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Hypertension, Antihypertensive Medication Use, and Risk of Renal Cell Carcinoma

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To investigate whether diuretic medication use increases risk of renal cell carcinoma (RCC), the authors conducted a case-control study of health maintenance organization members in western Washington State. Cases (n = 238) diagnosed between January 1980 and June 1995 were compared with controls (n = 616) selected from health maintenance organization membership files. The computerized health maintenance organization pharmacy database provided information on medications prescribed after March 1977. Additional exposure information was collected from medical records. For women, use of diuretics was associated with increased risk of RCC (odds ratio (OR) = 1.8, 95% confidence interval (CI) 1.0-3.1), but the association was not independent of a diagnosis of hypertension (adjusted for hypertension, OR = 1.1, 95% CI 0.5-2.1). Similarly, nondiuretic antihypertensive use was associated with increased risk, but only when unadjusted for hypertension. For men, neither diuretic nor nondiuretic antihypertensive use was associated with risk of RCC. A diagnosis of hypertension was clearly associated with RCC risk for women (OR = 2.5, 95% CI 1.2-5.1), but not men (OR = 1.3, 95% CI 0.7-2.5). High systolic and diastolic blood pressures were associated with increased risk in both sexes. These results do not support the hypothesis that use of diuretic medication increases RCC risk; they are more consistent with an association between RCC and high blood pressure. *Am J Epidemiol* 1999;149:521–30.

antihypertensive agents; blood pressure; carcinoma, renal cell; case-control studies; diuretics; hypertension

Diuretics are one of the most commonly prescribed medication classes in the United States. Therefore, results from several studies suggesting a strong positive association with renal cell carcinoma (RCC), particularly in women, have raised concerns. However, use of diuretics and hypertension are highly correlated, so it is difficult to disentangle their effects. It is unclear whether the associations that have been found are due to an effect of diuretic medications, to other antihypertensive medications, or to the hypertension for which the medications are usually prescribed.

For women, nine previous population-based studies that have examined the association between use of diuretic medications and RCC have reported positive associations prior to adjustment for hypertension (1–9). However, results after adjustment for hypertension have been inconsistent (1–9). For men, most previous studies that have examined the association between use of diuretics and RCC risk after adjustment for hypertension have reported little or no association with use of diuretics (1, 2, 4–8).

The primary aim of this study was to investigate the hypothesis that use of diuretic medications increases the risk of RCC. To do so, we conducted a population-based case-control study among members of Group Health Cooperative of Puget Sound (GHC). Detailed exposure information available from the GHC pharmacy database and medical records enabled us to examine the relation of RCC with hypertension, blood pressure, and both diuretic and nondiuretic antihypertensive medication use.

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Abbreviations: BMI, body mass index; CI, confidence interval; GHC, Group Health Cooperative of Puget Sound; OR, odds ratio; RCC, renal cell carcinoma.

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MATERIALS AND METHODS

Subject selection

This was a population-based case-control study among members of GHC, a large health maintenance organization in western Washington State. RCC cases were identified through the Cancer Surveillance System, a population-based cancer registry in western Washington State that is part of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Cases consisted of all GHC members aged 18–84 years diagnosed with a primary RCC between January 1, 1980, and June 30, 1995. Cases identified incidentally at autopsy and cases with a prior diagnosis of kidney cancer were excluded.

Controls without a history of kidney cancer were randomly selected from computerized GHC membership files. They were matched to the cases on sex, year of birth in 5-year categories, GHC enrollment during the year of case diagnosis, GHC geographic clinic region during the case diagnosis year, and approximate length of GHC enrollment in 3-year categories on the basis of information in the computerized GHC membership files. Matched controls were assigned an index date of June 15th of the case diagnosis year. The ratio of controls to cases was 1.5:1 for men and 4:1 for women. Because there were fewer RCC cases in women, a higher control-to-case ratio was used to provide more-precise estimates of associations.

All exposure information was collected only for the period prior to the reference date, defined as 2 years prior to the date of diagnosis for cases and the corresponding index date for matched controls.

All analyses were restricted to subjects with at least 7 years of GHC enrollment prior to the diagnosis or index date (5 years prior to reference date), according to GHC computerized membership files. This restriction was chosen primarily because of the likelihood of misclassification of exposure variables for those subjects with shorter lengths of enrollment. Six cases (2 percent) and five controls (1 percent) were subsequently excluded from analyses because their medical records were missing. After these exclusions, 238 cases and 616 controls were available for analysis.

Data collection

The GHC computerized pharmacy database provided detailed information on medications dispensed by the GHC pharmacy after March 1, 1977. This database included information on the medication name, dose, date dispensed, and quantity dispensed for each medication prescription.

Information on medications of interest not dispensed by GHC or dispensed before March 1, 1977, was abstracted from medical records. Medication information abstracted from the medical records included dose, dosage interval, duration of use, number of prescription notations, and indication for use of medications. For medications dispensed at GHC after the pharmacy database was operational, the only information collected from the medical records was the indication for use.

Additional information collected from the medical records included race, smoking, history of certain diseases, blood pressure, height, and weight. For weight and blood pressure measurements, the first notations each year (when the subject was not pregnant) were collected, not including blood pressures from the emergency room and from inpatient hospital stays. Subjects were classified as having a diagnosis of hypertension if this diagnosis was noted in the medical record or if the patient was prescribed antihypertensive medications with no recorded indication but had a blood pressure of at least 140 mmHg systolic blood pressure or 90 mmHg diastolic blood pressure at that visit. These subjects were classified as "hypertensive," and all other subjects were classified as "normotensive."

For cases, information was abstracted on the reason for the initial procedure that detected the tumor and, therefore, ultimately led to the diagnosis of RCC. Tumors were classified as incidentally detected if they were discovered during a routine physical examination or at an examination for diseases or symptoms that were not likely to have been caused by the RCC tumor. Patients with tumors not classified as "incidentally detected" had hematuria, flank pain, weight loss, nausea, vomiting, anemia, metastases, and/or noticeable abdominal masses (10, 11).

Data analysis

Duration of medication use was calculated from the medical record as the number of months between the notation of first use and the discontinuation date for each episode of use of a medication. If no discontinuation date was noted, the date of the last refill or continuation notation plus 30 days was used as the discontinuation date. If there had been no refill and no continuation or discontinuation dates were noted, the episode of use was assigned a duration of 30 days.

Duration of medication use was calculated from the pharmacy database as the number of months between filling the first and the last prescriptions for each episode of medication use. In addition, the final prescription was assigned a duration of 30 days. An episode of use was defined as a sequence of one or more prescription fills for medications from the same

medication class, with no more than 180 days between subsequent prescription fills. Episodes of use with only one prescription were assigned a duration of 30 days.

Subjects with no or only one prescription notation for a medication class were counted as never users of that class of medication.

Diuretic medications were classified as follows: chlorthalidone, other thiazide derivatives, loop diuretics, potassium-sparing diuretics, and carbonic anhydrase inhibitors. Chlorthalidone was analyzed separately from other thiazide derivatives because of its different chemical structure and site of action within the kidney (12, 13). There were too few users of carbonic anhydrase inhibitors to analyze these as a separate class. Nondiuretic antihypertensive medications were stratified into the following classes: beta-adrenergic blockers, adrenergic inhibitors other than beta-blockers, direct-acting vasodilators, calcium antagonists, and angiotensin-converting enzyme inhibitors.

Maximum body mass index (BMI) was calculated by dividing the maximum nonpregnant weight recorded in the medical record (in kilograms) by the square of height (in meters). BMI was then divided into approximate quartiles according to the distribution of values in the controls for men and women separately.

Additional factors that were assessed as potential confounders included age, reference year, length of GHC enrollment, GHC clinic region, race, diabetes, hypertension, and cigarette smoking. Potential confounders that changed the odds ratios of interest by more than 10 percent were included in the final models.

Unconditional logistic regression was used to estimate the odds ratios and 95 percent confidence intervals presented in this paper. Results for the primary models were very similar when analyzed with conditional logistic regression. All regression analyses were conducted using EGRET software (Statistics and Epidemiology Research Corporation, Seattle, Washington).

All results are presented separately for men and women because the associations between several exposure variables and RCC were substantially different for men and women.

RESULTS

Results for women

Among women, cases were more likely than controls to be hypertensive and to have a high BMI (table 1). Use of diuretics was associated with an increased risk of RCC among women prior to adjustment for hypertension (for ever use compared with never use, odds ratio (OR) = 1.8, 95 percent confidence interval (CI) 1.0–3.1) (table 2). There was an increased risk associated with ever use of each of the different classes of diuretics (compared with never use of any diuretic), although there were small numbers of users of chlorthalidone and loop diuretics (table 2). Most users of nonthiazide diuretic medications had also used thiazides, so we could not examine the exclusive use of these medications. The odds ratio associated with long-term duration of use of diuretics was similar to that associated with short-term duration of use (table 2).

Nondiuretic antihypertensive use was associated with a similarly increased risk of RCC prior to adjustment for hypertension (for ever use compared with never use, OR = 1.7, 95 percent CI 1.0–3.0) (table 3). The point estimates for the association with RCC were greater than 1.0 for each type of nondiuretic antihypertensive (table 3). However, several classes of medications had small numbers of exposed subjects.

When compared with never use of any antihypertensive medication, use of only diuretics, use of only nondiuretic antihypertensives, and use of both types of medications were associated with increased risk of RCC in women, unadjusted for hypertension (table 4).

Neither use of diuretics nor nondiuretic antihypertensives was associated with increased risk of RCC after adjustment for hypertension (for diuretics, OR = 1.1, 95 percent CI 0.5–2.1; for nondiuretic antihypertensives, OR = 1.3, 95 percent CI 0.7–2.3) (data not shown). Results were similar when diuretic and nondiuretic antihypertensive use were adjusted for each other in addition to hypertension (table 5). Use of nondiuretic antihypertensives was associated with an OR of 2.6 among normotensive women, but this association was based on only five exposed cases and 18 exposed controls, and the confidence interval was wide (table 5). A diagnosis of hypertension remained associated with an increased risk of RCC after adjustment for use of diuretics and nondiuretic antihypertensives and BMI (OR = 2.5, 95 percent CI 1.2–5.1) (table 5). In addition, a diagnosis of hypertension was associated with an increased risk of RCC among never users of antihypertensive medication (OR = 3.1, 95 percent CI 1.1–8.8).

The association of hypertension with RCC in women was similar when we excluded cases with small tumors (30 mm or less) and when we excluded cases with tumors of localized stage. The association of hypertension with RCC in women became stronger when we excluded cases whose tumors were likely to have been incidentally detected (OR = 4.0, 95 percent CI 2.0–8.0, adjusted for age and BMI).

Among women with 10 or more years of GHC enrollment before the reference date, we examined the

TABLE 1. Selected characteristics of renal cell carcinoma cases and controls, Group Health Cooperative of Puget Sound, 1980–1995

Characteristic	Women				Men			
	Controls (*n* = 355)		Cases (*n* = 83)		Controls (*n* = 261)		Cases (*n* = 155)	
	No.	%	No.	%	No.	%	No.	%
Age at diagnosis/index date (years)								
35–49	36	10.1	8	9.6	30	11.5	13	8.4
50–59	68	19.2	15	18.1	66	25.3	39	25.2
60–69	120	33.8	29	34.9	78	29.9	49	31.6
70–79	112	31.5	27	32.5	61	23.4	44	28.4
80–84	19	5.4	4	4.8	26	10.0	10	6.5
Years of GHC* enrollment to diagnosis/index date								
7–10	85	23.9	22	26.5	61	23.4	32	20.6
11–14	53	14.9	10	12.0	37	14.2	25	16.1
15–19	92	25.9	21	25.3	69	26.4	35	22.6
20–24	56	15.8	16	19.3	44	16.9	33	21.3
≥25	69	19.4	14	16.9	50	19.2	30	19.4
Race								
White	244	68.7	57	68.7	181	69.3	99	63.9
Nonwhite	22	6.2	5	6.0	19	7.3	11	7.1
Unknown	89	25.1	21	25.3	61	23.4	45	29.0
Hypertension†								
No	214	60.3	27	32.5	150	57.5	81	52.3
Yes	141	39.7	56	67.5	111	42.5	74	47.7
Quartiles of maximum BMI‡								
1 (lowest)	80	22.5	6	7.2	57	21.8	21	13.5
2	82	23.1	18	21.7	58	22.2	30	19.4
3	79	22.3	20	24.1	57	21.8	27	17.4
4 (highest)	81	22.8	30	36.1	56	21.5	52	33.5
Unknown	33	9.3	9	10.8	33	12.6	25	16.1

* GHC, Group Health Cooperative of Puget Sound.

† Hypertension diagnosis in medical record or placement on antihypertensive medications with no recorded indication but a blood pressure of ≥140 mmHg systolic pressure or ≥90 mmHg diastolic pressure at that visit.

‡ Body mass index (BMI) is calculated as weight (kg)/height^2 (m^2), using maximum weight recorded in the medical record. Quartiles of the control distribution are calculated separately for men and women. For women, quartiles are: <23.35, 23.35–26.04, 26.05–30.08, and >30.08. For men, quartiles are: <25.38, 25.38–27.23, 27.24–29.48, and >29.48.

association of RCC with time since the diagnosis of hypertension. The association between RCC and hypertension was strongest for hypertension diagnosed within the 5-year period immediately prior to reference date (OR = 4.2, 95 percent CI 1.6–11.2, adjusted for age, BMI, and years of GHC enrollment), but there was still an increased risk of RCC associated with hypertension first diagnosed 10 or more years prior to the reference date (OR = 2.4, 95 percent CI 1.0–5.6).

Elevated blood pressure levels during both the 5-year period immediately prior to the reference date and the period 3–8 years prior to the reference date were associated with increased risk of RCC (table 6). Median systolic pressure of 160 mmHg or greater during the period 3–8 years prior to the reference date, compared with less than 140 mmHg, was associated with an OR of 1.7 (95 percent CI 0.7–4.0). Median diastolic pressure of 90 mmHg or greater during this time period, compared with less than 85 mmHg, was associated with an OR of 2.9 (95 percent CI 1.5–5.5). There were similar associations with high systolic and diastolic pressures when analyses were restricted to subjects who never used antihypertensive medications.

Results for men

Among men, cases were more likely than controls to be hypertensive and to have a high BMI (table 1). Use of diuretics or nondiuretic antihypertensive medications was not generally associated with increased risk

TABLE 2. Association of diuretic use with renal cell carcinoma, unadjusted for hypertension, Group Health Cooperative of Puget Sound, 1980–1995*

Exposure	Women						Men					
	Controls (*n* = 322)		Cases (*n* = 74)		OR†	95% CI‡	Controls (*n* = 228)		Cases (*n* = 130)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
Any diuretic												
Never use	188	58.4	29	39.2	1.0	Reference	149	65.4	79	60.8	1.0	Reference
Ever use	134	41.6	45	60.8	1.8	1.0–3.1	79	34.6	51	39.2	1.0	0.6–1.6
<5 years	75	23.3	23	31.1	1.7	0.9–3.2	40	17.5	30	23.1	1.2	0.7–2.2
≥5 years	59	18.3	22	29.7	1.9	0.9–3.8	39	17.1	21	16.2	0.8	0.4–1.5
Thiazide derivatives (other than chlorthalidone)												
Ever use	124		41		1.8	1.0–3 1	72		45		1.0	0.6–1.6
<3 years	46		16		1.9	0.9–3.9	30		20		1.0	0.5–2.0
≥3 years	78		25		1.7	0.9–3.2	42		25		0.9	0.5–1.7
Potassium-sparing diuretics												
Ever use	51		21		2.0	1.0–4.0	27		17		0.9	0.4–1.7
<3 years	22		13		2.8	1.2–6.7	16		5		0.4	0.1–1.2
≥3 years	29		8		1.3	0.5–3.4	11		12		1.5	0.6–3.8
Chlorthalidone	14		12		3.9	1.6–9.7	18		12		1.0	0.4–2 2
Loop diuretics	19		9		2.1	0.7–6.1	15		9		0.9	0.4–2.3
Potassium-wasting diuretics§												
Ever use	107		36		1.8	1.0–3.3	68		45		1.0	0.6–1.6
<3 years	56		16		1.5	0.8–3.1	32		28		1.3	0.7–2.5
≥3 years	51		20		2.1	1.0–4.3	36		17		0.7	0.4–1.4

* Only subjects with at least one body mass index (BMI) value recorded in the medical record are included in these analyses.
† All odds ratios (OR) are adjusted for maximum BMI recorded in the medical record (quartiles of the control distribution) and age group (35–49, 50–59, 60–69, 70–79, and 80–84 years). The reference group for all odds ratios is never users of diuretics.
‡ CI, confidence interval.
§ Without concurrent potassium supplement or potassium-sparing diuretic use.

of RCC (for ever use of diuretics compared with never use, OR = 1.0, 95 percent CI 0.6–1.6; for ever use of nondiuretic antihypertensives compared with never use, OR = 0.9, 95 percent CI 0.6–1.5), even without adjustment for hypertension (tables 2 and 3). When compared with never use of any antihypertensive medication, use of diuretics alone and use of nondiuretic antihypertensives alone appeared to be associated with a slightly increased risk prior to adjustment for hypertension, while use of both types of medications was not (table 4). There was an elevated odds ratio for ever use of diuretics among normotensives, but this association was based on only five exposed cases and five exposed controls (table 5).

In men, a diagnosis of hypertension was only weakly associated with RCC (OR = 1.3, 95 percent CI 0.7–2.5, after adjustment for diuretic and nondiuretic antihypertensive use and BMI) (table 5). Among never users of antihypertensive medication, a hypertension diagnosis was not associated with increased risk of RCC (OR = 1.1, 95 percent CI 0.5–2.5) (data not shown). However, elevated blood pressure levels during both the 5-year period immediately prior to the reference date and the period 3–8 years prior to reference date were associated with an increased risk of RCC (table 6). Median systolic pressure of 160 mmHg or greater during the period 3–8 years prior to the reference date, compared with less than 140 mmHg, was associated with an increased risk of 2.6 (95 percent CI 1.1–6.2). Median diastolic pressure of 90 mmHg or greater during this time period, compared with less than 85 mmHg, was associated with an increased risk of 1.8 (95 percent CI 1.1–3.2). There were similar associations with high systolic and diastolic pressures when analyses were restricted to subjects who had never used antihypertensive medications.

DISCUSSION

Although all published studies have reported positive associations of diuretic medication use with RCC risk in women prior to adjustment for hypertension, results from analyses that adjust for hypertension have not been consistent (1–9). In our study, use of diuretics was associated with increased risk among women, but the odds ratio was reduced to 1.1 after adjustment for hypertension. This result appears to be consistent with the recent large pooled international analysis of six case-control interview studies with 682 female cases (7). While the international analysis did not present results separately

TABLE 3. Association of nondiuretic antihypertensive use with renal cell carcinoma, unadjusted for hypertension, Group Health Cooperative of Puget Sound, 1980–1995*

Exposure	Women						Men					
	Controls (*n* = 322)		Cases (*n* = 74)		OR†	95% CI‡	Controls (*n* = 228)		Cases (*n* = 130)		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
Any nondiuretic antihypertensive												
Never use	238	73.9	44	59.5	1.0	Reference	157	68.9	85	65.4	1.0	Reference
Ever use	84	26.1	30	40.5	1.7	1.0–3.0	71	31.1	45	34.6	0.9	0.6–1.5
<5 years	51	15.8	19	25.7	1.9	1.0–3.6	44	19.3	23	17.7	0.8	0.4–1.4
≥5 years	33	10.2	11	14.9	1.5	0.7–3.4	27	11.8	22	16.9	1.2	0.6–2.2
Beta-blockers												
Never use	256	79.5	51	68.9	1.0	Reference	181	79.4	95	73.1	1.0	Reference
Ever use	66	20.5	23	31.1	1.6	0.9–2.8	47	20.6	35	26.9	1.2	0.7–2.0
<3 years	32	9.9	12	16.2	1.7	0.8–3.7	25	11.0	16	12.3	1.0	0.5–2.0
≥3 years	34	10.6	11	14.9	1.4	0.6–3.0	22	9.6	19	14.6	1.4	0.7–2.7
Adrenergic inhibitors (other than beta-blockers)												
Never use	298	92.5	66	89.2	1.0	Reference	202	88.6	113	86.9	1.0	Reference
Ever use	24	7.5	8	10.8	1.1	0.5–2.7	26	11.4	17	13.1	1.0	0.5–1.9
Direct-acting vasodilators												
Never use	315	97.8	71	95.9	1.0	Reference	220	96.5	126	96.9	1.0	Reference
Ever use	7	2 2	3	4.1	1.4	0.4–5.9	8	3.5	4	3.1	0 7	0.2–2.5
Calcium antagonists												
Never use	301	93.5	66	89.2	1.0	Reference	214	93.9	116	89.2	1.0	Reference
Ever use	21	6.5	8	10.8	1.7	0.7–4.2	14	6.1	14	10.8	1.4	0.7–3.2
ACE‡ inhibitors												
Never use	315	97.8	70	94.6	1.0	Reference	222	97.4	121	93.1	1.0	Reference
Ever use	7	2.2	4	5.4	2.0	0.6–7.4	6	2.6	9	6.9	2.4	0.8–7.0

* Only subjects with at least one body mass index (BMI) value recorded in the medical record are included in these analyses.
† All odds ratios (OR) are adjusted for maximum BMI recorded in the medical record (quartiles of the control distribution) and age group (35–49, 50–59, 60–69, 70–79, and 80–84 years).
‡ CI, confidence interval; ACE, angiotensin-converting enzyme.

TABLE 4. Association of antihypertensive medication use with renal cell carcinoma, unadjusted for hypertension, Group Health Cooperative of Puget Sound, 1980–1995*

Antihypertensive medication use	Controls		Cases		OR†	95% CI‡
	No.	%	No.	%		
Among women						
Never used	162	50.6	23	31.1	1.0	Reference
Used diuretics only	74	23.1	21	28.4	1.6	0.8–3.3
Used nondiuretics only	24	7.5	6	8.1	1.7	0.6–4.7
Used both	60	18.8	24	32.4	2.4	1.2–4.7
Among men						
Never used	134	58.8	64	49.6	1.0	Reference
Used diuretics only	23	10.1	20	15.5	1.6	0.8–3.3
Used nondiuretics only	15	6.6	14	10.9	1.5	0.7–3.5
Used both	56	24.6	31	24.0	0.9	0.5–1.6

* Only subjects with at least one body mass index (BMI) value recorded in the medical record are included in these analyses.
† All odds ratios (OR) are adjusted for maximum BMI recorded in the medical record (quartiles of the control distribution) and age group (35–49, 50–59, 60–69, 70–79, and 80–84 years).
‡ CI, confidence interval.

for women, the authors stated that findings were similar for men and women, and they reported a summary odds ratio of 1.0 for use of diuretics adjusted for hypertension and sex (7). In contrast to our results and those of McLaughlin et al. (7), four of six prior case-control studies that examined the association between use of diuretics and RCC in women reported approximately twofold to fourfold increased risks even after adjust-

TABLE 5. Association of antihypertensive use with renal cell carcinoma, adjusted for hypertension, Group Health Cooperative of Puget Sound, 1980–1995*

Exposure	Women						Men					
	Controls		Cases		OR†	95% CI‡	Controls		Cases		OR†	95% CI
	No.	%	No.	%			No.	%	No.	%		
Medication use and hypertension adjusted for one another												
Diuretic use					1.0	0.5–2.0					0.9	0.5–1.8
Nondiuretic antihypertensive use					1.2	0.7–2.3					0.8	0.5–1.5
Hypertension§					2.5	1.2–5.1					1.3	0.7–2.5
Medication use stratified by hypertensive status§												
Diuretic use among normotensives												
Never	156	83.4	20	83.3	1.0	Reference	122	96.1	57	91.9	1.0	Reference
Ever	31	16.6	4	16.7	0.8	0.2–2.6	5	3.9	5	8.1	2.4	0.6–9.8
Nondiuretic antihypertensive use among normotensives												
Never	169	90.4	19	79.2	1.0	Reference	115	90.6	57	91.9	1.0	Reference
Ever	18	9.6	5	20.8	2.6	0.8–8.2	12	9.4	5	8.1	0.6	0.2–2.1
Diuretic use among hypertensives												
Never	32	23.7	9	18.0	1.0	Reference	27	26.7	22	32 4	1.0	Reference
Ever	103	76.3	41	82.0	1.3	0.5–3.1	74	73.3	46	67.6	0.7	0.4–1.5
Nondiuretic antihypertensive use among hypertensives												
Never	69	51.1	25	50.0	1.0	Reference	42	41.6	28	41.2	1.0	Reference
Ever	66	48.9	25	50.0	1.1	0.5–2.1	59	58.4	40	58.8	0.9	0.5–1 7

* Only subjects with at least one body mass index (BMI) value recorded in the medical record are included in these analyses.
† All odds ratios (OR) are adjusted for maximum BMI recorded in the medical record (quartiles of the control distribution) and age group (35–49, 50–59, 60–69, 70–79, and 80–84 years).
‡ CI, confidence interval.
§ Subjects classified as hypertensive either had a hypertension diagnosis in the medical record or were prescribed antihypertensive medications with no recorded indication but a blood pressure of at least 140 mmHg systolic pressure or 90 mmHg diastolic pressure at that visit. All other subjects were classified as normotensive.

ment for hypertension (1, 3–5). The remaining two case-control studies presented results stratified by hypertension. McLaughlin et al. (2) reported an increased risk associated with use of diuretics only among normotensive women, and Weinmann et al. (6) only among hypertensives. Two cohort studies have examined the association of RCC with use of diuretics in women (8, 9). Prineas et al. (9) reported a weak association with the use of diuretics, whether or not the diuretic was used for hypertension. In a mortality study, Heath et al. (8) found a weak association with use of diuretics among normotensives (relative risk = 1.4).

Among men, we found that the use of diuretics was not associated with RCC either before or after adjustment for hypertension. All seven prior studies that examined the association between use of diuretics and RCC in men reported an odds ratio of 1.5 or less after adjustment for hypertension (1, 2, 4–8).

The association of nondiuretic antihypertensive medication use with RCC risk has been specifically examined in only two previous studies. These studies reported elevated odds ratios for RCC associated with use for both sexes combined, unadjusted for hypertension (6, 7). One of these studies reported their results adjusted for hypertension: The remaining association with nondiuretic antihypertensive use was weak (OR = 1.3) (7). Similarly, we found that nondiuretic antihypertensive use was not associated with an increased risk of RCC in either sex after adjustment for hypertension.

Antihypertensive medications vary greatly in their mechanism of action for reducing blood pressure (14). The finding of increased risks associated with several different antihypertensive medication classes makes it less plausible that the associations are due to the effect of the medications rather than to the underlying hypertension for which they were usually prescribed. The increased risk that we found associated with hypertension among subjects who had never taken antihypertensive medications further supports an independent effect of hypertension rather than an effect of any particular antihypertensive medication.

Of the population-based studies that examined the association in both men and women (1, 4–8, 15–20), 10

TABLE 6. Association of blood pressure level with renal cell carcinoma, Group Health Cooperative of Puget Sound, 1980–1995*

Exposure	Women		Men	
	OR†	95% CI‡	OR†	95% CI
Median blood pressure during the 5-year period prior to reference date (mmHg)§				
Systolic				
<140	1.0	Reference	1.0	Reference
140–159	1.5	0.8–2.7	2.1	1.3–3.6
≥160	2.3	1.0–5.4	2.0	0.9–4.2
Diastolic				
<85	1.0	Reference	1.0	Reference
85–89	1.9	0.9–4.0	1.9	1.0–3.6
≥90	2.3	1.2–4.4	1.3	0.8–2.3
Median blood pressure during the period 3–8 years prior to reference date (mmHg)¶				
Systolic				
<140	1.0	Reference	1.0	Reference
140–159	1.2	0.7–2.3	1.6	0.9–2.6
≥160	1.7	0.7–4.0	2.6	1.1–6.2
Diastolic				
<85	1.0	Reference	1.0	Reference
85–89	2.7	1.3–5.8	1.3	0.6–2.5
≥90	2.9	1.5–5.5	1.8	1.1–3.2

* Only subjects with at least one body mass index (BMI) value recorded in the medical record are included in these analyses.

† All odds ratios (OR) are adjusted for maximum BMI recorded in the medical record (quartiles of the control distribution) and age group (35–49, 50–59, 60–69, 70–79, and 80–84 years).

‡ CI, confidence interval.

§ Median blood pressure recorded in the medical record during the 5-year period immediately prior to reference date. Eight female controls, 10 male controls, and six male cases were excluded because they were missing information on blood pressure during this time period.

¶ Median blood pressure recorded in the medical record during the period 3–8 years prior to reference date. Twenty female controls, four female cases, 19 male controls, and 10 male cases were excluded because they were missing information on blood pressure during this time period.

reported that hypertension or high blood pressure was associated with elevated RCC risk in both sexes, at least when unadjusted for antihypertensive medication use (4–7, 15–20), while two studies (one of RCC mortality) reported an association in women, but little or no association in men (1, 8). Six additional studies that reported results for only one sex all reported positive associations, four for men (two for kidney cancer mortality) (21–24) and two for women (3, 9). However, after adjustment for or stratification by diuretic or antihypertensive medication use, previous studies have not reported consistent results with respect to the association with hypertension (1, 3–9, 18, 23).

It is difficult to separate out the effect of hypertension from the effect of antihypertensive medication use, since most diagnosed hypertensives, especially those with severe hypertension, will have taken some type of antihypertensive medication. In the current study, we found that a diagnosis of hypertension, whether or not it was adjusted for use of antihypertensive medications, was associated with an increased risk of RCC for women, but not for men. However, we found that a high blood pressure level was associated with an increased risk of RCC for both men and women, even among subjects who never took antihypertensive medications. Few studies have examined the association of blood pressure levels with RCC risk. Two small cohort studies in men, with 5–17 kidney cancer cases or deaths, reported positive associations of blood pressure at the baseline examination with kidney cancer incidence or mortality (21, 23). A large cohort study in men, with 398 kidney cancer deaths, also reported a positive association of baseline blood pressure with kidney cancer mortality (24).

The effects of hypertension on the kidney are complex. Hypertension can cause the arterioles supplying

the kidney to thicken, resulting in kidney damage due to reduced blood flow (25). This damage can eventually lead to the death of kidney cells (25). If there were increased cell proliferation to replace lost kidney cells, this would be expected to increase the probability of genetic mutations leading to cancer.

RCC may also cause hypertension by increasing the production of the enzyme renin (26, 27), which could explain an association of hypertension with RCC. However, in our study, the association of hypertension with RCC did not appear to be solely due to the effect of RCC on hypertension. We found that there was still an over twofold increased risk associated with a diagnosis of hypertension in women 10 or more years prior to the reference date (12 or more years prior to the RCC diagnosis or control index date). In addition, elevated blood pressure during the period 3–8 years prior to reference date (5–10 years prior to the diagnosis or index date) was associated with increased risk of RCC in both men and women.

No previous study has examined the possibility that detection bias could explain the association between RCC and hypertension and/or antihypertensive medication use. Hypertensives may be more likely to have their RCC diagnosed incidentally because of their frequent contact with the medical system and because they may be more likely to undergo ultrasonography or computerized tomography. Several authors have suggested that hypertensive patients should be screened for RCC (28, 29). In a Japanese study, 79 of 1,422 incidentally detected RCC cases were detected during examination or treatment for hypertension (30). In a study of RCC detected by intravenous urography at a New York hospital, the indication for the procedure in seven of 16 incidentally detected RCC cases was hypertension (31). However, in our study, only one case had a notation in the medical record that the RCC tumor was detected during an evaluation of hypertension. When we excluded the 18 RCC tumors in women that appeared likely to have been incidentally detected for any reason (based on notations in the medical record), the association of RCC with a diagnosis of hypertension in women became stronger. Therefore, there was no evidence that the association with hypertension in our study was due to detection bias.

There are several limitations to this study. Although we did have detailed information on medication for many subjects for the period after the pharmacy database was operational, complete information on other exposures or on medication exposures before this period may not always have been recorded in the medical chart. In particular, for many subjects, there was little or no information on use of antihypertensive medications or other exposures before enrollment in GHC. For some analyses, we had to exclude subjects who did not have information recorded in the medical record on a particular exposure, such as weight, height, or blood pressure. Some of our analyses were also limited by small numbers.

Our study has several advantages over interview studies of this topic. The GHC medical records and pharmacy database provided more-detailed information on blood pressure, medication use, and other exposures than is often available from interview studies that rely on self-report. We had particularly detailed information on medication use from the pharmacy database for medications dispensed at the GHC pharmacy after March 1, 1977. In addition, because all exposure information was recorded in the medical records and the pharmacy database before the diagnosis of RCC, it was not subject to recall bias. Because we did not have to contact subjects to ask them to participate, we also minimized potential selection bias resulting from nonparticipation.

In conclusion, these results do not support the hypothesis that diuretics or other antihypertensive medications increase the risk of RCC. These results are more consistent with an effect of high blood pressure on RCC risk.

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