.61–1.13)

[a] ORs were calculated using an unconditional logistic regression model that also included six age-sex strata, level of education (high school or less, college or above), the number of cigarettes smoked per day, and current smoking status (no, yes).
[b] The reference group.

0.92–1.67) in former smokers, and 1.67 (95% CI, 1.32–2.11) in current smokers.

Table 3 presents the association between detailed smoking patterns and the risk of RCC among cigarette smokers. Two-thirds of cigarette smokers reported smoking mainly filtered cigarettes. Compared with those who smoked filtered cigarettes, individuals who smoked mainly nonfiltered cigarettes did not show an increased risk of RCC after adjustment for age, sex, level of education, the number of cigarettes smoked per day, and current smoking status. No increased RCC risk was observed among those who inhaled cigarette smoke deeply relative to those who inhaled lightly.

We repeated all analyses after excluding the 98 case-control pairs in which controls were not matched by race to the index cases. The exclusion did not materially change the smoking-RCC associations. We also conducted separate analyses on case-control pairs with the first eligible controls (n = 834) and those with the replacement controls (n = 370). The associations between cigarette smoking and RCC were comparable between these two subgroups.

Discussion

To our knowledge, the present study is the largest case-control study of RCC conducted in a single geographically defined study population. Our study provides detailed quantitative evidence on the association between cigarette smoking and RCC. The risk was significantly elevated in both former and current smokers relative to lifelong nonsmokers and increased with increasing number of cigarettes smoked per day or over a lifetime. The positive association between cigarette smoking and RCC was remarkably similar in detail between men and women. Our data did not demonstrate measurable differences in the risk of RCC between filtered and nonfiltered cigarette smokers or between those who inhaled cigarette smoke deeply and those who inhaled lightly after an adjustment for the number of cigarettes smoked per day.

Our findings on cigarette smoking and RCC are generally comparable to those based on a multicenter study that included 1832 cases and 2309 controls from Berlin and Heidelberg (Germany), Denmark, Minnesota (United States), Sydney (Australia), and Uppsala (Sweden; Ref. 14). The multicenter study demonstrated a statistically significant 30% increase in the risk of RCC among ever smokers and a 2-fold increase in risk among current smokers who smoked more than 20 cigarettes/day (14). In the present study, we observed a 35% increase in the risk of RCC among ever smokers and a nearly 2-fold increase in risk among current smokers who smoked 40 or more cigarettes/day.

Cessation of smoking affected the risk of RCC. In our study, those who quit smoking 10 or more years ago experienced a statistically significant 30% reduction in risk as compared with current smokers. In the multicenter study mentioned earlier (14), there was a 15–25% reduction in the risk of RCC in those who quit smoking for 15 or more years relative to that in current smokers.

Two case-control studies reported that those who smoked nonfiltered cigarettes experienced a higher risk of RCC than those who smoked filtered cigarettes, but these studies had few study subjects who were exclusive users of nonfiltered cigarettes (9, 22), and results were not adjusted for the number of cigarettes smoked per day or over a lifetime. In our study, those who smoked mainly nonfiltered cigarettes smoked more cigarettes/day than those who smoked filtered cigarettes. Our data demonstrated that there was no difference in the risk of RCC between nonfiltered and filtered cigarette smokers after an adjustment for the number of cigarettes smoked per day.

We also examined the association between inhalation patterns and the risk of RCC, but we did not find that those who reported that they inhaled cigarette smoke deeply experienced a higher risk than those who inhaled lightly. Kreiger *et al.* (17) reported that deep inhalation of cigarette smoke was associated with a significantly increased risk of RCC in women, but not in men. Mellemgaard *et al.* (8) reported that smoking with inhalation was associated with a higher risk of RCC than smoking without inhalation, but the investigators also noted that heavy smokers were more likely to inhale than light smokers.

Overall, noncigarette smokers had used tobacco products other than cigarettes for a shorter period of time and lesser amounts than cigarette smokers. In controls, for example, noncigarette smokers had smoked cigars or pipes for 10 years on average, whereas cigarette smokers averaged 27 years. Nonetheless, in the present study, we observed a statistically significant increase in the risk of RCC in heavy cigar smokers that could not be explained by cigarette smoking. This positive result should be confirmed in future studies. A few studies have reported an association with smokeless tobacco (22–25). However, the results from these studies were not adjusted for the effects of cigarette smoking. We found no evidence of an association between use of smokeless tobacco and RCC risk, but we had few study subjects who used chewing tobacco or snuff exclusively (five cases and four controls).

It is not entirely clear which constituents of cigarette smoke are responsible for the development of RCC. The urine of cigarette smokers shows increased mutagenic activity (26). *N*-Nitrosodiemethylamine, which causes kidney tumors in a number of animal species, is found in tobacco smoke (27). The level of increased risk of RCC with smoking is well below that observed with cancer of the renal pelvis and ureter (28, 29). The transitional cell urothelium of the renal pelvis and ureter is exposed to the same potential urinary carcinogen(s) as the renal tubular cells that give rise to RCC. Either the tubular cells are less sensitive to the putative carcinogen(s) in cigarette smoke, or the exposure level to these carcinogens is substantially higher in the collection area of the kidney (*i.e.*, the renal pelvis), thereby accounting for the much stronger cancer risk.

In summary, this large-scale population-based case-control study confirms that cigarette smoking is a causal factor for RCC development. Seventeen percent of RCC (21% in men and 11% in women) in Los Angeles, California can be attributed to cigarette smoking.

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