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Risk Factors for Kidney Cancer in New South Wales—I. Cigarette Smoking

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In a population-based case–control study of kidney cancer in New South Wales, data from structured interviews with 489 cases of renal cell cancer (RCC), 147 cases of renal pelvic cancer (CaRP) diagnosed in 1989 and 1990, and 523 controls from the electoral rolls confirmed an increased risk associated with cigarette smoking in both types of cancer. The risk among current smokers was consistently higher than among ex-smokers, and was nearly twice as great for CaRP than for RCC. Additional information provided by this study includes reduced risks following cessation of smoking within 12 years for CaRP, but only after 25 years for RCC. Starting to smoke before, rather than after, the age of 18 years is linked independently with almost twice the risk for CaRP, but does not affect the risk for RCC. No independent trend was found with number of cigarettes smoked per day.
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INTRODUCTION

WHILE THE International Agency for Research on Cancer has found "sufficient evidence" for a carcinogenic role of tobacco smoking in cancer of the renal pelvis, such a ruling has not yet been made for cancer of the renal parenchyma (renal cell carcinoma, RCC) [1]. Case–control studies have not consistently found an association between RCC and tobacco smoking, the estimated odds ratios being generally in the order of 1.5–2.0, whether the studies were population-based [2–7], hospital-based [8–14], or within a cancer registry [15].

To clarify the role of tobacco and other suspected risk factors in this cancer of uncertain aetiology, an international collaborative population-based case–control study of RCC was undertaken under the coordination of the US National Cancer Institute. The participating centres, either in areas of high incidence of RCC or with a particular interest in kidney cancer, were in the United States (Minnesota), Denmark, Sweden, Germany (two centres), and Australia (New South Wales). The analysis of results from New South Wales pertaining to tobacco smoking is presented here, together with data from a parallel investigation into renal pelvic cancer.

METHODS

Potential cases comprised all incident cases in 1989–1990 of cancer of the renal parenchyma (ICD-9 189.0, RCC) and renal pelvis (ICD-9 189.1, CaRP) in residents of New South Wales (NSW) who were aged 20–79 years at diagnosis. Controls were selected from the electoral rolls using proportional random sampling based on the expected age distribution of the cases. The study population was confined to subjects whose names were in a current electoral roll, whose telephone number could be found, and who could speak English.

Cases were identified through statutory notification to the NSW Central Cancer Registry by hospitals, pathology laboratories and radiotherapy departments [16], as well as by regular contact with urologists throughout NSW. In the period up to 31 July 1991 (allowing for late notifications) 744 eligible cases of RCC and 200 of CaRP were identified. Permission was requested from the attending doctor for inclusion in the study, followed by a letter to the case seeking participation. The release of information from the Cancer Registry was made conditional upon adherence to a strict protocol which did not permit repeated approaches to either the doctor or the patient, nor could information be obtained from relatives of the patients. For RCC, attrition due to death (23%), refusal (doctor, 2%; patient, 1%) or non-response (doctor, 1%; patient, 5%) resulted in a case group comprising 322 men and 181 women. For CaRP, 59 men and 90 women were interviewed, death (15%), refusal by doctor (1%) or patient (5%) and non-response by doctor (3%) or patient (2%) accounting for the remainder. In each of the twelve 5-year age groups between 20 and 79 years, the percentages of the potential RCC cases who participated were 80, 100, 83, 77, 79, 78, 75, 79, 74, 65, 55 and 47% respectively. For CaRP, the percentages who participated in the nine 5-year age groups between 35 and 79 years were 100, 100, 89, 89, 84, 90, 74, 58 and 59%.

The diagnosis of interviewed cases was based on histopathology of the kidney (87% RCC, 92% CaRP) or other tissue (1% RCC), fine needle aspiration cytology of the kidney (4% RCC), or by computerised tomography, ultrasound or contrast radiography (8% of each).

Of the proportional random sample of the population obtained from the current NSW electoral rolls, telephone numbers were found for 803. An initial letter seeking participation in the study was followed, if necessary, by a second letter and up to 10 telephone calls. The information on the rolls was out of date for 60 subjects (52 moved, 8 dead) and 18 could not speak English. Of the remaining 725, 74% were interviewed, the remainder comprising refusals (ill health 7%, senility < 1%, other reason 2%, no reason 16%) and non-respondents (2%). Among men, the proportions of interviewed controls in each 10-year age group were not significantly different from those of the non-respondents ($\chi^2 = 1.03$, df = 3, $P = 0.79$) but the women who were not interviewed were slightly older than those who were (65 ± 8 vs. 62 ± 9 years, $t = 3.092$, df = 389, $P < 0.001$).

One trained interviewer carried out all the interviews between

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Table 1. History of cigarette smoking—distribution of cases and controls, New South Wales, 1989–1990

Cigarette smoking	Population controls		Renal cell cancer		Renal pelvic cancer	
	Male (n = 231)	Female (n = 292)	Male (n = 310)	Female (n = 179)	Male (n = 58)	Female (n = 89)
In subjects who had never smoked a cigar or pipe regularly						
Non-smokers (smoked < 100 cigarettes in lifetime)	81	190	69	98	11	41
Smoked ≥ 100 cigarettes in lifetime but never "regularly"	3	2	8	4	—	1
Ex-smoker	65	45	78	30	15	14
Current smoker	28	55	74	47	22	33
In subjects who also smoked a cigar or pipe regularly						
Non-smokers	4	—	2	—	—	—
Never "regular" smokers	2	—	—	—	—	—
Ex-smoker	33	—	51	–	4	—
Current smoker	15	—	28	—	6	—

May 1989 and July 1991. Of the cases, all but 10 (7 RCC, 3 CaRP) were interviewed within 1 year of diagnosis (55, 87 and 96% within 3, 6 and 9 months of diagnosis, respectively). Face-to-face interviews were held in the homes of all subjects who lived in the Sydney metropolitan area (256 RCC, 71 CaRP, 232 controls). For subjects living in the remainder of NSW (233 RCC, 76 CaRP, 291 controls), the checklists to be used in conjunction with the standard questionnaire were mailed with a request to keep them unopened but accessible for a subsequent telephone interview. Self-administered questionnaires were completed by 14 RCC cases, 2 CaRP cases and 12 controls as this was the only means by which these subjects would participate.

The questionnaire which was identical to those used in the other collaborating centres for the core questions, sought information about the regular consumption of tobacco as well as about other suspected risk factors or confounders. The type of tobacco smoked, the usual number of cigarettes, pipes or cigars smoked per day and the precise period of consumption were sought, explicitly excluding the period after 1 January 1987 for all subjects. Lifetime cigarette consumption was calculated in pack-years (packs per day × years smoking) assuming 20 cigarettes per pack. Non-smokers were those who had smoked less than 100 cigarettes and who had never smoked cigars or pipes. Information about snuff or chewing tobacco was not obtained due to the low prevalence of these habits in NSW [17].

Analysis

Initial evaluation included inspection of frequencies of the variables. As the 28 self-administered questionnaires contained an unacceptably high level of missing data, it was decided to restrict the analysis to the 489 RCC cases, 147 CaRP cases and 523 controls who were interviewed either face-to-face or by telephone. Categories of pack-years, age started smoking and years since stopped smoking were calculated on the basis of their distribution in the entire control group; tertiles for age were based on cases and controls combined. Adjustment was made for two possible confounding factors: consumption of

Table 2. Risk of kidney cancer associated with cigarette smoking, New South Wales, 1989–1990

	Renal cell cancer RR (95% CI)*	Renal pelvic cancer RR (95% CI)†
Entire data set		
Non-smokers	1	1
Ex-smokers	1.41 (1.03–1.95)	1.18 (0.67–2.07)
Current smokers	2.17 (1.55–3.02)	4.16 (2.49–6.97)
Subjects who had never smoked cigar or pipe regularly		
Non-smokers	1	1
Ex-smokers	1.31 (0.92–1.85)	1.26 (0.69–2.28)
Current smokers	2.16 (1.52–3.07)	4.27 (2.50–7.29)
Men		
Non-smokers	1	1
Ex-smokers	1.54 (1.01–2.35)	1.18 (0.52–2.71)
Current smokers	2.94 (1.80–4.78)	5.86 (2.54–13.51)
Women		
Non-smokers	1	1
Ex-smokers	1.32 (0.77–2.24)	1.67 (0.73–3.83)
Current smokers	1.60 (1.00–2.56)	3.33 (1.68–6.60)
Subjects aged ≤ 58 years		
Non-smokers	1	1
Ex-smokers	1.34 (0.77–2.35)	1.60 (0.48–5.33)
Current smokers	2.30 (1.38–3.83)	2.93 (1.02–8.39)
Subjects aged 59–67 years		
Non-smokers	1	1
Ex-smokers	1.70 (0.96–3.01)	2.51 (0.90–6.96)
Current smokers	2.01 (1.12–3.61)	7.72 (3.03–19.68)
Subjects aged ≥ 68 years		
Non-smokers	1	1
Ex-smokers	1.17 (0.67–2.05)	0.56 (0.24–1.35)
Current smokers	2.28 (1.14–4.55)	3.98 (1.72–9.22)

Models adjusted for age, sex, method of interview, and *body mass index, or †analgesics containing phenacetin.

Table 3. Risk ratios (and 95% confidence intervals) for kidney cancer associated with lifetime consumption of cigarettes, New South Wales, 1989–1990*

Lifetime cigarette consumption	Renal cell cancer					Renal pelvic cancer				
	None†	Low	Medium	High	χ^2‡	None	Low	Medium	High	χ^2
Ever smokers	1.00	1.27 (0.86–1.88)	1.62 (1.12–2.35)	2.34 (1.62–3.37)	7.22	1.00	1.90 (0.99–3.63)	1.88 (1.04–3.42)	3.32 (1.89–5.84)	3.05
Current smokers	1.00	2.01 (1.01–4.00)	1.61 (0.98–2.65)	2.96 (1.88–4.66)	1.06	1.00	3.72 (1.14–12.18)	3.47 (1.70–7.09)	5.43 (2.80–10.54)	0.31
Age started < 18 years	1.00	2.54 (0.60–10.75)	2.47 (1.17–5.19)	3.07 (1.75–5.39)	0.34	1.00	11.12 (1.78–69.47)	5.78 (1.89–17.63)	7.12 (3.04–16.69)	0.14
Age started ≥ 18 years	1.00	1.94 (0.90–4.17)	1.27 (0.68–2.39)	3.34 (1.75–6.40)	0.33	1.00	1.68 (0.34–8.43)	2.87 (1.24–6.61)	4.27 (1.77–10.32)	0.97
Ex-smokers	1.00	1.12 (0.72–1.74)	1.70 (1.05–2.75)	1.80 (1.10–2.95)	2.61	1.00	1.68 (0.80–3.55)	0.84 (0.31–2.24)	1.40 (0.59–3.31)	0.01
Stopped 1–19 years	1.00	1.37 (0.74–2.56)	2.33 (1.31–4.14)	2.01 (1.14–3.54)	0.34	1.00	2.27 (0.77–6.65)	1.13 (0.36–3.53)	1.11 (0.40–3.04)	0.19
Stopped ≥ 20 years	1.00	0.98 (0.56–1.73)	0.81 (0.36–1.81)	1.23 (0.52–2.89)	0.00	1.00	1.30 (0.49–3.43)	0.36 (0.06–2.09)	1.61 (0.40–6.45)	0.01

*Models adjusted for age, sex and method of interview, and body mass index (RCC), or analgesics containing phenacetin (CaRP).
†The reference category represents subjects who never smoked tobacco of any kind.
Tertiles of lifetime consumption of cigarettes are ≤ 15.9, 16.0–34.2 and ≥ 34.3 pack-years.
The χ^2 test for trend excludes the "never smoked" category.
‡$P = 0.007$.

phenacetin-containing analgesics (ever vs. never regular [18]) for CaRP; and body mass index (BMI) for RCC. BMI was calculated as weight/(height)^2 for men and weight/(height)$^{1.5}$ for women, and tertiles were derived from the male and female control groups separately.

Relative risks (RR), together with 95% confidence intervals (CI), were estimated from multivariate logistic regression using EGRET [19], according to Breslow and Day [20]. Tests for trend were obtained by scoring the levels of the categorised exposure (the reference group being excluded from the score) and treating the scored variable as continuous.

RESULTS

A history of cigarette smoking is given for cases of renal cell cancer (RCC) and renal pelvic cancer (CaRP) and population controls in Table 1, according to whether or not subjects had also smoked a cigar or pipe regularly. Current cigarette smokers were more common among cases (RCC: 33.1% male, 26.3% female; CaRP: 48.3% male, 37.1% female) than controls (18.9% male, 18.8% female) as were "ever regular" cigarette smokers. No woman had been a regular smoker of cigars or pipes.

"Ever regular" smoking of cigarettes significantly increased the risk of RCC in men (RR = 1.96, 95% CI 1.33–2.89) and women (RR = 1.47, 95% CI 1.00–2.18), and of CaRP in men (RR = 2.34, 95% CI 1.14–4.84) and women (RR = 2.56, 95% CI 1.41–4.66), the estimates being adjusted for age, sex, method of interview, and for the previously recognised risk factors for RCC (obesity) and CaRP (phenacetin-containing analgesics).

The risk of each type of kidney cancer has been estimated for current smokers and ex-smokers of cigarettes (Table 2). The risk was consistently higher among current smokers than ex-smokers, a pattern which was seen for each type of cancer, for each sex, for each tertile of age, and whether or not the calculation had been restricted to subjects who had never smoked cigars or pipes regularly. In almost every instance, the risk in ex-smokers was about the same for the two types of cancer but the risk for current smokers was nearly twice as great for CaRP as for RCC. Regular smoking of cigars or a pipe was not linked with an increased risk of kidney cancer once the effect of cigarette smoking had been taken into account (RR = 0.97, 95% CI 0.63–1.49 for RCC; RR = 0.54, 95% CI 0.24–2.47 for CaRP); hence no adjustment was made for cigar or pipe smoking in further analyses.

The risk associated with the lifetime consumption of cigarettes (calculated in pack-years) is shown in Table 3. For "ever smokers", while a dose–response was demonstrated only for RCC, in each tertile the risk of CaRP was greater than that in non-smokers and the largest risk was found for those who had smoked the greatest amount. However, as these estimates are confounded by duration of smoking and by the effect of stopping smoking, two sets of risk estimates are presented separately for current and ex-smokers (Table 3). For current smokers, the age at which cigarette smoking started appeared to affect the risk to a greater degree than the actual amount smoked. In general, smokers who began the habit before the age of 18 years rather than after this age were at a higher risk of kidney cancer, the difference being particularly marked for CaRP. Amongst ex-smokers, those who had stopped smoking for more than 20 years were at a lower risk of both types of kidney cancer than those who gave up the habit more recently.

To examine the independent effects of duration of smoking, number of cigarettes smoked per day, and cessation of smoking amongst "ever smokers", terms for these variables were included in the same model (Table 4). As all four time-related variables cannot be included together [21], age at starting to smoke replaced duration of smoking in a second model in Table 4. After cessation of smoking, the risk fell to about half that in current smokers, but only after 25 years for RCC; in the case of CaRP the risk fell within 12 years, and perhaps to a greater degree. Subjects starting to smoke before the age of 18 years, rather than after this age, had a significantly higher risk (almost twice) of CaRP but this was not true for RCC. A non-significant

Table 4. Risk of kidney cancer amongst ever smokers according to duration or age at starting smoking, intensity of smoking, and number of years since cessation, New South Wales, 1989–1990

	Renal cell cancer			Renal pelvic cancer		
	Cases/ controls	Crude OR	RR* (95% CI)	Cases/ controls	Crude OR	RR† (95% CI)
Model 1						
Duration (years)						
1–19	57/73	1	1	12/73	1	1
20–34	126/85	1.90	1.46 (0.88–2.44)	28/85	2.00	1.36 (0.55–3.38)
35+	125/83	1.93	1.50 (0.75–3.01)§	54/83	3.96	2.03 (0.68–6.12)‡‡
Cigarettes/day						
1–12	67/79	1	1	27/79	1	1
13–20	122/94	1.53	1.16 (0.73–1.82)	36/94	1.12	0.75 (0.37–1.51)
21+	119/68	2.06	1.42 (0.88–2.30)‖	31/68	1.33	0.97 (0.47–1.99)§§
Cessation						
Still smoking	149/99	1	1	61/99	1	1
1–12 yr	70/47	0.99	0.85 (0.53–1.38)	13/47	0.45	0.33 (0.15–0.74)
13–24 yr	59/45	0.87	0.89 (0.52–1.53)	10/45	0.36	0.44 (0.17–1.09)
25+ yr	30/50	0.40	0.47 (0.22–1.00)¶	10/50	0.32	0.38 (0.13–1.37)‖‖
Model 2						
Age at starting (years)‡						
9–17	143/100	1	1	49/100	1	1
18+	159/141	0.79	1.07 (0.74–1.57)	43/141	0.62	0.55 (0.30–1.00)
Cigarettes/day						
1–12	67/79	1	1	26/79	1	1
13–20	122/94	1.49	1.18 (0.75–1.85)	36/94	1.16	0.87 (0.43–1.75)
21+	119/68	2.01	1.46 (0.90–2.35)**	30/68	1.34	1.05 (0.51–2.17)¶¶
Cessation						
Still smoking	144/99	1	1	60/99	1	1
1–12 yr	70/47	1.02	0.86 (0.53–1.38)	12/47	0.42	0.33 (0.15–0.74)
13–24 yr	58/45	0.89	0.83 (0.51–1.36)	10/45	0.37	0.36 (0.15–0.83)
25+ yr	30/50	0.41	0.37 (0.21–0.66)††	10/50	0.33	0.27 (0.11–0.67)***

Models adjusted for age, sex, method of interview, and *body mass index, or †analgesics containing phenacetin.
‡Age at starting to smoke not available for some subjects.
χ^2 test for trend. §$P = 0.253$, ‖$P = 0.141$, ¶$P = 0.134$, **$P = 0.120$, ††$P = 0.003$, ‡‡$P = 0.188$, §§$P = 0.964$, ‖‖$P = 0.028$, ¶¶$P = 0.879$, ***$P < 0.001$.

Table 5. Risk of kidney cancer associated with type of cigarette and method of smoking amongst current smokers, New South Wales, 1989–1990

Current smokers only	Renal cell cancer RR* (95% CI)	Renal pelvic cancer RR† (95% CI)
Non-smokers	1‡	1‡
Type of cigarette		
Filtered	2.26 (1.55–3.30)	3.36 (1.82–6.18)
Non-filtered	2.84 (1.26–6.40)	6.88 (2.41–19.65)
Both equally	1.84 (0.95–3.57)	6.72 (2.87–15.74)
Inhale cigarette smoke		
Yes	2.32 (1.63–3.31)	4.90 (2.82–8.54)
No	1.73 (0.75–3.98)	1.70 (0.42–6.87)
Pattern of inhalation		
Deeply	1‡	1‡
Moderately	0.75 (0.39–1.45)	1.24 (0.47–3.21)
Lightly	0.60 (0.26–1.39)	1.03 (0.32–3.29)

Models adjusted for age, sex, method of interview, and *body mass index, or †analgesics containing phenacetin. ‡Reference category.

rise in risk with increasing duration of smoking was seen for CaRP but not RCC, while the number of cigarettes smoked per day did not independently affect the risk of either form of cancer.

In an analysis restricted to current smokers, the risk for each cancer associated with filtered cigarettes was less than that from non-filtered cigarettes, but was still significantly raised over that for non-smokers (Table 5). Inhaling cigarette smoke was associated with a 2-fold risk for RCC and an almost 5-fold risk for CaRP but no statistical difference in risk was shown between those who inhaled cigarette smoke deeply, moderately or lightly.

DISCUSSION

Cigarette smoking significantly increased the risk of both types of kidney cancer by magnitudes similar to those reported in previous studies [2–15, 22–26]. However, there were subtle differences between the cancers in respect of their relationship to smoking.

The risk for CaRP was nearly twice as great as for RCC among current smokers, but fell earlier, and probably to a greater extent with cessation of smoking, confirming a pattern for urothelial cancer demonstrated by McLaughlin *et al.* for renal pelvic cancer [22] and by Vineis *et al.* for cancer of the bladder [27]. It

appeared to be only after 25 years that the risk for RCC fell to less than half that in current smokers.

Although no association was found between the age of starting to smoke and RCC, starting smoking at a young age was linked with a doubling of the risk of subsequent CaRP, even when the model had been adjusted for the number of cigarettes smoked per day and cessation of smoking. Such adjustment was necessary as the age at which smoking began has been found to be related to the total number of years of smoking and to the number of cigarettes smoked per day in adulthood [28].

When current and ex-smokers were considered together, an increasing risk with increasing lifetime consumption of tobacco could be shown for CaRP only if non-smokers were included in the test for trend, as had been done in previous studies [22–26]. Using the more strict criterion of including only the exposed in the test, there was a non-significant tendency for the risk for CaRP to rise with increasing duration of smoking, but not with daily consumption of cigarettes. In respect of RCC, there was a significant trend with lifetime cigarette consumption only when current and ex-smokers were considered together. The lack of a trend with respect to intensity of exposure, as measured by daily consumption (Table 3) or degree of inhalation (Table 5), might suggest that passive smoking would increase the risk for cancer of the kidney. However, in this study, no questions were asked addressing this point.

The representative nature of the control group is confirmed by comparison with a large national survey which estimated the prevalence of smoking in Australia in 1989 [29]. When the age- and sex-specific proportions from that survey were applied to our control group, the observed numbers of current smokers and ex-smokers did not differ significantly from those expected.

More than one third of CaRP can be attributed to smoking (population attributable risks being 46 and 35% in men and women, respectively); the other major risk factor in New South Wales, consumption of phenacetin-containing analgesics, accounting for another 12% in men and 67% in women [18]. The population attributable risks for RCC calculated from this study are less (men 37%, women 14%; compared with 30 and 24%, respectively in the USA [2]). No other single factor has been identified that accounts for a significant proportion of RCC whose aetiology, on the whole, remains undefined.

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