Risk of Renal Cell Cancer in Relation to Diuretics, Antihypertensive Drugs, and Hypertension

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Abstract

Although recent data have suggested an association between renal cell cancer and the use of diuretics, it remains unclear whether these medications or hypertension is the important risk factor. In a population-based case-control study including 440 renal cell cancer cases, spouses of an additional 151 cases, and 691 controls, we assessed renal cell cancer risk associated with hypertension and use of diuretics and other antihypertensive medications. Risks increased with the use of diuretics or other drugs that lower blood pressure, especially among persons who reported no history of hypertension. After adjustment for hypertension, the use of diuretics alone was associated with a 40% excess risk (OR = 1.4; 95% CI = 0.8–2.2), while use of other antihypertensive drugs was linked to a 2-fold risk (OR = 2.0; 95% CI = 1.2–3.3). The excess risk was not restricted to any specific products, and no trend was observed with estimated lifetime consumption of any product. Furthermore, risk was not potentiated by the presence of both hypertension and the use of antihypertensive drugs. Among persons who did not use antihypertensive drugs, a history of hypertension was associated with a significant 40–50% excess risk of renal cell cancer. Excluding subjects with hypertension diagnosed within 5 years of cancer diagnosis or interview had only a small effect on risk. These findings suggest small effects on renal cell cancer risk associated with hypertensive disease and with the use of diuretics and other antihypertensive drugs, but it is difficult to disentangle the separate effects due to potential misclassification of highly correlated events. Further large scale studies should be considered, especially in populations that have regular blood pressure measurements and more detailed documentation of medication use.

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Introduction

Since a link between renal cell cancer and the use of diuretics was first reported (1), epidemiological evidence has accumulated to support this association (2–10). However, it remains unclear whether diuretics or the primary medical indication, hypertension, is the important risk factor. In studies that examined both diuretic use and hypertension, associations with these drugs independent of hypertension were usually found (1, 2, 4–7). On the other hand, an association with hypertension independent of diuretics was noted in a few studies (10, 11), while one study noted a relation to non-diuretic antihypertensive drugs, particularly β-blockers (11).

Because diuretics are one of the most commonly prescribed medications in the United States (12, 13), used mainly for hypertension and edema, it is important to determine their potential role in the etiology of renal cell cancer, especially in view of the rising incidence of this tumor (14). Also commonly used are the nondiuretic antihypertensive drugs, although indications for their use extend to other cardiovascular diseases such as coronary insufficiency. Using data from a large population-based case-control study of renal cell cancer in Minnesota, we attempted to sort out the effects of diuretics, other antihypertensive drugs, and hypertension.

Materials and Methods

Methods for this study have been described in detail elsewhere (15). Briefly, residents of Minnesota who were newly diagnosed with histologically confirmed renal cell cancer (International Classification for Diseases #9 code 189.0) between July 1, 1988 and December 31, 1990 were identified through the state cancer surveillance system (16). Cases were between 20 and 79 years of age. Of the 796 eligible cases, interviews were obtained for 690 (87%), including 241 interviews with the next of kin of patients who died or were too ill to be interviewed (NOK[3] cases).

Controls were sampled from residents in Minnesota with the use of a random digit dialing method (17) for those under age 65 and a systematic random sampling of Health Care Financing Administration files (18) for those ages 65 or older, and frequency matched to cases by gender and 5-year age groups. Interviews were obtained for 707 controls, resulting in an overall response rate of 87% for Health Care Financing Administration controls and 84% for random digit dialing controls (the product of a 93% response rate at the household-screening phase and a 90% response rate at the interview phase).

In-person structured interviews were conducted in the homes of the study subjects by trained interviewers to elicit information on demographic characteristics, use of prescription

[3] The abbreviations used are: NOK, next of kin; OR, odds ratio; CI, confidence intervals; BMI, body mass index.

diuretics and other antihypertensive drugs, history of hypertension and other selected medical conditions, height and weight, tobacco and alcohol consumption, and occupational history. After establishing a history of use of diuretics or other antihypertensive drugs for at least twice a week for 2 weeks or longer, detailed information was collected on overall pattern of use, including age started and stopped, total duration, and usual dose taken. For diuretics (but not other antihypertensive drugs), indication for use was ascertained. In addition, for personally interviewed cases and controls, detailed information was collected on the use of 13 specific diuretics and 22 other antihypertensive drugs (Appendix). Ever use of diuretic or nondiuretic antihypertensive drugs was established if a subject reported either general use or a specific brand name.

The ingredients of all prescription drugs used regularly by study subjects were sought through numerous pharmaceutical sources. Formulas, some dating back to the 1950s, were recorded in an ingredient matrix for diuretics and antihypertensive drugs. All changes in formulas over time were recorded, such as addition or removal of an ingredient or change in its amount. Annual exposure to each ingredient was estimated from the dose reported by the subjects and the amount in each drug during that year of exposure. Lifetime cumulative exposure (in kg) to each ingredient was then estimated by summing annual exposures across all diuretics and other antihypertensive drugs used regularly before 1987.

Data were analyzed with the use of stratified methods and logistic regression models to examine multivariate relationships and to adjust for confounding factors. Summary ORs and corresponding 95% CIs were computed (19). Continuous variables, such as age first used, years of use, and lifetime amount of use of diuretics or antihypertensive drugs, were grouped for analysis of dose-response. Subjects with missing information for BMI or smoking status, known risk factors for renal cell cancer (20), were excluded from the analysis. A total of 440 directly interviewed cases, 229 NOK cases, and 691 directly interviewed controls were available for the final analysis. Risk estimates were based only on information from directly interviewed cases and controls, while information from NOK cases was examined solely to evaluate the consistency in reported exposures. Since similar findings for use of diuretics and other antihypertensive drugs and a history of hypertension were observed in both sexes, results are presented for men and women combined.

Table 1 OR and 95% CI for renal cell cancer in relation to use of diuretics and nondiuretic antihypertensive drugs

Drug use	Control[a]	Case[a]	OR[b]	95% CI	OR[c]	95% CI
Diuretics						
No	503	282	1.0		1.0	
Yes	186	157	1.4	1.0–1.8	1.1	0.8–1.6
Age first used						
≤44	49	50	1.5	1.0–2.4	1.2	0.8–2.0
45–54	54	45	1.3	0.9–2.1	1.0	0.6–1.7
55–64	50	47	1.6	1.0–2.5	1.3	0.7–2.1
65+	30	11	0.6	0.3–1.3	0.5	0.2–1.1
Years of use						
≤1	53	27	0.8	0.5–1.4	0.7	0.4–1.2
2–4	23	22	1.4	0.8–2.7	1.2	0.6–2.3
5–9	41	28	1.2	0.7–2.0	0.9	0.5–1.7
10+	67	73	1.8	1.3–2.8	1.4	0.9–2.3
Antihypertensive drugs						
No	538	295	1.0		1.0	
Yes	151	142	1.6	1.2–2.2	1.5	1.0–2.1
Age first used						
≤44	24	26	1.7	1.0–3.1	1.6	0.8–3.0
45–54	37	37	1.6	1.0–2.7	1.5	0.9–2.6
55–64	49	42	1.5	0.9–2.3	1.4	0.8–2.3
65+	39	26	1.3	0.7–2.3	1.2	0.7–2.2
Years of use						
≤1	60	52	1.5	1.0–2.3	1.4	0.9–2.1
2–4	39	24	1.1	0.6–1.8	0.9	0.5–1.7
5–9	19	29	2.7	1.5–5.0	2.3	1.2–4.5
10+	31	30	1.7	1.0–2.9	1.5	0.8–2.6
Combinations						
None	458	233	1.0		1.0	
Diuretics only	80	62	1.4	1.0–2.1	1.4	0.8–2.2
Antihypertensives only	45	48	2.2	1.4–3.4	2.0	1.2–3.3
Combined use	105	93	1.6	1.2–2.3	1.5	0.9–2.4

[a] Subjects with missing information were excluded.
[b] Adjusted for age, sex, smoking, and usual body mass index.
[c] Adjusted for age, sex, smoking, usual body mass index, and a history of hypertension.

Results

Directly interviewed cases and controls were similar in distribution by gender (63% male cases and 67% male controls), age (median age was 64 years for both cases and controls), and educational level (25% each of cases and controls did not graduate from high school, while 32% cases and 34% controls had some college). Compared to controls, directly interviewed cases were heavier (34% cases *versus* 25% controls were in the highest quartile of body mass index) and were more likely to be current smokers (26% cases *versus* 22% controls).

After adjustment for age, gender, smoking status, and usual BMI, ever use of diuretics was associated with a 40% excess risk of renal cell cancer (Table 1). No excess risk was observed among those who first used diuretics at an older age (65+ years; OR = 0.6; 95% CI = 0.3–1.3). The highest risk was found among long-term users (10+ years; OR = 1.8; 95% CI = 1.3–2.8). Further adjustment for a history of hypertension reduced the associations with diuretics to nonsignificant levels. Ever use of nondiuretic antihypertensive drugs was associated with a 60% excess risk (Table 1). However, among persons who started use at age 65 years or older, the risk was increased to a lesser extent (OR = 1.3; 95% CI = 0.7–2.3). Again, the highest risk was found among long-term users (OR = 2.7 and 95% CI = 1.5–5.0 for 5–9 years; OR = 1.7 and 95% CI = 1.0–2.9 for 10+ years). Further adjustment for a history of hypertension reduced these associations slightly (Table 1). Results were not altered substantially when both diuretics and other antihypertensive drugs were included in the model, regardless of whether additional adjustment for hypertension was performed (data not shown). When compared with those who did not take either type of medication, users of only nondiuretic antihypertensive drugs had a greater risk than did users of only diuretics. Risk was not enhanced further among those who took both categories of drugs (Table 1).

Effect modifications of diuretics and other antihypertensive drugs are evaluated in Table 2. Risk of renal cell cancer increased consistently with duration of use of nondiuretic antihypertensive drugs mainly among nonusers of diuretics. Conversely, risks increased only among long-term users (5+ years) of diuretics who did not take other antihypertensive drugs.

Table 2 OR and 95% CI for renal cell cancer in relation to duration of use of diuretics and non-diuretic antihypertensive drugs

Duration of diuretic use	Duration of antihypertensive drug use					
	Not used		<5 yr		5+ yr	
	OR[a]	CI	OR[a]	CI	OR[a]	CI
Not used	1.0 (233/457)[b]		1.6 (27/32)	0.9–2.9	3.0 (17/12)	1.3–7.0
<5 yr	1.0 (22/35)	0.6–1.9	1.4 (23/28)	0.7–2.7	0.5 (3/11)	0.1–1.8
5+ yr	1.5 (37/45)	0.8–2.7	1.1 (22/36)	0.5–2.1	2.4 (37/27)	1.2–4.5

[a] Adjusted for age, sex, smoking, usual body mass index, and hypertension.
[b] Numbers in parentheses are directly interviewed cases and controls; subjects with missing information were excluded.

Table 3 OR and 95% CI for renal cell cancer in relation to hypertension and duration of use of diuretics or nondiuretic antihypertensive drugs

Hypertension	Duration of drug use					
	Not used		<5 yr		5+ yr	
	OR[a]	CI	OR[a]	CI	OR[a]	CI
			Diuretics			
No	1.0 (230/438)[b]		0.7 (12/25)	0.4–1.5	9.9 (5/1)	1.1–87.2
Yes	1.5 (49/63)	1.0–2.2	1.3 (37/51)	0.8–2.0	1.6 (94/107)	1.1–2.2
			Antihypertensive drugs			
No	1.0 (225/442)[b]		1.7 (17/21)	0.9–3.3	13.7 (6/1)	1.6–117
Yes	1.4 (69/95)	1.0–2.0	1.4 (57/77)	0.9–2.0	2.0 (51/49)	1.3–3.1

[a] Adjusted for age, sex, smoking, and usual BMI.
[b] Numbers in parentheses are directly interviewed cases and controls; subjects with missing information were excluded.

A history of hypertension was associated with an excess risk of renal cell cancer (OR = 1.5; 95% CI = 1.1–1.9). Risks were higher among persons diagnosed with hypertension under age 50 years (70% excess) than those diagnosed at older ages (10–30% excesses). After further adjustment for ever use of diuretics and other antihypertensive drugs, risks were reduced slightly and no longer statistically significant. However, among persons who did not use diuretics or other antihypertensive drugs, a 40–50% excess risk was linked to a history of hypertension (Table 3). The association with hypertension was reduced somewhat (OR = 1.3; 95% CI = 1.0–1.7) among subjects whose hypertension was first noted more than 5 years prior to cancer diagnosis or interview.

Effect modifications of drugs and hypertension are examined in Table 3. Among persons who did not report a history of hypertension, risk of renal cell cancer increased consistently with duration of nondiuretic antihypertensive drug use, while risk was elevated only among long-term users (5+ years) of diuretics. Among persons who reported a history of hypertension, risk was elevated only slightly among long-term users (5+ years) of nondiuretic antihypertensive drugs but essentially was not increased among users of diuretics. In addition, no consistent pattern of risk was observed in relation to the time interval between age first diagnosed with hypertension and age when diuretics or other antihypertensive drugs were first used (data not shown). The majority of subjects (17 cases and 26 controls) with no history of hypertension reported taking diuretics for edema or weight reduction; 6 cases and 1 control reported taking diuretics for heart disease. Reasons for using other antihypertensive drugs were not ascertained.

We examined risk for specific classes of medication, including loop diuretics, potassium-sparing agents, and thiazides. Antihypertensive drugs included central acting antiadrenergic agents, calcium channel blockers, and β-blockers. Elevated risks were seen for each class of medication, but there were no consistent trends with increasing lifetime consumption (data not shown).

Risks associated with diuretics, other antihypertensive drugs, and hypertension were not affected by further adjustment for a history of renal diseases or protein intake, another potential risk factor observed in our data (15). The use of diuretics (based on responses to the general question only) was similar between NOK cases and directly interviewed cases (31.0 *versus* 32.6%, respectively), as was use of nondiuretic antihypertensive drugs (24.2 *versus* 24.0%, respectively). History of hypertension was reported in 41% of the NOK cases compared with 42% in directly interviewed cases.

Discussion

An excess risk of renal cell cancer has been reported among users of diuretics in a number of epidemiological studies. The magnitude of the risk has varied, being 3-fold or higher in several studies (1–4, 6, 7), while only slightly or not increased in other investigations (5, 11, 21). Cohort studies of patients with conditions likely to be treated with diuretics have shown excess risks around 2-fold or less (8, 9). In previous studies of diuretics and renal cell cancer, assessment of dose-response has produced inconsistent findings (6, 7, 11). In our study, the risk associated with diuretic use was confined to long-term users and was observed mainly among those without a reported history of hypertension. This finding is consistent with results of an earlier investigation (2) but is different from others (1, 5).

Little effort has been made to evaluate the effect of nondiuretic antihypertensive drugs on the risk of renal cell cancer. McCredie and Stewart (11) observed a 50% excess risk after adjustment for diuretic use and hypertension, which resembles the level of risk seen in our study. In addition, we found greater risks among subjects taking these drugs for 5 or more years compared to those using them for shorter periods. The risks also were higher among those without a reported history of hypertension than among hypertensive patients. We did not collect information on the indications for using nondiuretic antihypertensive drugs, although several medications on our list (Appendix) are prescribed for cardiovascular conditions other than hypertension, such as coronary insufficiency or arrhythmias (22). Misclassification of hypertension status also is possible since subjects might not have reported hypertension after the disease was under control. Contrary to McCredie and Stewart (11), who observed an increased risk mainly among users of β-blockers, we found that the association was not restricted to any particular class of antihypertensive agents. In addition, we found no dose-response with any specific drug as measured by estimated lifetime consumption.

The role of hypertension in the etiology of renal cell cancer is unclear. Several studies have reported an elevated risk

of renal cell cancer among persons with a history of hypertension (10, 11, 23–25). In other studies, the association with hypertension disappeared or was reduced greatly after adjustment for use of diuretics or other antihypertensive drugs (1, 4, 6, 7). In our study, risk was clearly attenuated by adjusting for use of diuretics or other antihypertensive drugs, but a slight excess risk associated with hypertension persisted, particularly among those who were untreated with drugs. Hypertension may be an early manifestation of renal cell cancer, but the excess risk in our study persisted among subjects reporting the occurrence of hypertension more than 5 years before the cancer diagnosis.

In epidemiological studies, it is often difficult to distinguish treatment effects from the underlying disease. In separating the role of hypertension from the specific medications in our study, problems could arise from misclassification of such highly correlated events, due to either errors in reporting by the respondents or incomplete information available to the subjects concerning their disease status or therapy. We attempted to verify the history of hypertension or diuretic use of the subjects with the use of a questionnaire mailed to physicians, but findings were not altered with the additional information. Uncertainty also results from difficulties in the definition of hypertension and from possible confounding by factors that influence the risk and/or course of hypertension and renal cell cancer such as obesity and smoking (26). Although the available evidence indicates that some combination of antihypertensive medications and/or hypertension affects the development of renal cell cancer, the precise risk factors and mechanisms involved are unclear. Only limited studies have been carried out in laboratory animals, with the administration of diuretics such as hydrochlorothiazide and furosemide (27) and other antihypertensive agents such as reserpine (28) providing no clear evidence of carcinogenic effects.

In summary, our case-control study of renal cell cancer indicates some elevated risks associated with diuretics, nondiuretic antihypertensive drugs, and hypertension, but potential misclassification of these highly correlated events makes it difficult to disentangle their separate effects. Further large scale studies are needed, especially in populations with more thorough documentation of the diagnosis and treatment of hypertension.

Appendix List of prescription diuretics and nondiuretic antihypertensive drugs ascertained in study

Diuretics	Nondiuretic antihypertensive drugs
Aldactazide	Aldomet
Aldactone	Aldoril
Diuril	Apresazide
Dyazide	Apresoline
Enduron	Calan
Esidrix	Capoten
Hydrochlorothiazide	Cardizem
Hydrodiuril	Catapres
Hygroton	Corgard
Lasix	Diupres
Metahydrin	Hydropres
Oretic	Inderal
Zaroxolyn	Lopressor
	Minipress
	Procardia
	Raudixin
	Regroton
	Reserpine
	Salutensin
	Serapes
	Serpasil
	Tenormin

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