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Risk Factors for Renal Cell Carcinoma in Denmark: Role of Medication and Medical History

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Background. Several recent studies of risk factors for renal cell carcinoma have indicated that use of diuretics may increase risk of this cancer. It has also been suggested that use of weak analgesics, which are known to increase risk of cancer of the renal pelvis and ureter, may also be associated with an increased risk of renal cell carcinoma—the most frequent type of kidney cancer.

Methods. A population-based case-control study was undertaken to investigate the role of diuretics, other anti-hypertensive drugs, analgesics, and medical history in the aetiology of renal cell carcinoma. The study base was the total Danish population, and 368 histologically verified cases and 396 sex- and age-matched controls who were interviewed from February 1989 to May 1992.

Results. Response rates were 76% among cases and 79% among controls. We found no general increase in risk among users of diuretics or analgesics, although women taking loop diuretics and heavy users of acetyl salicylic acid had slightly increased risks. The use of nondiuretic anti-hypertensive medications was associated with decreased risk in women. We found non-significantly increased risks for history of hypertension and other cardiovascular disorders. We also observed elevated risks for urological disorders in both sexes which may be a result of recall bias.

Conclusion. This study provides only limited support for the suggested association between risk of renal cell carcinoma and use of diuretics and analgesics. The coexistence of renal cell carcinoma and cardiovascular diseases could be caused by risk factors that are common to these conditions.

Kidney cancer, of which renal cell carcinoma (RCC) is the most common form, is the ninth most common cancer in Denmark with an incidence rate of 8 per 100 000.[1] Rates of a similar magnitude are found in other Scandinavian countries as well as in several countries in northern Europe, and the US.[2] The aetiology of RCC remains unresolved. However, a number of studies have identified cigarette smoking and high relative weight to be consistent risk factors for RCC.[2] The findings from a case-control study from Los Angeles,[3] indicate that diuretics may increase the risk of RCC and supportive evidence for this association has been found in subsequent studies.[4–8] Diuretics are predominantly used in the treatment of hypertension, congestive heart failure, and renal failure, but in some situations may also be used for weight control. Hypertension and other cardiovascular disorders, which may be treated with diuretics, have been reported to coexist more often in RCC cases than controls, and other kidney diseases may predispose to kidney cancer.[9]

Since the use of diuretics is extensive in western countries and the incidence of RCC is rising in many of these countries, an international collaborative population-based study of RCC was undertaken in Australia, Denmark, Germany, Sweden and the US. The findings from Denmark relating to use of diuretics, other anti-hypertensive drugs, analgesics and previous medical history are presented here.

MATERIAL AND METHODS

Histologically confirmed RCC cases who were diagnosed between 1 February 1989 and 31 May 1991, were 20–79 years old, were born in and lived in Denmark, were included. Cases were identified from notifications to the Danish Cancer Registry and by regular review of all pathology department files in Denmark. Of 482 cases identified, 44 (9.1%) died before they could be contacted, 26 (5.4%) were too ill to participate, 33 (6.8%) refused to be interviewed and

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we were unable to contact 11 (2.3%). The remaining 368 (76.3%) were interviewed by a trained interviewer in the subject's home approximately 3–5 months after diagnosis.

Population-based controls were sampled from the Central Population Register which keeps a record of all Danish inhabitants. Controls were frequency-matched on gender and age in 5–year groups. An initially sampled control group was found to be unevenly distributed with respect to region of residence. This prompted us to investigate the procedures used in the creation of the Central Population Register, and we discovered that, contrary to intentions, personal identification numbers were assigned to individuals in groups according to place of residence in 1968 when the system was implemented. To avoid the problem, the number of controls from regions that were underrepresented was increased by adding a new age– and sex-matched random sample from that region. Because of the need for additional data collection the median time for interview of the controls was 9 months later than for cases. A total of 500 controls were selected. Of these, 72 (14.4%) refused to participate, 20 (4.0%) were too ill, and we were unable to contact 12 (2.4%).

Information on drug use, medical history, weight, height, education, occupation, reproductive history, and diet was collected by means of a structured questionnaire during a personal interview. The subjects were asked to disregard any exposure or drug use for the 12 months prior to interview. A complete history of use of diuretics, non-diuretic anti-hypertensive drugs, and analgesics was sought by supplying the subject with lists and pictures of the available drugs. Because the composition of the drugs, especially analgesics, has changed over time, the information on brand names was converted to information on active ingredients by using a matrix, which included ingredients of the drug used over the past 30–40 years. The drug-exposure matrix incorporates information obtained from the drug companies on composition of the drugs and the data of their entry and exit from the market. If a subject reported using a drug that was outside the period when the drug was available, a period of 1 year before or after the marketing period was allowed. Usage outside this period was censored. If the subjects did not provide the strength of the drug, the minimum strength available at the time of usage was assigned. If the subject indicated that he or she was a regular user of a particular drug, but did not provide the duration of use, or number of pills, a minimal period of consumption was assumed. For diuretics and other anti-hypertensives the minimal consumption was twice weekly for 2 weeks, for analgesics twice weekly for 1 month. Furthermore, subjects were asked about the reason for taking a particular drug. Information on history of circulatory disorders, kidney disease, and metabolic disturbances was elicited along with age at diagnosis.

Potential confounding by suspected risk factors (cigarette smoking and high relative weight) was avoided by including these factors in unconditional multivariate models.[10] Relative weight, which was found to be a risk factor in women only, was calculated using the body mass index (height/weight^2 for men and height/weight$^{1.5}$ for women).[11] Pack-years were used to control for the effect of cigarette smoking which was a risk factor in men only. Socioeconomic status (SES) was found, in our data, to be inversely related to risk of RCC.[12] As a result we adjusted our findings for this factor using the longest held occupation for men. For married women, the highest SES within the spouse pair was used, and for single women her own SES was used. The SES was grouped in three categories according to a modification of the definitions developed by the Danish National Institute of Social Research;[13] I: administrative and managerial workers, and academics; II: sales people, clerical workers, and teachers; III: skilled and unskilled workers. Men and women were analysed separately, and since smoking was a risk factor only among men and relative weight only among women different adjustment variables were used.

RESULTS

There were 226 male and 142 female cases of RCC, and 237 male and 159 female controls. Of the male cases, 19% versus 15% of the male controls had used diuretics, while 44% of the female cases versus 35% of the female controls used these medications.

Table 1 presents the OR associated with diuretic use stratified for hypertension status, and OR associated with hypertension stratified for diuretic use. As can be seen there was a moderate insignificant increase in risk among men and women for diuretic use, but after stratification for hypertension status the initial effect of diuretic use disappears. The elevated risk associated with hypertension remains regardless of diuretic use. In Table 2, a more detailed analysis of exposure to specific diuretics is presented. Since a few subjects reported use of a diuretic of unknown type, the numbers of exposed cases and controls are slightly lower than in Table 1. In general, there is no significant increase in risk among diuretic users, and no signs of dose-response effect. However, among women it appears that use of loop diuretics may be associated with a slightly increased risk. This association with loop diuretics among women was also evident when amount taken was examined

TABLE 1 *Risk factors for renal cell carcinoma. Role of diuretic use and hypertension*

	Men				Women			
	Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[b] (95% confidence interval)
Ever used diuretics								
No	182	201	1	1	79	103	1	1
Yes	44	36	1 3	1.4 (0.8–2.2)	63	56	1.5	1.5 (0.8–2.1)
No history of hypertension								
Used diuretics								
No	160	184	1	1	68	94	1	1
Yes	14	17	0.9	0 7 (0.4–2.0)	21	24	1.2	1.4 (0.6–2.9)
Has hypertension								
Used diuretics								
No	22	17	1	1	11	9	1	1
yes	30	19	1.2	1.6 (0.5–3.5)	42	32	1.1	0.9 (0.2–3.5)
Ever diagnosed with hypertension								
No	174	201	1	1	89	118	1	1
Yes	52	36	1.7	1.8 (1.0–2.7)	53	41	1.7	1.8 (1.1–3.2)
Never used diuretics								
Hypertension								
No	160	184	1	1	68	94	1	1
Yes	22	17	1.6	1.5 (0.7–2.9)	11	9	1 6	2.3 (0.8–6.6)
Used diuretics								
Hypertension								
No	14	17	1	1	21	24	1	1
Yes	30	19	1.9	3 3 (1 0–11)	42	32	1.5	1.3 (0.5–3.2)

[a] Odds ratio estimated in models including terms for age.
[b] Odds ratio estimated in models with age, smoking, socioeconomic status and body mass index.

within time period of use (Table 3). However, this observation is based on small numbers and none of the increased risks reached statistical significance. For men, a similar, but weaker, and equally non-significant effect was noted for thiazide use.

The OR for use of non-diuretic anti-hypertensive drugs are shown in Table 4. We found no increase in risk for use of these drugs. Conversely, decreased risks were observed for female users of beta blockers and perhaps also ACE inhibitors. Table 5 examines the risk for use of analgesics. Overall, modestly increased risks were found for use of these drugs, and when examined by amount, heavy users of acetyl salicylic acid (ASA) and perhaps also phenacetin had a non-significant increased risk. No association was found for paracetamol (acetaminophen).

A number of medical conditions were examined in relation to risk of RCC (Table 6). Non-significant excess risks were seen for angina pectoris and myocardial infarction. Kidney stones, injury, and infections were also reported by more cases than controls in both sexes. Diabetes and thyroid gland disorders were associated with RCC among women but not men, as were stroke and bladder infection. Only one male control and one female case reported having any of the vascular diseases within the last year. A urological disorder within the last year was reported by 14 male cases, 1 male control, 4 female cases and 1 female control. Excluding these subjects reduced the risk estimates for the urological conditions, while risk estimates for the vascular conditions remained (data not shown). The risk estimates for the vascular conditions, which could be secondary to hypertension, remained when adjusted for history of hypertension (data not shown).

DISCUSSION

The information on exposures in this study comes entirely from the subjects. Although efforts were made to ensure correct information, misclassification of

TABLE 2 *Risk of renal cell carcinoma (RCC) with diuretic use by amount and length of use prior to diagnosis*

	Men				Women			
	Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[c] (95% confidence interval)
Never used diuretics	182	201	1	1	79	103	1	1
Type used:								
Any	40	33	1 3	1.1 (0.6–2.0)	60	50	1.6	1.1 (0.6–1.9)
Loop	12	10	1.2	1.1 0.4–2.6)	18	9	2.7	1.6 (0.6–4 0)
Thiazide	28	23	1.3	1.1 (0.5–2.2)	46	41	1.5	1.0 (0.5–1.9)
Potassium sparing	5	2	2.7	2.2 (0.4–12.6)	9	10	1.2	0.8 (0.3–2.2)
Amounts (g)								
Loop								
<15 g	7	3	2.4	2.1 (0.5–8.4)	11	5	2.9	1.6 (0 5–5.2)
>15 g	5	7	0.8	0.6 (0.2–2.1)	7	4	3.2	1.6 (0.4–6.1)
Thiazide								
<1 g	7	6	1.3	0.9 (0.3–3.1)	5	10	0.7	0.5 (0.1–1.6)
1–5 g	7	6	1.3	0.9 (0.3–3.0)	16	6	3 5	2.3 (0.8–7.0)
5–20 g	7	6	1.3	0.9 (0.3–3.0)	11	16	0.9	0.5 (0.2–1 4)
>20 g	7	5	1.5	2.0 (0.5–8 7)	14	9	2 0	1.5 (0.5–4.0)
Time period before RCC diagnosis (years)								
Loop								
1–3	10	9	1.1	1.0 (0.4–2.6)	12	6	2.7	1.6 (0.5–4.9)
3–8	11	7	1.6	1.4 (0.5–3.8)	13	7	2.5	1.5 (0.5–4.3)
8–13	3	4	0.8	0.7 (0.2–3.1)	11	4	3.6	2.4 (0.7–8.4)
>13	1	3	0.4	0.3 (0.03–3.2)	6	3	2.6	1.9 (0 4–9.1)
Thiazide								
1–3	24	14	1 9	1.6 (0.7–3.8)	30	29	1 4	0.8 (0.4–1.9)
3–8	22	17	1.4	1.2 (0.5–2 7)	30	34	1.2	0.8 (0.3–1 7)
8–12	13	12	1.1	1.0 (0.4–2.7)	23	23	1.4	0.8 (0.3–2.0)
>13	8	8	1.1	1.1 (0.3–3.6)	23	18	1.7	1.1 (0.5–2.6)

[a] Odds ratio estimated in a model including terms for age.
[b] Odds ratio estimated in a model including terms for age, smoking, socioeconomic status (SES) and history of hypertension.
[c] Odds ratio estimated in a model including terms for age, history of hypertension, SES, and body mass index.

exposure is a concern. As misclassification tends to drive risk estimates towards 1, it would cause negative findings. In Denmark, diuretics are only available on prescription by a physician, and it is unlikely that an individual would be ignorant of the nature of the drug. Weak analgesics, however, are available over-the-counter and it is possible that users of these drugs shift between different types of analgesics. Hence, although exposure misclassification may be present, especially for analgesics, we find it unlikely that this explains the negative findings for diuretics.

Controls were interviewed with a median time of interview 9 months later than cases. This is a problem if the exposure rates of the risk factors are changing during the study period. This is only the case for ACE inhibitors where use has been increasing. The consumption of diuretics, beta blockers and calcium channel blockers has remained stable.[14] Thus the difference in time of interview will not affect the findings for diuretics, but may partially explain the decreased risk observed for use of ACE inhibitors.

This study provides only limited support for the suggested association between risk of RCC and use of diuretics. We observed the relation among women using loop diuretics, of which furosemide is the most common type, and among male users of thiazides. Loop

TABLE 3 *Risk of renal cell carcinoma (RCC) for diuretic use by amount within period of diagnosis*

	Men				Women			
	Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[c] (95% confidence interval)
Never used diuretics	182	200	1	1	78	103	1	1
Loop (use years prior to RCC)								
1–3 years								
<5 g	6	2	3.1	2.6 (0.5–13.6)	6	4	2.0	1.3 (0.3–5.3)
>5 g	4	7	0.6	0.5 (0.1–1 8)	6	2	4.0	2.2 (0.4–12.6)
3–8 years								
<5 g	5	2	2.6	2.2 (0 4–12.0)	6	4	2.0	1.2 (0 3–4.8)
>5 g	6	5	1 2	1 1 (0.3–3.7)	7	3	3.2	1.9 (0.4–8.2)
8–13 years								
<5 g	2	0	–	–	5	3	2.2	1.4 (0.3–6 8)
>5 g	1	4	–	–	6	1	8.0	5.2 (0.6–48)
>13 years								
<8 g	0	1	–	–	1	2	2.6	1.7 (0.1–25 3)
>8 g	1	2	–	–	4	2	2.6	2 0 (0.3–13.1)
Thiazides (use years prior to RCC)								
1–3 years								
<5 g	18	10	2.0	1.5 (0.6–4.0)	21	20	1.4	0.8 (0.3–2.8)
>5 g	6	4	1.6	1.7 (0.4–7 6)	9	9	1.4	0.9 (0 9–1.7)
3–8 years								
<5 g	12	12	1.1	0.7 (0.3–1.9)	18	23	1 0	0.6 (0.3–1.6)
>5 g	10	5	2.2	2.9 (0.7–11.7)	12	11	1.5	1.0 (0.3–2.7)
8–13 years								
<5 g	6	7	0.9	0.6 (0 2–2.1)	13	16	1.1	0 6 (0.2–1.8)
>5 g	7	5	1.5	2.1 (0 5–8.7)	10	7	2.0	1.2 (0.4–3.8)
>13 years								
<5 g	5	5	1.1	0.8 (0.2–3.2)	1	9	1.1	0.7 (0.2–2.1)
>5 g	3	3	1.1	2.4 (0.2–25.6)	2	14	2.8	1.7 (0.6–5.1)

[a] Odds ratio estimated in a model including terms for age.
[b] Odds ratio estimated in a model including terms for age, smoking, socioeconomic status (SES) and history of hypertension.
[c] Odds ratio estimated in a model including terms for age, history of hypertension, SES, and body mass index.

diuretics exert their action primarily on the loop of Henle rather than the proximal convoluted tubules, the site of origin of RCC.

The two earlier case-control studies which first reported a link between RCC and diuretic use, found the risk only among women.[3,4] A recent large-scale population-based study in Canada has also reported a significantly elevated risk for RCC and diuretics restricted to women.[8] Cohort studies, however, have reported associations among men.[5–7] In a recent Australian study non-diuretic anti-hypertensive medication, but not diuretics, was found to increase the RCC risk.[15] In our study we found no evidence for non-diuretic anti-hypertensive medication as a risk factor for RCC, on the contrary decreased risks were observed. There is limited animal evidence that furosemide[16] and hydrochlorothiazide,[17,18] the two most common diuretics, are linked to renal tumours. In our study, we have found a consistent increase in risk for individuals with a history of hypertension. The increased risk was present regardless of length of time between diagnosis of hypertension and RCC and regardless of what type of drug was used to treat the hypertension. In case series, hypertension has been found to be present in a varying percentage of cases and it has been proposed that RCC induces hypertension by increasing the renin level in the patient, although increased levels of renin have been observed in only a limited number of patients.[9,19] Elevated risks, however not significant, were found for other cardiovascular

TABLE 4 *Risk of renal cell carcinoma for use of non-diuretic antihypertensive drugs*

	Men				Women			
	Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[c] (95% confidence interval)
Never used anti-hypertensive drugs	199	212	1	1	121	134	1	1
Type								
Any	21	19	1 2	0 6 (0 2–1 4)	16	23	0 8	0 4 (0 1–0.8)
Beta blockers	15	12	1.3	0.6 (0.2–1.6)	11	18	0 7	0.3 (0 1–0.7)
ACE inhibitors	1	3	0.3	0.1 (0.0–1.4)	1	1	1.1	0 5 (0.02–9.7)
Calcium channel blockers	5	2	1 7	1.1 (0 2–6.9)	4	3	1 4	0 8 (0.2–4.4)
Alpha blockers	2	1	2.2	0.7 (0.1–9.0)	2	4	0 5	0 2 (0.04–1.4)

[a] Odds ratio estimated in a model including terms for age.
[b] Odds ratio estimated in a model including terms for age, history of hypotension, socioeconomic status (SES) and smoking.
[c] Odds ratio estimated in a model including terms for age, history of hypertension, SES, and body mass index.

TABLE 5 *Risk of renal cell carcinoma for use of analgesics*

	Men				Women			
	Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[c] (95% confidence interval)
Never used analgesics	181	202	1	1	105	126	1	1
Ever used:								
Any	39	27	1.6	1.3 (0.9–2.5)	31	32	1.2	1.1 (0.6–2.0)
ASA	34	22	1.7	1.4 (0 8–2 7)	24	22	1 3	1 3 (0 7–2 6)
paracetamol	11	10	1.3	1.1 (0.5–3.0)	11	14	0.9	1.0 (0.4–2.5)
phenacetin	7	6	1.3	1.9 (0 3–2.9)	9	2	5.4	5 9 (1 2–28.9)
phenazone	5	4	1.5	1.6 (0.3–4.1)	8	4	2.4	2.2 (0.6–7.8)
salicylamide	2	3	0.8	0.9 (0 1–3.8)	4	3	1.6	1.4 (0.3–6 6)
Never used analgesics	181	202	1	1	105	126	1	1
Amounts used (g)								
ASA								
<200	7	5	1.6	1.6 (0 5–5 2)	4	6	0.8	0.8 (0.2–2.8)
200–800	9	7	1.5	1.2 (0.4–3.4)	2	4	0 6	0.5 (0.1–2.9)
800–2500	5	3	1 4	1 5 (0.4–5 8)	5	5	1.2	1.2 (0.3–4.2)
2500–10 000	8	6	1.5	1.5 (0 5–4.5)	6	5	1.5	1.6 (0 5–5 7)
>10 000	5	1	5.6	3.1 (0.3–29)	7	2	4.1	4.0 (0.8–20.3)
Paracetamol								
<1000	16	11	1.5	1.4 (0.5–4.3)	8	5	1.9	2.0 (0.6–6.5)
>1000	7	13	1.1	0.9 (0.2–4.0)	3	9	0.4	0.5 (0.1–1.8)
Phenacetin								
<1000	6	5	0.6	0.4 (0.1–2.5)	4	1	5.0	6.0 (0.6–57)
>1000	10	3	2.7	1.9 (0.3–11.1)	5	1	5.8	5.9 (0 6–53)

[a] Odds ratio estimated in a model with terms for age.
[b] Odds ratio estimated in a model with terms for age, smoking, history of hypertension and socioeconomic status (SES).
[c] Odds ratio estimated in a model with terms for age, body mass index, history of hypertension, and SES.

TABLE 6 *Risk of renal cell carcinoma for previous medical history*

		Men				Women			
		Cases	Controls	OR[a]	OR[b] (95% confidence interval)	Cases	Controls	OR[a]	OR[b] (95% confidence interval)
Angina pectoris	no	203	224	1	1	122	148	1	1
	yes	23	13	1.9	1 8 (0.8–3.9)	20	11	2.2	1.6 (0 7–3.6)
Myocardial infarction	no	209	224	1	1	133	158	1	1
	yes	17	13	1.4	1.2 (0.6–2.7)	9	1	10.8	7 0 (0.9–57)
Stroke	no	220	228	1	1	135	157	1	1
	yes	6	9	0.7	0.6 (0 2–1.7)	7	2	4.0	3.1 (0 6–17)
Diabetes	no	216	226	1	1	129	154	1	1
	yes	10	11	0 9	0 9 (0.4–2.3)	13	5	3 1	2.3 (0.7–6.9)
Thyroid disorders	yes	220	232	1	1	124	145	1	1
	no	6	5	1.2	0.8 (0.2–3.4)	18	14	1 5	1 6 (0 8–3.5)
Kidney stone	no	186	214	1	1	128	148	1	1
	<10 years	16	4	4.5	6.5 (1 8–24)	4	1	5.0	4.8 (0.5–47)
	>10 years	24	19	1.5	1.6 (0.8–3.1)	10	10	1.1	1.0 (0.4–2.5)
Kidney injury	no	217	236	1	1	137	157	1	1
	<10 years	2	0	–	–	3	1	3.5	3.7 (0.3–39)
	>10 years	6	1	6.5[c]	–	2	1	2.3	2.5 (0.2–32)
Kidney infection	no	217	231	1	1	113	139	1	1
	<10 years	4	1	4.3	4.6 (0.5–45)	9	4	2.8	2 8 (0.8–9.9)
	>10 years	4	5	0 8	0.8 (0.2–3.3)	19	16	1 5	1.1 (0.5–2.3)
Bladder infection	no	190	194	1	1	63	89	1	1
	<10 years	13	19	0.7	0.5 (0.2–1.1)	16	15	1.5	1.4 (0.6–3.2)
	>10 years	22	21	1.1	1.1 (0.6–2.1)	46	44	1.5	1.3 (0.7–2.2)

[a] Odds ratio estimated in model with terms for age.
[b] Odds ratio estimated in model with terms for age, smoking, body mass index and socioeconomic status.
[c] Crude odds ratio.

disorders such as angina pectoris and myocardial infarction. This may suggest that hypertension is not an early symptom of RCC but rather that the two conditions coexist in the same individual more frequently than would be expected from chance alone, perhaps because of overlapping risk factors for RCC and cardiovascular disorders.

We observed no significantly elevated risk with analgesic use in Denmark. We found limited evidence of an increased risk of RCC among heavy users of phenacetin, a known cause of transitional cell cancer.[2] Our observation lends support to a number of earlier case-control studies which reported an association with phenacetin.[2] The modest increase in risk for heavy users of ASA does not support results from a Californian cohort study of a large increase in risk of RCC among ASA users.[20] Virtually all other studies of RCC and ASA have found no association,[2] including a recent study from Australia.[21] Paracetamol, the major metabolite of phenacetin, was not related to risk in our study, although the Australian study did report some increase in risk.[21] Further monitoring of this analgesic is necessary because of the pharmacological similarity to phenacetin and its widespread use. Overall, the weak to moderate excess risks associated with analgesic use were similar to those we observed among patients likely to use analgesics heavily.[22]

Various kidney diseases were more common in cases than controls in both sexes, although only the occurrence of kidney stones among men was significant.

Thyroid disease and diabetes were reported more often by female cases than controls, but male cases reported these diseases in about equal frequency compared with controls, confirming an earlier report of cancer risk in individuals with diabetes.[23] The association with kidney stones and infection was most pronounced if diagnosed less than 10 years before the diagnosis of RCC, and therefore may indicate an early symptom of cancer, while a history of kidney injury increased the risk for RCC even if the injury happened many years before the RCC. As we lack a biological explanation for the association between trauma and subsequent cancer, recall bias remains a likely explanation for this association.

CONCLUSION

The findings of our study offer only limited support to the hypothesis that diuretic use is related to risk of RCC, although slightly increased risks were observed for male users of thiazides and female users of loop diuretics. Non-diuretic anti-hypertensive medication may be associated with a decrease in risk. Overall, analgesics were not associated with RCC except for some elevation in risk among heavy phenacetin and ASA users. Medical history of hypertension, angina pectoris, myocardial infarction and various kidney disorders was more common among cases than controls.

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