Cancer Causes and Control, 3, 309-312

Diuretics may increase risk of renal cell carcinoma

Anders Mellemgaard, Henrik Møller, and Jørgen H. Olsen

(Received 30 December 1991; accepted in revised form 16 April 1992)

The risk for kidney cancer was examined in a Danish cohort of 192,133 people on a hospital discharge register who had been given a diagnosis of hypertension, heart failure, or edema, and were presumed to be probable users of diuretics. The subjects were identified from 1977 to 1987 and followed-up for cancer through 1987. A total of 10,630 cancers was observed. While the risk for all cancers was increased slightly (standard mortality ratio [SMR] = 122, 95 percent confidence interval [CI] = 120-124), the risk for renal cell carcinoma was more than doubled (SMR_{men} = 221, CI = 192-253; SMR_{women} = 246, CI = 213-283). Increased risks were found in all age groups, and, although surveillance bias was present initially, the risk increased consistently in the years following discharge. Risk estimates for individuals discharged with hypertension were similar to those for the total cohort. Use of diuretics was validated in a random sample of 100 individuals. More than 70 percent were taking diuretics at the time of discharge. The increased risk for renal cell carcinoma in this cohort may indicate either that diuretics are involved in the etiology of renal cell carcinoma or that the risk can be attributed to confounders, including smoking, which affect risk for both the discharge diagnosis and renal cell carcinoma.

Key words: Cohort study, Denmark, diuretics, kidney cancer, renal cell carcinoma.

Introduction

While the etiology of parenchymal kidney cancer is still largely unknown, the risk factors for cancer of the renal pelvis and for ureteral cancer which arise in the urothelium have been identified. Smoking and the use of compound analgesics containing phenacetin are considered to be carcinogenic to the pelvis and ureter in humans.[1,2] Suspected risk factors for parenchymal kidney cancer (almost all of which are renal cell carcinomas) include smoking, analgesic use, and obesity.[3-8] Two case-control studies[4,6] of renal cell carcinoma showed increased risks among users of diuretics. Further, a cohort study of Japanese-American men found an association between elevated blood pressure and the incidence of kidney cancer; however, after adjustment for use of antihypertensive medication, the effect of hypertension became nonsignificant.[9]

In order to investigate the association between the use of diuretics and renal cell carcinoma, we studied the occurrence of renal cell carcinoma and cancer of the pelvis and ureter in a cohort of presumed users of diuretics in Denmark.

Materials and methods

In order to establish a cohort of individuals exposed to diuretics, patients were identified in the National Hospital Discharge Register who had received a primary or secondary diagnosis of hypertension, heart failure, or edema (ICD-8[10] codes 400, 401, 402, 427.09, 427.11, 428, 519.19, 782.69). A total of 95,900 men and 96,233 women with a relevant diagnosis were identified. The cumulated time at risk for the cohort was 574,190 years. The Discharge Register, set up in 1977, contains dates of admission and discharge, and discharge diagnoses, but no information on treatment, smoking, or other details of the medical history of the individual.

Authors are with the Danish Cancer Registry, Danish Cancer Society, Rosenvængets Hovedvej 38, Box 839 Copenhagen DK-2100 Ø, Denmark. Address correspondence to Dr Mellemgaard.

Cancer incidence in the cohort was established through the Danish Cancer Registry;[11] deaths occurring in the cohort were obtained from the Danish National Death Registry. Linkage was done using the personal identification number that is unique to every Danish inhabitant. Expected numbers of cancer cases were calculated by applying sex-, age-, period- and site-specific incidence rates, supplied by the Danish Cancer Registry, to time at risk, calculated from date of discharge to date of death or 31 December 1987, whichever came first. Cancer cases diagnosed prior to, or in the same month of, hospitalization—which was the point of entry into the study—were not included. As an increased risk for renal cell carcinoma was found only in women without hypertension in a previous study,[6] a subcohort of 44,479 men and 53,925 women with hypertension was identified. Standardized morbidity ratios (SMR) were computed as the ratio between the observed and expected numbers of cancer cases. Assuming a Poisson process, 95 percent confidence intervals (CI) were computed. In order to validate the use of diuretics in the cohort, a random sample of 100 individuals was drawn, and their discharge records for the hospitalization at the time of entry to the study were procured and diuretic use registered.

Results

The overall risk for cancer was increased (SMR = 122), and significantly increased risks were found for cancers of the respiratory tract, the gastrointestinal tract, and cancers of the urinary tract. The SMRs for developing kidney cancer and for cancers at two other sites for which tobacco smoking is also a risk factor (namely lung and bladder) are shown in Table 1. The SMRs for cancer at all sites, and for lung cancer, were highest in the first year after discharge. The risk for kidney cancer, and particularly parenchymal kidney cancer, was increased significantly up to more than 10 years after discharge. The risk for bladder cancer was marginally increased. The SMRs for renal cell carcinoma are shown in Table 2 by age and period. Although the risk was increased in all age groups, it was highest in younger people (χ^2 for trend = 26.30, $P = 0.001$). The risk in the first period was higher than in the last; however, the relatively short time during which the Discharge Register has been in operation does not allow any real evaluation of changes over time. The SMRs for parenchymal and urothelial kidney cancer in the subcohort of hypertensive individuals were similar to those in the whole cohort (Table 3). In this subcohort, 8,401 persons were registered with both a discharge diagnosis of hypertension and heart failure. The results of the validation of diuretic use are shown in Table 4. Seventy-one percent of the sample was using diuretics at the time of discharge. The most frequently used type of diuretic was loop diuretics (53 percent), followed by thiazides (28 percent) and potassium-sparing diuretics (19 percent).

Table 1. Standardized morbidity ratios (SMR) for cancers at all sites, and of the lung, kidney, and bladder in a cohort of 192,133 individuals presumably treated with diuretics, by years after discharge (latency)

Site	No. of cases	Latency (years)				Total
		<1	1-4	5-9	10+	
All	10,630	137[a]	117[a]	118[a]	137[a]	122[a]
Lung	1,498	178[a]	120[a]	113	122	133[a]
Kidney	454	277[a]	197[a]	171[a]	400[a]	213[a]
Renal cell carcinoma	409	299[a]	219[a]	184[a]	267	232[a]
Pelvis/ureter	93	207[a]	137	144	833	158[a]
Bladder	1,044	116	101	118	286[a]	109

[a] Confidence interval excludes the value of 1.

Discussion

The risk for renal cell carcinoma was increased in this cohort of individuals who had greater than average

Table 2. Standardized morbidity ratios (SMR) and 95% confidence intervals (CI) for renal cell carcinoma by age and period

Site	Men ($n = 95,900$)			Women ($n = 96,233$)		
	No. of cases	SMR	CI	No. of cases	SMR	CI
Age group (years)						
50-59	26	306	200-448	16	363	208-591
60-69	59	228	173-294	50	342	254-452
70-79	84	224	179-277	71	217	170-274
80+	40	172	123-235	54	200	151-265
Period						
1977-82	88	259	208-320	85	317	253-392
1983-87	126	200	167-239	110	209	172-252

Table 3. Standardized morbidity ratio (SMR) and 95% confidence intervals (CI) for kidney cancer by subtype in a cohort of hypertensive individuals

Site	Men ($n = 44,479$)			Women ($n = 53,925$)		
	No. of cases	SMR	CI	No. of cases	SMR	CI
Parenchymal	111	215	177-259	120	234	194-280
Urothelial	29	162	108-232	31	177	120-252

Table 4. Actual consumption of diuretics in sample from cohort of discharged patients presumed to be treated with diuretics

	Subjects	%
Did not use diuretics	28	29
Used diuretics	70	71
One drug	57	59
Two drugs	10	10
Three drugs	3	3
No records available	2	—

exposure to diuretics. Although the risk was highest at the time of discharge, indicating that surveillance bias and perhaps selection bias were present, the risk was increased consistently and significantly throughout the follow-up period.

Our finding that more than 70 percent of a random sample of the cohort was taking diuretics at the time of discharge indicates the minimal consumption rate in the cohort, because the treatment for those who were not taking diuretics at the time of discharge may have included diuretics at other times.

Confounding by risk factors that are common for both the relevant discharge diagnosis and kidney cancer was addressed. Smoking is an important risk factor for cardiovascular disease, and there is reason to believe that smoking causes kidney cancer.[3-5,7] In this study, we found increased SMRs for tobacco-related cancers such as those of the lung and bladder (men only); however, the risk for renal cell carcinoma was higher than that for lung and bladder cancer, indicating that smoking accounted for only a small proportion of the elevated risk. Obesity has been found to be an independent risk factor for renal cell carcinoma in several studies. As it also increases the risk for cardiovascular disease, it may be considered another possible confounder; however, we were unable to investigate this issue.

Linkage studies, such as the present one, can provide the basis for hypotheses or they can be used to elucidate suggested relationships, although various biases and confounding must be anticipated. In this study, there is misclassification of exposure since only 71 percent of the individuals in the cohort were found to be taking diuretics at the time of discharge. This bias tends to reduce elevated risk estimates. Selection bias was prevented by omitting cancer cases diagnosed before or during the hospitalization that was the point of entry. Surveillance bias probably was limited because macroscopic hematuria, the most frequent symptom of kidney cancer, almost always leads to systematic screening for abnormalities in the urinary tract. Screening for microscopic hematuria, however, probably is performed more often in individuals with hypertension and other cardiovascular disorders. Surveillance bias poses a significant problem only if the registration of the condition in question is not complete. The Danish Cancer Registry, which has been in operation since 1943, is very close to being complete, especially with respect to common, often lethal tumors.

Hypertension and the use of antihypertensive medications are very closely related, and the independent risk of each is difficult to ascertain. In a study of 812 people with hypertension who were evaluated extensively with urography, abdominal aortography, selective renal arteriography, and determination of renin levels in blood and tumor tissue, six were found to have renal tumors. In four of these, hypertension appeared to be unrelated to the neoplastic process.[12] In a case series of renal carcinoma,[13] hypertension was seen in approximately 20 percent of patients. This number may vary according to the definition of hypertension. The prevalence of hypertension in the general population can be ascertained by cross-sectional studies such as the Copenhagen City heart study.[14] In this study, hypertension was considered, rather conservatively, to be present if the systolic blood pressure was greater than 110 mm Hg plus the age of the individual, or the diastolic blood pressure was equal to or above 95 mm Hg. Hypertension was found in 22 percent of men aged 50-59, in 20 percent of men aged 60-69, and in 18 percent of men aged 70-79. The corresponding percentages for women were somewhat lower. Hypertension therefore appears to be present in renal carcinoma patients at approximately the same frequency as in the general population.

Two case-control studies showed an association between use of diuretics and renal cell carcinoma. In a study by Yu *et al*[4] of 160 cases, both diuretic use (RR = 4.5) and hypertension (RR = 2.3) were risk fac-

tors in women. Diuretics remained a significant risk factor after control for hypertension, but smoking and body mass index were not controlled for. In a study of 495 cases by McLaughlin *et al*,[6] an increased risk was found in women (RR = 1.9) and particularly among those who were not hypertensive (RR = 5.3).

In a follow-up study of 34,198 Seventh-day Adventists,[15] increased risks for kidney cancer were associated with hypertension (RR = 2.57) and use of antihypertensive drugs (RR = 4.04) after controlling for smoking. The antihypertensive medication was not further specified. In contrast, in a follow-up study of 12,799 people who had been prescribed with thiazides and 2,303 who had been prescribed with furosemide, no excess risk for kidney cancer was found.[16] A possible explanation for this negative finding is that prescribed drugs are not necessarily taken. In a follow-up study of the relationship between hypertension and cancer,[9] the only cancer for which elevated blood pressure was associated with an increased risk was kidney cancer (subtype not indicated). None of the above-mentioned studies provides data on use of different types of diuretics. If the diuretics themselves are involved in the carcinogenic process, the risk should differ with type of diuretic. If diuretics act as promoters, the increased risk will be associated with diuretics of all kinds. This issue requires clarification.

Studies on mice and rats exposed to thiazides and furosemide have given no firm indication that these diuretics induce tumors. Hydrochlorothiazide was reported to induce an insignificant increase in the incidence of tubular neoplasms in rats,[17,18] and furosemide, a marginal increase in the incidence of tubular cell neoplasms in male rats.[19]

Mercurial diuretics have not been used in Denmark for many years, and the members of our cohort probably would not have been exposed to these drugs.

Our results, although consistent, cannot clarify whether diuretic use confounds a real risk factor or whether diuretics are associated, in fact, with the carcinogenic process in renal cell carcinoma.

References

1. Jensen OM, Knudsen JB, McLaughlin JK, *et al.* The Copenhagen case-referent study of renal pelvis and ureter cancer: the role of smoking and occupational exposures. *Int J Cancer* 1988; **41:** 557-61.
2. IARC Working Group. Phenacetin and mixtures containing phenacetin. Lyon, France: International Agency for Research on Cancer, 1987; IARC Monographs suppl. 7: 310-2.
3. Armstrong B, Garrod A, Doll R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer* 1976; **33:** 127-36.
4. Yu MC, Mack TM, Hanish R, *et al.* Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *JNCI* 1986; **77:** 351-6.
5. McLaughlin JK, Mandel JS, Blot WJ, *et al.* Population based case-control study of renal cell carcinoma. *JNCI* 1984; **72:** 275-84.
6. McLaughlin JK, Blot WJ, Fraumeni JF. Diuretics and renal cell carcinoma. *JNCI* 1988; **80:** 378.
7. McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. *Int J Cancer* 1988; **42:** 13-6.
8. Asal NR, Risser DR, Kadami S, *et al.* Risk factors in renal cell carcinoma. I. Methodology, demographics, tobacco, beverage use, and obesity. *Cancer Det Prev* 1988; **11:** 359-77.
9. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol* 1991; **134:** 942-7.
10. World Health Organization. *International Classification of Diseases, Injuries and Causes of Death. Eighth Revision (1968).* Geneva: WHO, 1969.
11. Storm HH, Manders T, Sprøgel P, *et al. Cancer Indicidence in Denmark 1987.* Copenhagen: Danish Cancer Society, 1990.
12. Kirchner FK, Braren V, Smith C, *et al.* Renal carcinoma discovered incidentally by arteriography during evaluation for hypertension, *J Urol* 1976; **115:** 643-5.
13. Sufrin G, Murphy GP. Renal adenocarcinoma. *Urol Surveys* 1980; **30:** 129-44.
14. Appleyard M (ed.). The Copenhagen City Heart Study. *Scan J Soc Med* 1989; **Suppl. 41:** 113.
15. Fraser GE, Phillips RL, Beeson WL. Hypertension, antihypertensive medication and risk of renal carcinoma in California Seventh-day Adventists. *Int J Epidemiol* 1990: **19;** 832-8.
16. Selby JV, Friedman GD, Fireman BH. Screening prescription drugs for possible carcinogenicity: 11-15 years of follow-up. *Cancer Res* 1989; **49:** 5736-47.
17. Lijinsky W, Reuber MD. Pathological effects of chronic administration of chlorothiazide, with and without sodium nitrite, to F344 rats. *Toxicol Ind Health* 1987; **3:** 413-22.
18. National Toxicology Program. Toxicology and Carcinogenesis Studies of Hydroclorothiazide in F344/N Rats and B6C3F Mice. NTP Technical Report No. 357. Research Triangle Park, North Carolina, 1989.
19. National Toxicology Program. Toxicology and carcinogenesis studies of furosemide in F344/N rates and B6C3F mice. NTP Technical Report No. 356. Research Triangle Park, North Carolina, 1989.