BJU International (2000), **86**, 20–27

REVIEW

Risk factors for adult renal cell carcinoma: a systematic review and implications for prevention

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Introduction

RCC accounts for ≈ 3% of cancers in adults and ≈ 85% of all primary malignant kidney tumours. The incidence of RCC has been steadily increasing for several years. In France, the incidence of RCC according to cancer registers was 12 per 100 000 men and 6 per 100 000 women in 1995, and mortality rates were over 7.5 per 100 000 men and 4.0 per 100 000 women, similar to reports from other European countries [1,2].

About half the cases of RCC diagnosed are currently discovered by chance during ultrasonography. This suggests that these tumours could be detected more frequently by simple imaging techniques at earlier stages of the disease, when surgical treatment is curative. The 5-year survival rate is 88–100% for localized tumours but only 20% or less for metastatic tumours [3]. As patients with localized RCC survive longer than those with disseminated disease, it is likely that a screening programme for RCC would improve disease prognosis. However, in the absence of known high-risk populations, systematic early detection of RCC may not be cost-effective.

Several potential risk factors for RCC have been identified in previous epidemiological studies. Discrepancies between these studies and the weakness of associations between various types of exposure and RCC make it difficult to identify unequivocally the true risk factors. We attempted to rank the most consistent associations and to define populations at high-risk of RCC by systematically reviewing published analytical epidemiological studies.

Methods

We searched the Medline™ database for studies published from 1987 to 1998, using a strategy including the following medical subject headings: heading 'renal cell carcinoma' and subheadings 'risk factors' or 'epidemiology'. This screening was supplemented by manually searching for all the references from retrieved articles.

To be included, epidemiological studies of RCC had to be cohort or case-control studies, and results had to be expressed as relative risk (RR) or odds ratio (OR), respectively, with 95% CI. A multivariate analysis had to have been performed to adjust for the main confounding variables. Only articles written in English about primary adenocarcinomas in adults were considered in the analysis. If an author(s) published several papers based on the same study, only data from the most recent publication were included. Studies of RCC occurring during dialysis or in transplant recipients were excluded.

Method of analysis

If several types of exposure were considered in a study, the results obtained were analysed for each of them separately. For each study, an association between an exposure and RCC was confirmed if the 95% CI for the RR or OR did not include unity. Such studies were defined as positive for this exposure. For each exposure, the number of studies relating to the association was counted. For each relevant study, the number of patients and controls, and the results expressed as RR or OR according to the level of exposure if possible, were recorded; any adjustment for confounding factors was also recorded.

An exposure was considered to be a risk or protective factor if the following criteria were met [4]: an association was observed in more than half of the studies (consistency between studies); and a dose-dependent effect shown. If only the first criterion was met, the exposure was considered to be a risk marker. If neither criterion was met, the exposure was not considered to be associated with RCC.

Results

Of the 128 articles selected from the screening, 44 were considered relevant (36 case-control and eight cohort

Accepted for publication 29 March 2000

studies). These studies analysed the effects of tobacco use, obesity, kidney diseases, hypertension, drug intake, occupational factors, hormonal status, socio-economic status, alcohol, and coffee or tea intake.

Tobacco

Ten case-control studies [5–14] and one cohort study [15] investigated the relationship between tobacco use and RCC. ORs were adjusted for age in all studies. Seven studies (Table 1) showed an association between tobacco smoking and RCC; the ORs were 1.3–9.3. In these studies, a dose-dependent effect was shown in men with a higher risk of RCC, proportional to tobacco consumption. Only consumption over 20 pack-years (PY) led to a significant association. For consumption of 20–40 PY, ORs were 1.3–1.6, and for consumption of >40 PY, ORs were 1.5–9.3; at <20 PY, there was no increase in risk.

ORs were studied separately for both sexes in five studies [6,10–14]; the association between tobacco consumption and RCC was significant only for men in four of them. Only one study showed an association between RCC and tobacco consumption in both women and men [6]. No risk from tobacco was shown for female heavy-smokers (>40 PY) in the other studies. Only two studies showed no relationship between smoking and RCC [7,8]. However, in these studies, inpatients were used as controls and heavy smokers (>40 PY) were not considered separately. Thus heavy smoking can be considered as a risk factor for RCC.

Obesity

The association between obesity and RCC was analysed in eight case-control studies [5–8,16–19]. Weight was expressed as body mass index (BMI), calculated at various times in the subjects' life (the year before diagnosis, at different 10-year intervals) or by comparison with normal adult weight. Only one study found no association between BMI and RCC [8], but BMI was not analysed separately in men and women. Another seven studies showed an association between obesity and RCC, with ORs of 1.1–4.6 (Table 2) [5–7,16–19]. Obesity was identified as a risk factor for women in four studies [16–19], and for both men and women in three others [5–7].

The age at which the subjects became obese did not seem to affect the association between RCC and obesity. There was an association between obesity and RCC only for severe obesity, defined as a BMI above the fourth quartile. In none of the relevant studies were hypertension and calorific intake regarded as confounding variables and no adjustments for these conditions were made. However, severe obesity can be classified as risk factor for RCC.

Pre-existing kidney disease

Kidney stones In four of the six studies on this topic, there was an association between a history of kidney stones

Table 1 Risk of RCC from tobacco smoking according to tobacco consumption (dose-dependent response), from positive studies in a systematic review

Year	*Reference*	*Country*	*Cases/controls* (n/n)	*Tobacco consumption**	*OR (95% CI)*
1988	[9]	Australia	360/985	100–249 kg	1.3 (0.9–1.9)
				≥ 250 kg	1.9 (1.3–2.7)
1990	[4]	USA	203/605	≥ 3 pack/day	1.7 (1.1–2.8)
				Men	1.7 (0.9–3.2)
				Women	
1992	[5]	USA	90/91	Men >20 PY	9.2 (2.1–45.2)
1993	[6]	Canada	655/1536	Men >20 PY	2.2 (1.5–3.3)
				Women >20 PY	2.2 (1.4–3.4)
1994	[10]	Denmark	368/396	Men >40 PY	2.3 (1.1–5.1)
				Women >40 PY	1.3 (0.3–5.3)
1995	[12]	Germany	273/277	Men >40 PY	2.15 (0.99–4.65)
				Women >40 PY	2.21 (0.72–6.81)
1995	[11]	Australia, Denmark, Germany, USA and Sweden.	1732/2309	20.2–36.9 PY	1.3 (1.0–1.6)
				>36.9	1.7 (1.4–2.1)
1995	[13]	USA	788/779	Men >40 PY	1.5 (1.2–2.1)
				Women >40 PY	1.1 (0.6–1.8)

*As kg tobacco or cigarette in pack-years.

Table 2 Severe obesity (BMI over the fourth quartile) and risk of RCC, from positive studies

Year	*Reference*	*Country*	*Cases/controls* (n/n)	*Men/women*	*OR (95% CI)*
1993	[7]	France	196/347	Men	2.4 (1.0–5.9)
				Women	3.5 (1.0–11.8)
1994	[6]	Sweden	NA	Women	2.4 (1.12–5.16)
1993	[16]	Canada	95/148	Men	1.2 (1.5–3.2)
				Women	2.2 (1.4–3.5)
1994	[17]	Denmark	368/396	Women	2.2 (1.1–4.4)
1995	[18]	Australia, Denmark, Germany, USA and Sweden	NA	Men	1.4 (0.9–1.8)
				Women	2.5 (1.8–3.5)
1996	[19]	USA	441/707	Women	3.8 (1.7–8.4)
1992	[5]	USA	54/39	Men	3.6 (1.1–12.6)
				Women	3.6 (0.9–14.7)

NA, not available.

and RCC [9,14,20,21], with ORs of 1.3–6.5 (Table 3). No association was found in the other studies [6,22]. ORs were studied separately for both sexes in two studies, but the association between stones and RCC was shown only for men.

UTI Four studies investigated the relationship between a history of UTI and RCC. Three showed a weak association (Table 3), with low ORs of 1.2–1.7 [6,9,21], and one showed no association [20].

Kidney injury Two studies were identified which had conflicting results; the first showed no association [20], whereas the second showed an association between a history of kidney injury and RCC (OR 3.2, 95% CI 1.9–5.5) in both men and women [21].

A history of kidney disease, such as previous kidney stones and UTI, can only be considered to be a risk marker because the relationship between RCC and the duration of exposure was not examined.

Hypertension

Many studies of the relationship between hypertension and RCC have been published, eight of which were selected using the current criteria of inclusion. Four case-control studies found an association between a history of hypertension and RCC [20,21,23,24]; the OR (95% CI) were between 1.4 (1.2–3.7) and 3.2 (1.4–1.9). In two studies, the OR was adjusted for most confounding variables (age, tobacco smoking, BMI), but not for antihypertensive drugs [20,21].

Another case-control study [13] showed that hypertension was not itself a risk factor for RCC, but that there was an interaction between high BMI and hypertension in men (OR 1.9, 95% CI 1.01–3.5) and women (3.2, 1.3–7.7). Three cohort studies [25–27] showed an association between hypertension and RCC, with RRs of 1.12 (1.06–1.18) to 2.2 (1.4–3.5), and two were negative [28,29]. Nevertheless hypertension can only be classified as risk marker, not as a risk factor, because no dose-dependent effect was shown.

Medication

Analgesics (paracetamol, aspirin, phenacetin) Exposure to aspirin was analysed in four studies and none detected an association with RCC [9,20,30,31]. Paracetamol intake was not associated with RCC in six studies [9,20,30–32]. There was an association between phenacetin and RCC in three studies [16,20,31], with ORs (95% CI) of 2.9 (1.5–5.4), 5.9 (1.2–28.9) and 2.1 (1.0–4.4). Three other studies showed no association [6,8,30]. The risk of RCC was higher if phenacetin was consumed regularly, and although there was no clear relationship between the amount taken and the size of the risk, the highest risk was associated with the greatest exposure of >1.1 kg cumulative consumption [9]. This association was considered separately for men and women in two studies, and was found to apply only in women [20,31]. Adjustments were made for age, sex and tobacco smoking in studies reporting a significant association [9,20,31].

Antihypertensive drugs The only antihypertensive drugs found to be associated with RCC in two studies were thiazidics, with an OR of 2.3 (1.3–4.0) and 4 (1.5–10.8), respectively [6,33]. Adjustment was made for hypertension. In the two studies, there was an association between unrestricted intake of one class of diuretics and RCC only in women. Another case-control

Table 3 Medical history (history of kidney stones and infection) and the risk of RCC, from positive studies

Disease	*Year*	*Reference*	*Country*	*Cases/controls*	*Men/women*	*OR (95% CI)*
Kidney stone	1994	[20]	Denmark	16/4	Men	6.5 (1.8–24)
Kidney stone	1996	[21]	Australia, Denmark, Germany, USA, and Sweden	48/48	Men	1.3(1.1–1.7)
Kidney stone	1988	[9]	Australia	NA	NA	1.7 (1.2–2.4)
Kidney stone	1990	[14]	USA	203/605	NA	2.3 (1.3–4.1)
Kidney infection	1993	[6]	Canada	38/93	Women	1.9 (1.2–2.9)
Kidney infection	1988	[9]	Australia	NA	Women	1.7 (1.2–2.4)
Kidney infection	1995	[21]	Germany	216/156	Both	1.2 (1.0–1.6)

NA, not available.

study showed an association between diuretics and RCC in both women and men with ORs of 2.2 (1.2–3.9) in men and 1.8 (1.01–3.2) in women, but exposure to diuretics and hypertension were not analysed separately [34]. Two other studies showed no association [20,35]. Thus thiazidic and phenacetin intakes can be considered as risk markers for RCC.

Occupational exposure

One cohort and 10 case-control studies [12,36–45] analysed the association between various types of occupational exposure and RCC. Two case-control studies showed an association between occupational exposure to iron or steel and RCC [12,36], with ORs of 1.6 (1.2–2.2) and 1.6 (1.07–2.48), and one showed no association [41]. This risk was reported only for an exposure of >3 years.

An association between occupational exposure to petrol and RCC was reported in two studies [36,39], with ORs of 1.3 (1.2–2.0) and 1.6 (1.4–2.5). In the cohort study [44], a significant increase in risk was identified (RR 1.3, 1.0–1.7). Risk related to hydrocarbon exposure was analysed in three studies [12,36,40] and only one showed an association (OR 1.6, 1.3–2.1) [36]. A high risk related to occupational exposure to asbestos or cadmium was reported in only one case-control study, with ORs of 1.4 (1.1–1.8) and 2.0 (1.0–3.9), respectively [36].

Textile workers were found to be at higher risk in only one study (OR 6.2, 1.1–33.8) [38]. Dry-cleaning solvent use was investigated in two studies; there was an association in one (OR 1.4, 1.1–1.7) for exposure of $>$ 5 years [36], but not in the other [37]. Fire-fighters (OR 3.51, 2.08–5.92) and glass-workers (OR 3.47, 1.64–7.35) were other occupational categories at higher risk of RCC [37].

Several occupations were not associated with RCC, including dentists, printers and architects. Occupations in the oil refinery industry and in chemistry [45] were reported not to be associated with RCC.

In most of these studies, the duration of exposure was not assessed. If the sexes were analysed separately, there was an association of RCC with occupational factors only in men. Adjustment was made for tobacco smoking in the studies assessing the association of RCC with petrol exposure, hydrocarbon exposure and iron/steel industry workers.

Thus some occupations involving iron, steel and petrol exposure appear to be risk markers for RCC. Fire-fighters and glass-workers may also be at risk of RCC, but no dose-dependent effect has been observed.

Socio-economic status

In three case-control studies [10,16,36] the association between RCC and socio-economic status was analysed. A protective effect of the highest social status was shown in two [10,36], with ORs of 0.4 (0.02–0.9) and 0.7 (0.6–0.9). These studies were adjusted for age, BMI and tobacco use, but not for occupation, a possible confounder.

Medical history

No significant increase of risk was found in the study that analysed the risk of RCC in patients with heart disease [20]. Three case-control studies analysed metabolic diseases, diabetes and thyroid diseases [18,20,21]. An association was found in only one study, for diabetes [18] (OR 1.4, 1.0–1.8) and thyroid diseases (OR 1.6, 1.3–2.2).

Coffee and tea consumption

Coffee consumption was analysed in five case-control studies [6,7,10,18,46]; only one showed an association between coffee intake and RCC [46], in women only (OR

2.1, 1.2–3.7). No association was shown in any of the other studies, even for high consumers. Four studies investigated tea consumption [6,7,10,18] and only one found a possible association with RCC in men (OR 1.9, 1.0–3.6) [10].

Alcohol

Six case-control studies assessed the relationship between alcohol consumption and RCC [10,13,18,46,47]. A protective effect was detected in three studies, with ORs of 0.4 (0.2–0.9), 0.5 (0.29–0.84) and 0.7 (0.5–1.0) [10,18,47]. This effect was apparent only in women and for the consumption of >2 drinks per week. Only moderate alcohol intake of 2–10 drinks per week was analysed. The risk of RCC was lower for higher levels of alcohol intake, with an inverse dose-dependence effect relationship. No association between alcohol intake and RCC was observed in men.

Reproductive and hormonal factors

Reproductive factors were analysed in three case-control studies [5,19,35], but no association was detected between age at menarche, age at first pregnancy, number of births and RCC.

Oral contraceptive use was apparently protective against RCC [17,18,35], with ORs of 0.7 (0.5–0.9), 0.4 (0.1–1.0) and 0.5 (0.3–0.9), respectively. This effect was seen only in non-smokers and after 10 years of oral contraceptive use [18]. There was no relationship between oestrogen-replacement treatment and RCC.

The association of RCC with a history of hysterectomy and oophorectomy was investigated in two studies [19,35] and was significant in both, with ORs of 2.3 (1.3–4.2) and 1.7 (1.0–3.1).

Discussion

The aim of this assessment was to identify populations at risk of RCC, by systematically reviewing the numerous studies published; to our knowledge, this is the first such review in this field. RCC is a relatively rare disease, so most of the studies included were of case-control. We are aware of only eight published cohort studies. RCC was associated with tobacco smoking, obesity, contraceptive use, moderate alcohol consumption, a history of kidney disease and hypertension (Table 4). RCC is probably also associated with some occupational factors, treatment with thiazidic drugs and socio-economic status. No association was found with coffee and tea consumption, or oestrogen-replacement therapy. Associations with other types of exposure were found, but in too few case-control studies; further studies are required for these factors to be clearly identified.

Tobacco smoking and obesity are risk factors, as they met criteria for this definition [4] (consistency of the studies, dose-dependent effect, strength of the association). A history of hypertension, thiazidic drug intake and occupational exposure can only be regarded as risk markers because there was no relationship with dose or the duration of exposure.

There was a dose-dependent effect of tobacco smoking in all the positive studies when consumption was >20 PY; only two studies showed no such association, possibly because of the design of these studies and their lack of power for identifying statistically significant associations. The increase in RCC risk related to tobacco smoking was lower than for lung and bladder cancers; however, this exposure affects a large population [48]. Thus, although the association between RCC and tobacco is weak, the unadjusted risk attributable to this exposure is high. With an estimated OR of 2 and 20–40% of the adult population smoking tobacco, 16–28% of the RCC cases in this population could be prevented by eliminating smoking. This risk factor appeared to sex-linked and was shown to affect only men, with no effect in women, even those who smoked heavily.

A relationship between severe obesity (defined as a BMI over the fourth quartile) and RCC was identified in seven of eight studies. This increase in risk was found only in women, but the effect of the duration of obesity was not analysed, and the age at which the subject became obese did not affect the results. Overweight women have been shown to have significantly higher rates of endometrial, gall bladder, cervical, ovarian and breast cancers [49]. The mechanisms by which obesity may affect cancer include changes in hormone patterns, including those for sex hormones and insulin, or in growth factors, and in factors such as the distribution of body fat and changes in adiposity at various ages [50]. Obese women have higher concentrations of oestrogen than those who are not, and oestrogen and progesterone receptors have been detected in normal and malignant renal cells [51].

Associations were found between RCC and pre-existing diseases of the kidney and urinary tract, including stones and infections. These associations were weak but statistically significant and were found in most of the studies. Urinary stasis during obstruction episodes may be involved in the development of the neoplasm. The duration of kidney disease, e.g. prolonged urinary obstruction, which may affect the impact of this factor, has not been evaluated.

In this review, alcohol and some hormonal factors were protective in women and did not affect the risk of RCC in men. A protective effect of alcohol was found only for moderate consumption, with an inverse dose-dependent effect. Oral contraceptive use was protective against RCC, depending on its duration.

Table 4 A summary of risk and protective* factors for RCC from the systematic review

	No. of studies				
Exposure	*Total*	*Positive*	*Negative*	*Dose-response*	*References*
Tobacco	10	8	2	4	[5–14]
Obesity	8	7	1	3	[5–8,16–19]
Kidney stones	6	4	2	0	[6,9,14,20–22]
Kidney infection	4	3	1	0	[6,9,20,21]
Kidney injury	2	1	1	0	[20,21]
Hypertension	7	6	1	0	[13,20,21,23–29]
Phenacetin	6	3	3	0	[6,8,16,20,30,31]
Antihypertensive drugs	5	3	2	0	[6,20,33–35]
Petrol occupational exposure	3	3	0	0	[36,39,44]
Iron steel industry	2	1	1	0	[16,36,41]
Hydrocarbons occupational exposure	3	1	2	0	[12,36,40]
Alcohol*	6	3	3	0	[6,10,13,18,46,47]
Oral contraceptive*	3	3	0	5	[17,18,35]
Socio-economic status (high vs. low)*	3	2	1	2	[12,20,36]

Several occupational factors, including exposure to hydrocarbons and their derivatives (petrol, solvents), and occupations such as fire-fighting and working in the iron and steel industry that result in such exposure, led to a higher risk of RCC. The association of exposure to hydrocarbons with RCC was weak but was apparent in several studies. This risk was independent of tobacco use. The duration of occupational exposure was >30 years when reported. Other types of occupational exposure (asbestos, solvents) were analysed in only one study. Thus, even if associations of these types of exposure with RCC were strongly suggested, further work is required to confirm the risk.

More than half of the studies dealing with the effects of medication failed to show an association between diuretic intake and RCC, thereby excluding this type of exposure as a risk factor. Phenacetin has been implicated in urothelial carcinogenesis [52]; there was an association between phenacetin intake and RCC in almost all the studies examining this factor. This drug has now been withdrawn from the market. No association with RCC was shown for exposure to other analgesics such as paracetamol and aspirin.

Socio-economic status seems to have a minor effect on the risk of RCC. The highest status may protect against RCC independently of tobacco consumption, but occupational exposure was not considered as a potential confounder.

The present review has several limitations. A meta-analysis of the published data would have been the best method for identifying and ranking risk and protective factors for RCC, but this was not possible because there were too few studies dealing with each selected factor and they were heterogeneous. A systematic review of these published studies was the only analysis possible.

Conclusion

Several independent risk and protective factors for RCC were identified. Protective factors such as oral contraceptive use and moderate alcohol consumption were only identified in women. Tobacco consumption and severe obesity were the main independent risk factors. However there were other modifiable risk markers, e.g. occupational exposure, thiazidic drug intake and UTIs. The associations between risk factors and RCC were weak, even for tobacco, for which the association was weaker than that for lung cancer. However, the identified risks involve a large proportion of the population, and the risk attributable to these types of exposure is high.

Our recommendations for the prevention of RCC are therefore similar to those for the prevention of cardiovascular disease and cancer, and should be disseminated to the general population. The high-risk groups identified are too large for a specific early screening programme for RCC, but such screening might be more appropriate if restricted to selected age groups.

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