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Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA)

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Renal cell carcinoma has been linked to hypertension and antihypertensive medications. We investigated the association between renal cell carcinoma and the use of thiazide in a case-control study of 167 men and 90 women. Subjects were members of the Kaiser Permanente Medical Care Program in northern California (United States) who had taken a multiphasic health check-up from 1964 through 1988 and who were evaluated for cancer until the end of 1989. Control subjects received the same check-up, were matched by gender, year of check-up, and age at check-up, and had to be in the health plan until the date on which renal cell carcinoma was diagnosed. Data on known and potential risk factors, including hypertension, body mass index (BMI), and smoking status, were collected from the record of the check-up. Thiazide use was abstracted from the medical chart, which was reviewed from the date of the first entry until the date on which the cancer was diagnosed or the equivalent date for control subjects. The mean follow-back to check-up was 11.3 years. Among women, we found a significantly elevated risk of 4.0 (95 percent confidence interval [CI] 1.5-10.8) associated with ever having used thiazide after we adjusted for smoking, BMI, hypertension, and history of kidney infection at check-up. We did not find a statistically significantly elevated risk in men. Smoking was related to renal cell carcinoma in men (odds ratio [OR] 2.5, CI = 1.1-5.4) for those who smoked at least one pack per day compared with those who had never smoked, but was not related in women. We found a statistically nonsignificant relation between BMI and renal cell carcinoma. After we adjusted for thiazide use, we did not find that hypertension was a statistically significant risk factor for renal cell carcinoma. Analysis of the dosage of thiazide measured by time since first use, duration of use, number of mentions of use in the chart, and an estimate of total grams of exposure did not result in any convincing dose-response relation. These findings are consistent with a growing body of data linking antihypertensive medication with renal cell carcinoma. We are unable to conclude whether thiazide use or some other characteristic of hypertensive persons taking these medications is responsible for the association. *Cancer Causes and Control* 1994, **5**, 319 - 325

Key words: Antihypertensive agents, diuretics, gender, hypertension, kidney neoplasms, renal cell carcinoma, smoking, USA

Introduction

Within the last few years, at least five case-control studies[1-5] and four cohort studies[6-9] have found a link between renal cell carcinoma and hypertension or the use of prescription antihypertensive or diuretic agents. The relation is almost always confined to women. Epidemiologists should find this link of particular interest

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for a cancer which has few recognized risk factors beyond male gender, smoking, and body mass index (BMI).[4] The general finding for antihypertensive agents has, thus far, been remarkably consistent. However, difficulty has arisen in isolating the possible effect of antihypertensive medication from the effect of hypertension itself or another factor associated with being hypertensive. In addition, the type of antihypertensive agent may be important, and information on the dose-response characteristics of various suspected medications is lacking. Four of the five case-control studies have been interview-questionnaire studies and thus are subject to recall bias,[1-4] and the fifth was based on medical record review.[5] The cohort studies have either examined few cases or have included limited information on exposure to diuretics and antihypertensives as well as on other risk factors, such as smoking or hypertension.[6-9] However, no studies which have looked at the association between renal cell carcinoma and antihypertensive medication have found a complete absence of such an association. We previously observed an association between renal cell carcinoma and thiazide but not other antihypertensive agents as part of our ongoing surveillance of cancer outcomes among prescription drug users in Oakland, California (United States) (Van Den Eeden S, unpublished data). Our study thus looked specifically at thiazide, which until recently was the most commonly prescribed diuretic and antihypertensive medication. In the US in 1984 and 1985, hydrochlorothiazide/triamterene combinations were the most commonly prescribed medication type, and hydrochlorothiazide was the sixth most frequently prescribed generic drug in 1987 and 1988.[10]

Materials and methods

The study population was drawn from the Kaiser Permanente Medical Care Program in northern California, which currently has over 2.4 million members. Surveys and census-block group data have shown that the membership is similar to the general population enumerated by the census except for a slight underrepresentation of extremes of income.[11,12] About 30 percent of the population of the greater San Francisco Bay Area currently belong to this health plan.

Cases were selected from a cancer incidence file of all cancers diagnosed within the health plan membership since 1960. These cases were linked through a unique medical record number to persons who took a multiphasic health check-up (MHC) from 1964 through 1988 at the Oakland and San Francisco Kaiser Permanente Medical Centers. Members took the MHC as a baseline or periodic health appraisal and were usually not acutely ill. Persons taking an MHC tended to be more highly educated than the general health-plan population. In the period from 1964 through 1989, 1,644 renal cell carcinomas with the ICD-9[13] codes 189, 189.0, 189.9 were diagnosed; 360 of the patients who had these cancers had received an MHC. After medical chart review, 257 of the 360 were documented to have renal cell carcinoma and had received an MHC before their diagnosis. Control subjects were selected from persons who did not have renal cancer who had also taken the MHC and were matched by gender, year of MHC, and age at MHC $\pm$ 1 year. Control subjects must also have been in the Kaiser Permanente Medical Care Program when their case was diagnosed.

The MHC file provided data on potential risk factors, including race, education, hypertension, height and weight, smoking status, coffee and alcohol consumption, chronic medical conditions, including kidney infection and kidney stones, and medication. Hypertension was defined as the subject reporting a physician's diagnosis of hypertension or treatment for hypertension at MHC. Finally, we used a standard, precoded form to review the medical chart to supplement any data missing from the MHC and to obtain information on thiazide use from patient entry into the health plan to a point six months before diagnosis and an equivalent date for matched control subjects. The study focused entirely on the presence and frequency of thiazide use because thiazide was the most frequently used prescription diuretic and antihypertensive agent during the study period. To blind the medical chart analyst to the case or control status of the subject, charts were masked six months before the date of diagnosis by one medical chart analyst, and another analyst unaware of the case or control status of the subject reviewed the part of the medical chart which covered the period before that six-month period.

Standard analytic approaches for matched case-control studies were used. Continuous variables were divided into quartiles based on the distribution of all subjects for analysis. The odds ratio (OR) and 95 percent confidence interval (CI) for matched pairs were determined by conditional logistic regression. Variables which may have confounded the relation between renal cell carcinoma and thiazide use were included in models which evaluated the risk from ever having used thiazide as well as several quantitative measures of thiazide use, that is, duration (in years) from date of first use to renal cell carcinoma diagnosis; duration (in months) from first to last recorded use; number of mentions in the medical chart of a thiazide prescription; and estimate of total grams of exposure to hydrochlorothiazide equivalents. Total grams of exposure was calculated as the product of daily mil-

Table 1. Frequency distribution of case and control subjects with odds ratios (OR) and 95% confidence intervals (CI) for renal cell carcinoma and various risk factors determined at multiphasic health check-up (separate conditional logistic model for each variable)

	Men				Women			
	Cases	Controls	OR	(CI)	Cases	Controls	OR	(CI)
Smoking[a]								
Never	33	54	1.0	—	36	37	1.0	—
Past	49	49	1.6	(0.9-2.9)	14	11	1.1	(0.4-2.7)
Current								
0-1/2 PPD	22	16	2.1	(1.0-4.7)	11	11	0.9	(0.3-2.4)
1/2-1 PPD	12	11	1.8	(0.7-4.7)	7	8	1.0	(0.3-3.2)
⩾1 + PPD	49	36	2.3	(1.2-4.5)	20	18	1.2	(0.5-2.7)
Quetelet's index[b,c]								
Q1	40	44	1.0	—	21	23	1.0	—
Q2	42	38	1.0	(0.5-2.0)	22	22	1.2	(0.5-2.9)
Q3	44	35	1.2	(0.7-2.3)	24	18	1.8	(0.7-4.4)
Q4	37	44	0.9	(0.5-1.6)	21	25	1.2	(0.5-2.9)
Hypertension								
No	142	149	1.0	—	70	77	1.0	—
Yes	26	19	1.4	(0.7-2.6)	19	12	2.2	(0.9-5.1)
Kidney infection[d]								
No	133	138	1.0	—	71	72	1.0	—
Yes	10	2	5.5	(1.2-25.7)	3	4	2.2	(0.3-15.8)
Education[e]								
0-9 years	33	26	1.0	—	14	21	1.0	—
10-12 years	68	60	0.8	(0.4-1.5)	53	31	1.9	(0.8-4.7)
College	43	39	0.9	(0.4-1.8)	16	29	0.8	(0.3-2.1)
Postgraduate	20	37	0.4	(0.2-0.9)	5	8	0.8	(0.2-3.1)
Race[f]								
White	131	125	1.0	—	72	66	1.0	—
Other	35	39	0.9	(0.5-1.5)	16	21	0.8	(0.4-1.8)
Alcohol use[g]								
Never	16	16	1.0	—	17	28	0.8	—
Ever	149	150	1.2	(0.5-2.6)	70	60	1.7	(0.8-3.5)
Premenopausal[h]					28	28	1.0	—
Postmenopausal[h]					47	48	0.9	(0.4-2.1)

[a] Smoking status missing for 5 men + 5 women; PPD, packs per day. Categories of PPD for current smokers are presented as asked in questionnaire.
[b] Quetelet's index (body mass index) missing for 12 men + 2 women.
[c] In men, Q1, < 24.6; Q2, 24.7-25.9; Q3, 26.0-28.2; Q4, ⩾ 28.3; in women, Q1, < 21.8; Q2, 21.9-24.5; Q3, 24.6-27.7; Q4, ⩾ 27.8.
[d] Kidney infection status missing for 53 men + 28 women.
[e] Education status missing for 10 men + 1 woman.
[f] Race status missing for 6 men + 3 women.
[g] Alcohol status missing for 5 men + 3 women.
[h] Menopause status missing for 27 women.

ligram dose (in hydrochlorothiazide equivalents) and duration of use. Dose-response relations among persons exposed to thiazide were tested by using the Mantel-Haenszel test for trends. To evaluate the possible preclinical effect of renal cell carcinoma on the development of hypertension which led to the use of thiazide, we reanalyzed the data after we excluded use of thiazide two, four, and six years before diagnosis of renal cell carcinoma.

Results

The mean age of the 257 patients who had renal cell carcinoma was 50.7 years, and 34.6 percent of these patients were women. About 80 percent of such patients were White, and about 14 percent were Black, a distribution similar to that expected in the population who received an MHC in the Oakland and San Francisco facilities. The mean follow-back from diagnosis to MHC was about 11.3 years for both case and control subjects, and the mean follow-back to first thiazide use or the equivalent point was also comparable (9.3 ± 6.4 years for cases *cf* 8.6 ± 5.9 years for control subjects, $P = 0.5$). The histology of the renal cell carcinoma was documented in all cases by pathology reports in the medical chart. Data for men and women are presented

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for renal cell carcinoma for thiazide use adjusted for history of smoking, body mass index, hypertension, and kidney infection (conditional logistic regression)

	Men		Women	
	OR	(CI)	OR	(CI)
Thiazide ever used:				
No	1.0	—	1.0	—
Yes	1.2	(0.6-2.1)	4.0	(1.5-10.8)
Smoking[a]				
Never	1.0	—	1.0	—
Past	1.7	(0.8-3.3)	1.4	(0.4-4.4)
0-1/2 PPD	2.6	(1.0-6.8)	1.0	(0.3-3.7)
1/2-1 PPD	1.9	(0.6-6.1)	2.0	(0.4-10.2)
⩾1 PPD	2.5	(1.1-5.4)	1.2	(0.4-3.3)
Quetelet's index[b]				
Q1	1.0	—	1.0	—
Q2	0.9	(0.4-1.8)	0.6	(0.2-1.8)
Q3	0.9	(0.4-1.9)	0.6	(0.2-2.1)
Q4	1.4	(0.7-3.1)	1.2	(0.4-4.3)
Hypertension				
No	1.0	—	1.0	—
Yes	1.4	(0.6-3.2)	1.6	(0.5-4.7)
Kidney infection				
No	1.0	—	1.0	—
Yes	6.1	(1.2-29.8)	1.7	(0.2-14.5)

[a] Categories of PPD for smokers are presented as asked in questionnaire.

[b] In men Q1, < 24.6; Q2, 24.7-25.9; Q3, 26.0-28.2; Q4, ⩾ 28.3; in women Q1, < 21.8; Q2, 21.9-24.5; Q3, 24.6-27.7, Q4, ⩾ 27.8.

separately because of the difference in the presence and strength of risk factors based on gender.

Using univariate analysis, we found that smoking at least one pack per day was significantly related to renal cell carcinoma in men but not in women (Table 1). Quetelet's Index (or body mass index [wt (kg)/ht $(m)^2$]) measured at MHC was not associated with renal cell carcinoma in either gender. Indicators of hypertension at MHC conferred a nonsignificantly elevated risk for women (OR = 2.2, CI = 0.9-5.1) and men (OR = 1.4, CI = 0.7-2.6). A history of kidney infection conferred a significantly elevated risk in men (OR = 5.5, CI = 1.2-25.7) but not in women (OR = 2.2). Education, race, and alcohol and coffee consumption were not associated with increased risk of renal cell carcinoma in either gender.

For women, after adjustment for smoking, body mass, hypertension, and history of kidney infection at MHC, we found a markedly elevated, significant association between renal cell carcinoma and evidence of ever having used thiazide (OR = 4.0, CI = 1.5-10.8) which was absent among men (Table 2).

In this adjusted model, the risk of renal cell carcinoma associated with hypertension remained elevated but was still statistically nonsignificant for women, slightly lower than in the unadjusted model. Associations between renal cell carcinoma and smoking or kidney infection were essentially unchanged in men. Moreover, although the highest quartile of BMI for both genders was then associated with the highest risk, the effect was not statistically significant in either men or women. Our examination of the association between measures of quantitative exposure among thiazide users and renal cell carcinoma did not show any statistically significant dose-response relation despite an apparent trend between this cancer and time since first use of thiazide or total duration of thiazide use

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for renal cell carcinoma for quantitative measures of thiazide use adjusted for history of smoking, body mass index, hypertension, and kidney infection (conditional logistic regression; women only, $n = 89$)

	Cases	Controls	OR	(CI)	*P*(trend)
No exposure	40	58	1.0	—	—
Time since first exposure (yrs)					
0-4.9	11	9	2.1	(0.5-8.6)	0.44
5.0-11.4	17	10	5.0	(1.3-19.5)	
⩾11.5	21	12	5.8	(1.4-23.4)	
Duration of use (mos)					
0-19	13	10	3.6	(1.0-12.8)	0.90
20-74	16	11	3.6	(1.0-13.4)	
⩾75	20	10	5.3	(1.3-22.0)	
No. of mentions					
1-7	12	9	3.6	(1.0-13.3)	0.25
8-25	16	14	3.4	(0.9-12.8)	
⩾26	23	6	5.8	(1.4-24.8)	
Total g					
0-18	12	9	7.6	(1.6-35.2)	0.49
19-109	12	12	3.0	(0.8-11.0)	
⩾110	24	8	8.7	(1.8-42.8)	

Table 4. Studies of antihypertensive medication and renal cancer (in women, unless otherwise specified)

Author	Cases	Comparison	Data sources	Exposure	Risk	(CI)[a] or *P* value
Case-control studies:						
Yu *et al*[1]	51	51	Interview	Diuretic	4.5[b]	(1.6-14.5)
McLaughlin *et al*[2]	182	269	Interview	Diuretic	1.9[b]	0.05
Asal *et al*[3]	315[c]	313[d] 336[e]	Interview	Antihypertensive	2.6[b]	(1.3-5.3)
Kreiger *et al*[4]	201	705	Mailed questionnaire	Diuretic	2.3[b]	(1.3-4.0)
Finkle *et al*[5]	191	191	Medical chart	Diuretic	2.9	(1.7-4.7)
Hiatt *et al* (this study)	89	89	Medical chart	Thiazide	4.0[b]	(1.5-10.8[e])
					1.2	(0.6-2.1[e])
Cohort studies						
Fraser *et al*[6]	14[f]	34,184	Mailed questionnaire	Antihypertensive	4.5[h]	(1.6-15.0)
Grove *et al*[8]	17[c]	7,908	Interview	Hypertension	3.8[h]	(1.3-11.6)
Mellemgaard *et al*[7]	120	53,805	Medical chart	Hypertension	234[i]	(194-280)
Lindblad *et al*[9]	278	115,616	Record linkage	Diuretics	1.4[j]	(1.2-1.7[e])
					1.3	(1.1-1.5[e])

[a] (CI) = 95% confidence interval.
[b] Odds ratio.
[c] Men only.
[d] Hospital.
[e] Population.
[f] Women only.
[g] Men and women.
[h] Relative risk.
[i] Standardized mortality ratio (SMR).
[j] Standardized incidence ratio (SIR).

(Table 3). The use of thiazide to treat water retention or edema in 19 women was associated with an OR for development of renal cell carcinoma of 1.4 (CI = 0.5-3.7), and its use to treat hypertension was associated with a significantly elevated OR for development of renal cell carcinoma of 2.0 (CI = 1.1-3.8).

Finally, in evaluating a possible effect of preclinical renal cell carcinoma on development of hypertension and thus the use of thiazide, we censored thiazide exposure before diagnosis for both case and control subjects. This strategy reduced the level of risk associated with ever having used thiazide, but the risk remained significantly elevated for patients who had used thiazide two years (OR = 2.5, CI = 1.3-4.5), or even 10 years before the diagnosis of renal cell carcinoma (OR = 2.3, CI = 1.1-4.8).

Discussion

The level of risk of renal cell cancer we observed for ever having used thiazide is compatible to that reported in other previously published studies: the five case-control studies[1-5] of this relation reported risks associated with diuretic agent use of 1.9-4.5 among women; the cohort studies reported risks of 2.3-4.5 for exposure to nonspecified antihypertensive agents[6] or a history of hypertension (Table 4). In all cases, the finding was either confined to or strongest among women, if they were studied. The studies by Asal *et al*[3] and by Grove *et al*[8] were conducted among men only, and results in men and women were not reported separately by Fraser *et al.*[6] This finding in women of a relation between renal cancer and prior use of antihypertensive agents or in some cases diuretic agents specifically is highly consistent. The recent study by Finkle *et al*[5] was performed in the southern California region of the same health plan as the current study and produced remarkably similar results. Our study adds the finding that renal cancer may be associated with thiazide use in particular.

However, thiazide use may simply indicate either hypertension or some other factor associated with hypertension. Hypertension itself has been associated with renal cancer in some studies.[14] This idea is supported by our finding that even low dosages of thiazide are apparently associated with a significantly elevated risk and an absence of a significant dose-response relation. In addition, we did not control for hypertension which developed between the MHC and the diagnosis of cancer because hypertension was so closely linked with the prescription of thiazide. We did find similar point estimates of renal cell carcinoma risk for

thiazide prescribed for hypertension (OR = 2.0) and for edema (OR = 1.4), although the edema OR was not statistically significant in the small sample of women we studied. A causal role of thiazide use, as opposed to hypertension, in the development of renal cell carcinoma also was supported by our findings in women that hypertension at check-up lost its statistical significance for predicting the development of renal cell carcinoma when combined in a model with thiazide use.

The association between renal cancer and cigarette smoking has been demonstrated by several previous investigators: risk estimates have generally been about two and have been seen in both men and women.[4,15-17] Our finding of a lack of this association among women has no obvious explanation, although the suggestion of increased risk at higher intensity levels (Table 2) is certainly compatible with previous findings.[4,15-17]

We observed a significantly lower risk of renal cell carcinoma among men who had a postgraduate education (OR = 0.4, CI = 0.2-0.9). Other studies[4,6,16] which reported education found no relation, and the possibility that our finding was due to chance cannot be completely excluded.

Unlike most studies of renal cell carcinoma,[1,4,15,18] our study did not demonstrate a strong relation between this cancer and BMI, especially in women. However, time at which body mass is measured relative to the diagnosis is inconsistent in these studies,[4] and we may have missed this relation because we collected and analyzed only data on weight and height at MHC. In addition, the CI for our highest quartiles of body mass index in the adjusted models are highly consistent in showing a twofold increase in risk. Our patients were diagnosed at a mean age of about 51 years or about 10 years of age younger than that seen in other studies. We believe this was due to the young age at examination of our study group, and BMI could be more closely related to renal cell carcinoma in older women.

The strong relation between diuretic agents and renal cancer and in our study between thiazide and renal cell carcinoma in women is consistent yet unexplained. The hypothesis of McLaughlin *et al*,[2] that this relation might be due to women's use of diuretic agents for water retention and weight reduction instead of for hypertension, could explain the role of thiazide use as an indicator of high BMI. Our data do not support this idea because we found a strong association between renal cell carcinoma and thiazide use in the absence of a relation with BMI and a stronger point estimate of renal cell carcinoma risk among women who used thiazide for hypertension than among those who used thiazide for water retention. We also examined women's risk relative to their menopausal status and found no association. Finally, women may have more kidney infections than men, and kidney infection has been associated with renal cancer in several studies.[6,14] Our data showed a significant association between renal cell carcinoma and infection among men but not women, and we thus have no objective data to support this hypothesis.

Mechanisms by which thiazide may act on the kidney are currently only speculative. The International Agency for Research on Cancer[10] reported that mice fed ≤ 5 g hydrochlorothiazide/kg of diet for two years showed no difference in survival from control animals but did have significantly more hepatic adenomas ($P = 0.009$). No other neoplasms were observed. Lijinsky and Reuber[19] noted that among 48 rats fed powdered 0.1 percent hydrochlorothiazide for two years with and without sodium nitrite, three rats who consumed sodium nitrite and four rats who did not, developed renal tubular adenomas compared with none among controls, but the difference was not statistically significant. Lijinsky and Reuber[19] also have noted that a carcinogenic effect of thiazide has not been reported among humans, although thiazide has been in common clinical use since 1957.[10] Renal cortical microadenomas of unknown clinical significance are found in 15 to 22 percent of autopsies in humans, but these reports predate marketing of thiazide.[20] Such a finding suggests that thiazide may promote malignant expression of pre-existing renal adenomas; studies which evaluate the survival of patients with thiazide-associated renal cancers and stage at initial detection of thiazide-associated renal cancers compared with those not associated with thiazide use may be helpful.

We found no evidence that the effect on renal cell carcinoma of thiazide use which we observed was limited to the six years before diagnosis or was stronger up to that point. This finding is not compatible with a spurious association between thiazide use and renal cell carcinoma which operates through the preclinical hypertensive effect of a renal tumor. This finding also suggests that if thiazide promotes renal cell carcinoma, the latency period for this cancer is rather long.

More epidemiologic evaluation of this relation is needed. Thiazide has been and is still very commonly used internationally and remains an inexpensive and effective mainstay in various treatment regimens. The consistency of the epidemiologic data we have cited is not specific to thiazide but to diuretic or antihypertensive medication in general. Nevertheless, thiazide should be the most suspect diuretic or antihypertensive agent because of its extensive use. Additional studies should evaluate other antihypertensive agents, such as β-blockers, calcium-channel blockers, and angiotensin antagonists, especially because they are used for nonhypertensive conditions. In addition, further efforts

are needed to evaluate the dose-response relation between thiazide and renal cancer and to resolve the confounding of thiazide use by hypertension itself.

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