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ANTIHYPERTENSIVE MEDICATION USE AND RISK OF RENAL CELL CARCINOMA

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Abstract

Purpose: Use of antihypertensive medications has been associated with renal cell carcinoma (RCC), but it is unclear whether specific types of medications increase RCC risk independent of the effect of hypertension, or whether the association varies by histologic subtype. To address this question, we analyzed data from a U.S. population-based case-control study of RCC.

Methods: We collected information on participants' use of drugs to treat hypertension, heart problems, weight control, and swelling. We computed odds ratios (ORs) and 95% confidence intervals (CIs) for each of four major drug classes, separately for participants with (643 cases, 443 controls) and without (500 cases, 718 controls) a history of hypertension, using unconditional logistic and polytomous regression models.

Results: None of the antihypertensive drug types was associated with RCC overall. Among participants with a history of hypertension, papillary RCC was associated with long-term use of diuretics (OR=3.1, 95% CI=1.4–6.7 for 16+ years, 16 cases, 31 controls; Ptrend=0.014) and calcium channel blockers (OR=2.8, 95% CI=1.1–7.4 for 16+ years, 8 cases, 14 controls; Ptrend=0.18), while corresponding ORs for clear cell RCC were weaker (ORs 0.9 and 1.5, respectively) and nonsignificant. The only significant finding among those with no hypertension history was an association between calcium channel blockers and papillary RCC (OR=17.9, 95% CI=5.9–54.5) that was based on small numbers (8 cases, 9 controls). There was little evidence of an association between RCC and use of ACE inhibitors or beta blockers.

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Conclusions: Our study, while inconclusive for overall RCC, provides to our knowledge the first evidence supporting an association between antihypertensive medications and papillary RCC. These subtype-specific findings, although based on small numbers, warrant further investigation.

Keywords

Renal cell carcinoma; antihypertensive medications; hypertension; case-control study

INTRODUCTION

Kidney cancer, the deadliest of the urologic malignancies, was diagnosed in an estimated 65,150 Americans in 2013[1]. Renal cell carcinoma (RCC) comprises about 90% of kidney cancers and is made up of several histological subtypes, the most common of which are clear cell RCC (about 70% of RCC cases), papillary RCC (10–15%), and chromophobe RCC (about 5%) [2].

Established modifiable risk factors for RCC include smoking, obesity, and hypertension [3]. Hypertension and use of antihypertensive medications have each been associated with an elevated risk of RCC in epidemiologic studies [3]. Researchers have attempted to disentangle the effects of these highly correlated exposures using a variety of approaches, but it remains unclear whether specific types of antihypertensive medications increase RCC risk independent of the effect of hypertension.

We previously reported on the relationship between hypertension and risk of RCC in the U.S. Kidney Cancer Study, a large, population-based case-control study conducted in the Detroit and Chicago metropolitan areas [4]. We found that hypertension doubled RCC risk after adjusting for demographic characteristics, smoking, body mass index (BMI), and family history of cancer, and that the association appeared to be stronger among blacks than whites. Here, we use data from the U.S. Kidney Cancer Study to examine whether specific types of antihypertensive medications are associated with RCC risk, independent of hypertension. Because the RCC histologies may have distinct etiologies [2, 5], we also conducted analyses by subtype for clear cell and papillary RCC, the two major RCC histologies.

MATERIALS AND METHODS

Study population

The U.S. Kidney Cancer Study was conducted in Detroit, Michigan (Wayne, Oakland, and Macomb Counties) and Chicago, Illinois (Cook County). Methods for subject recruitment and data collection have been described [4]. Briefly, white and black men and women between 20 and 79 years of age who were newly diagnosed with histologically-confirmed RCC (ICD-O3-C64.9)] between 2002 and 2007 were eligible for study. In Detroit, cases were identified through the Metropolitan Detroit Cancer Surveillance System, a Surveillance, Epidemiology, and End Results Program member. In Chicago, cases were diagnosed through review of pathology reports at Cook County hospitals. Identification of histologic subtype was based on a centralized review of histologic slides by our expert renal

pathologist or information from the original diagnostic pathology reports [2]. Eligible controls were selected from the general population and were frequency matched to cases on age (5-year intervals), sex, race, and study center. Controls were identified from department of motor vehicle (DMV) records (ages 20 to 64) and Medicare eligibility files (ages 65 to 79).

To increase the number of black participants in the study, we recruited all black cases, while some strata (age-race-sex combinations) of white cases were sampled. We targeted frequency matching of controls to cases at a 2:1 ratio for blacks and a 1:1 ratio for whites. Because information on race was unavailable in the DMV records but addresses were available, we oversampled people in census block groups with a high proportion of black residents to help achieve the targeted matching ratios for blacks under age 65.

We identified 1,918 eligible cases for this study, of whom 171 died before contact or interview, 92 could not be located, 21 moved out of the area, and physicians of 63 refused permission to contact patients. Among the remaining 1,571 cases we sought to enroll, 221 declined participation and 133 were not interviewed due to serious illness, impairment, or nonresponse after multiple contact attempts. Thus, 1,217 cases (77.5% of the 1,571 we attempted to recruit) participated. We identified 2,718 presumed eligible controls, of whom 41 died before contact or interview, 345 were unlocatable, and 63 had moved away. Among the 2,269 controls we attempted to recruit, 677 declined participation and 357 were not interviewed due to serious illness, impairment, or not responding to multiple contact attempts. Thus, 1,235 eligible controls (54.4% of those we attempted to recruit) participated. Study procedures were approved by Institutional Review Boards at all institutions, and written informed consent was obtained from all participants before interview.

Assessment of exposure variables

Trained interviewers conducted in-home, computer-assisted interviews to elicit information on demographics, height and weight, medical history, smoking history, family history of cancer, and other potential risk factors. In a section of the interview focusing on medications, we asked participants if they ever took prescription medication for high blood pressure or heart problems at least once a week for a month or longer (excluding the two years before interview). Most of those responding in the affirmative had a history of hypertension, but some reported taking prescription medication for unspecified heart problems such as angina, arrhythmia, and congestive heart failure. All respondents who took prescription medication for high blood pressure or heart problems were asked to name each drug taken and were shown lists of drugs to stimulate memory. Those unable to identify a specific medication were asked to name the type of medication and were shown a list of commonly used medication types (ACE inhibitor, beta blocker, calcium channel blocker, diuretic, combination product). Interviewers ascertained the age/year each drug was first and last taken and, if either was unknown or use of the drug had been temporarily discontinued, the total duration of use. All participants were also asked about the use of prescription diuretics to control weight or swelling.

In a separate part of the interview focusing on hypertension, participants were asked if they were ever told by a health professional that they had high blood pressure. If so, a series of

questions was asked including age at diagnosis, whether antihypertensive medication was taken, and how well their blood pressure was controlled [4].

Statistical analysis

We placed each drug identified by study participants into one or more (if a combination product) of five groups: ACE inhibitor, beta blocker, calcium channel blocker, diuretic, or other (e.g., angiotensin II receptor blockers, alpha-blockers, central agonists, vasodilators, nitrates). We focused our analysis on the first four types, which were the most frequently identified. Analyses were conducted separately for participants with and without a self-reported history of physician-diagnosed hypertension. Of the 1,217 cases and 1,235 controls interviewed, we excluded 16 cases and 9 controls whose blood pressure was never measured or who could not remember whether they had ever been diagnosed with hypertension. We further excluded 35 hypertensive cases and 19 hypertensive controls who reported taking medication for high blood pressure in the hypertension questionnaire, but denied taking medication for high blood pressure or heart problems in the medications questionnaire. Finally, we excluded 23 cases and 46 controls who reported having high blood pressure but were never prescribed medication or could not remember if medication was prescribed. After these exclusions, 1,218 participants with no hypertension history (500 cases, 718 controls) and 1,086 participants with a hypertension history (643 cases, 443 controls) remained for analysis.

We computed adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from multiple unconditional logistic regression models that included study center, age at reference date (diagnosis date for cases, selection date for controls) (20–44, 45–54, 55–64, 65–74, 75+ years), self-reported race (white, black), sex, education (<12 years, high school graduate, some college, 4+ years of college), smoking history as of two years before the reference date (never, occasional, regular former, regular current), BMI (based on height at interview and weight five years prior to interview, <25, 25-<30, 30-<35, 35+ kg/m^2, unknown), family history of cancer (none, cancer other than kidney cancer, kidney cancer, unknown), and the extent to which hypertension was controlled (always well controlled, usually well controlled, rarely controlled, almost never controlled [4]). ORs and 95% CIs for clear cell and papillary RCC were computed using polytomous regression modeling, with adjustment for the factors specified above. Analyses were conducted using STATA (StataCorp, College Station, Texas) software version 11.

We evaluated risk associated with use of each of the four drug types, where the referent group was composed of participants who never took that drug type. For participants with a hypertension history, we assessed risk by duration of use in four categories, based on the cut points used in our previous analysis of hypertension and RCC risk (never, ≤5 years, 6–15 years, 16+ years). [4] Tests for trend were performed by treating categorical variables as continuous, where the value for each category was equal to the median value among controls. In separate models, we further adjusted for the number of years since hypertension diagnosis (<=5, 6–15, 16–26, 26+). [4] We did not assess duration of use among those without a history of hypertension because of small numbers. We ran the models for each drug type both with and without adjustment for use of the other drug types (including the

"other" category). For participants with no hypertension history, this adjustment was made by including a single yes/no indicator term for use of any of the other drugs; for those with a hypertension history, who had a higher prevalence of antihypertensive drug use, we included separate terms for each of the drug types.

We developed sample weights to reduce the potential for bias arising from differential sampling rates for controls and cases, survey nonresponse, and deficiencies in coverage of the population at risk in the DMV and Medicare files. Sample weights for controls also include a post-stratification adjustment, so that the weighted distribution of controls across the matching variables matches exactly the weighted distribution of cases. In addition to being consistent with the objectives of the frequency matching, the post-stratification adjustment reduces the variability of the weights [6]. Risk estimates from the multiple logistic regression models were estimated using the post-stratification weights. Jackknife replicate weights [7] were created to estimate standard errors for the calculation of 95% confidence intervals and computation of test statistics and P values.

RESULTS

Cases with and without a history of hypertension both had higher BMIs, and were more likely to be current smokers, than their respective controls (Table 1). Hypertensive controls were older than hypertensive cases. Among those without hypertension, controls had more years of education than cases, and cases were more likely than controls to have taken calcium channel blockers (p=0.033). Participants with a history of hypertension were older than those without a hypertension history, regardless of case-control status. Blacks were more likely than whites to have a history of hypertension. The distributions of histologic subtypes differed significantly by hypertension status (p=0.018). Although clear cell was the dominant histology regardless of hypertension status, there was a higher percentage of clear cell RCC among those with no hypertension history and a higher percentage of papillary RCC among those with a history of hypertension.

Among participants with previously diagnosed hypertension, none of the antihypertensive drug classes was significantly associated with RCC risk (Table 2). In subtype-specific analyses, use of diuretics for 16+ years tripled the risk of papillary RCC (OR=3.1, 95% CI=1.4–6.7) (Ptrend=0.014). This association persisted with adjustment for years since hypertension diagnosis (OR=2.5, 95% CI=1.1–5.7 for 16+ years of use, Ptrend=0.053) (Online Resource 1). Papillary RCC risk was also significantly associated with long-term use of calcium channel blockers (OR=2.8, 95% CI=1.1–7.4 for 16+ years) and ever use of ACE inhibitors (OR=1.6, 95% CI=1.02–2.6), but without a trend with duration of use for either drug (Ptrend=0.18 and 0.51, respectively). Findings for clear cell RCC were weaker and nonsignificant. Our findings did not meaningfully change when all five drug types were included in one model, either without (Online Resource 2) or with (Online Resource3) adjustment for years since hypertension diagnosis; when models were adjusted for a history of diabetes; or when participants with a history of renal failure and/or dialysis were excluded (data not shown). Hypertensive participants who took both diuretics and calcium channel blockers had no higher risk of kidney cancer than those who took only one of these two drug types (data not shown).

Among participants with no reported history of hypertension (Table 3), calcium channel blocker use was associated with papillary RCC (OR=17.9, 95% CI=5.9–54.5 compared to non-users of calcium channel blockers) but not with clear cell RCC (OR=1.0, 95% CI=0.3–2.8). These associations were based on small numbers of participants. RCC risk was not associated with any of the other drug types among those with no history of hypertension. Risk estimates were not meaningfully changed with adjustment for use of drugs other than the one being evaluated (Online Resource 4).

In subgroup analysis by race, among those with a history of hypertension, beta blocker use was associated with RCC risk among blacks (OR=1.7, 95% CI=1.02–2.9) but not whites (OR=0.9, 95% CI=0.6–1.3) (Pinteraction=0.07) (Online Resource 5). Beta blockers were not associated with RCC risk for either race in the absence of a hypertension history (Online Resource 6). Subgroup analysis did not reveal any differences by sex in the presence of a hypertension history (Online Resource 7). If no hypertension history was reported, women who had taken calcium channel blockers had a significantly higher risk of RCC (OR=17.2, 95% CI=5.5–53.5, 6 cases, 1 control) than did men (OR=1.7, 95% CI=0.6–4.6, 12 cases, 8 controls) (p for interaction=0.0014), based on small numbers (Online Resource 8).

Treatment with more than one type of antihypertensive drug was common among those with a history of hypertension. Excluding participants with an unknown drug type in their history, 40% of controls were treated with one drug type and the remainder received two, three, or four types of drugs (36%, 21%, 3%, respectively); the respective numbers for cases were 33%, 38%, 24%, and 5%. Kidney cancer risk increased modestly as the number of drugs types increased, reaching an OR of 1.5 (CI=0.9–1.7) (data not shown) for those taking four types of drugs. However, an increasing number of drugs is likely a marker for poor blood pressure control (Spearman’s rho=0.247, p<0.001), and the moderate association with kidney cancer risk is likely attributable to residual confounding by blood pressure control.

DISCUSSION

This study is the first, to our knowledge, to report associations with use of antihypertensive medications by histologic subtype for clear cell and papillary RCC. Among participants with a history of hypertension, papillary RCC was strongly associated with long-term use of both diuretics and calcium channel blockers, while findings for clear cell RCC were weaker and non-significant. Among participants without a history of hypertension, ever use of calcium channel blockers was significantly associated with papillary, but not clear cell, histology, albeit based on small numbers. There was little evidence of an association between RCC risk and use of ACE inhibitors or beta blockers.

The renal carcinogenicity of diuretics has been the subject of a large body of research. Studies with adjustment for hypertension generally support a positive association among women, but not men [8–14]. Reported associations among diuretic users without [8, 11–19] and with [12, 14, 16, 17, 19] a history of hypertension are mixed for both sexes.

A small number of studies have examined exposure-response relationships between diuretic use and kidney cancer risk while accounting for hypertension. Among studies with

adjustment for hypertension was an international, multi-center population-based case-control study that reported a 50% increase in RCC risk for people using diuretics for 15 years or longer (95% CI=1.0–2.1), but no increase for shorter term users [20]. In a population-based case-control study in Minnesota, the longest-term diuretic users (10+ years) experienced the highest risk of RCC, but the increase was modest (40%) and not statistically significant [21]. In two studies conducted within the Kaiser Foundation Health Plan, after adjustment for hypertension, a significant fivefold risk of RCC was observed among the women with the most diuretic prescriptions (30+) [8] and the women who used diuretics the longest (75+ months) [10]; however, risks were also elevated (about threefold) in the lower exposure categories and exposure-response trends were not significant.

Case-control studies that looked at duration of diuretic use and RCC risk among participants with no history of hypertension [20–22] report an OR of 1.0 or lower for fewer than 5 years of use, but elevated risk among longer-term users, with nonsignificant ORs of 1.4 [20] and 2.9 [22]. Yuan et al. found no association between lifetime cumulative dose of diuretics and risk of kidney cancer among men and women without a history of hypertension [23]. Studies comparing hypertensive diuretic users to non-users report mixed findings. Weinmann et al. observed a higher risk of RCC among 5+ years users (OR=1.8) than <5 year users (OR=1.5), but neither association was significant [22]. Yuan et al. reported a two-fold risk of RCC among hypertensives who used diuretics compared to those who did not, but there was no relationship with cumulative lifetime dose [23].

Although the evidence from the literature is inconsistent, it is suggestive of a possible association between long-term use of diuretics and an elevated risk of kidney cancer that is independent of hypertension. Our study supports such an association for papillary RCC, for which the trend with duration of use among participants with a history of hypertension persisted with adjustment for use of the other drug types and the years since hypertension diagnosis. Those without a reported hypertension history experienced a nonsignificant 60% increase in risk of papillary RCC. Evidence for an association with clear cell RCC was absent. Our study does not support previous findings of a stronger association among women compared to men.

Few studies have examined calcium channel blocker use and kidney cancer risk with adjustment for hypertension. In a Danish case-control study with adjustment for hypertension, no association was observed for either men or women [12]. An international case-control study found no trend between lifetime cumulative dose of calcium channel blockers and RCC risk after adjustment for hypertension, although risk was elevated in all dose categories [20]. Findings from studies of calcium channel blocker use and all cancers combined are conflicting, with early positive associations [24, 25] not supported in subsequent studies [26–34]. Our study provided only limited evidence of an association for calcium channel blockers that was largely restricted to papillary RCC and based on small numbers.

Our finding of an association with RCC risk for beta blocker use among blacks with a history of hypertension (OR=1.7, CI=1.02–2.9) but not whites (OR=0.9, CI=0.6–1.3) is noteworthy. This class of drugs treats hypertension more effectively in whites than blacks

when used as a monotherapy [35]; the extent to which hypertension was controlled was included in our models. We know of no other studies of the association between beta blocker use and RCC risk by race.

Associations between use of antihypertensive medications and kidney cancer risk are biologically plausible. It has been hypothesized that certain diuretics can be converted in the stomach to a mutagenic nitroso derivative [36–38], or that the chemical bombardment of the renal tubular cell (the target of diuretics) for many years might have a low-grade carcinogenic effect [37]. Rodents treated with diuretics have been reported to develop nephropathy and renal adenomas [37, 39]. It has also been suggested that calcium channel blockers can inhibit apoptosis and thus facilitate the division of cells with malignant potential [24]. The biologic basis for the different findings for clear cell versus papillary RCC is unclear. Given the small numbers of participants involved, it is important for these findings to be replicated before causal inferences are drawn.

In our previous analysis focusing on the relationship between hypertension and risk of RCC in this study population, [4] we found no association between use of antihypertensive drugs and RCC risk among participants with no previous diagnosis of hypertension. However, the previous analysis grouped all antihypertensive drugs types together and did not distinguish among RCC histologies. It is plausible, and our analysis suggests, that if associations do exist, they are likely to be drug-type- and histology-specific.

An important strength of our study is the detailed information available on antihypertensive medication use (specific drugs taken and duration of use), on the hypertension itself (years since diagnosis, extent of control), and on potential confounders such as smoking, BMI, and family history of cancer. In addition, to our knowledge, ours is the first RCC case-control study with enough black participants to evaluate the relationships among hypertension, antihypertensive drug use, and renal cancer risk by race. Central pathology review, histologically confirmed cancers, and a large sample size allowing analysis by major subtype, are additional strengths. Although there was no *a priori* expectation of different findings by histology, the strong association between diuretics and papillary RCC risk, if real, suggests that the biologic effects associated with use of diuretics might be particularly relevant to the pathogenesis of papillary RCC. Subtype-specific investigations in other studies are needed to confirm these novel findings.

A limitation of the study is that the information on hypertension history and medication use was based on self-report. It is possible that some participants categorized as having no history of hypertension, particularly those who reported taking drugs often prescribed for hypertension, had been unknowingly diagnosed with hypertension in addition to other heart conditions. Recall of the types of medications used and when they were first/last taken was difficult for some participants. If a participant could not remember the name of a drug that was taken, all of the drug types were coded as “don’t know” for that period of time. We also coded the drug type as “don’t know” if the participant reported taking the drug 10 years or more before it was approved by the Food and Drug Administration. Overall, 75 hypertensive cases (12%) and 56 hypertensive controls (13%) had at least one “don’t know” in their drug history. The overall similarity between cases and controls in this regard argues against

significant recall bias, which is always a concern in a case-control study. Although our study was relatively large, the number of long-term antihypertensive drug users diminished when stratified by histologic subtype. Our ability to conduct a detailed assessment for antihypertensive drug users without a history of diagnosed hypertension was also limited by small numbers. Our study was also limited by a low response rate among controls, which is characteristic of recent population-based case-control studies. Our use of sample weights helped to reduce the potential for bias arising from non-response across subgroups defined by factors (e.g., age, sex, county of residence) for which data were available for both respondents and nonrespondents.

In conclusion, our findings, while inconclusive for overall RCC, provide to our knowledge the first evidence supporting an association between antihypertensive medication use and papillary RCC. These subtype-specific findings, although based on small numbers, warrant further investigation, particularly for diuretics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of cases and controls, by hypertension status, Kidney Cancer Study, Detroit and Chicago, 2002–2007

	No history of hypertension				History of hypertension			
	Cases n=500		Controls n=718		Cases n=643		Controls n=443	
	No.	%[a]	No.	%[a]	No.	%[a]	No.	%[a]
Study Site								
Chicago	92	19.1%	113	15.6%	94	14.8%	68	18.2%
Detroit	408	80.9%	605	84.4%	549	85.2%	375	81.8%
Age (years)								
20–44	105	18.5%	157	15.9%	31	4.1%	11	1.7%
45–54	142	27.1%	201	28.5%	130	17.8%	52	10.2%
55–64	138	27.0%	177	26.6%	213	31.3%	152	33.3%
65–74	81	18.5%	137	20.3%	202	33.5%	171	38.0%
75+	34	9.0%	46	8.7%	67	13.4%	57	16.8%
Sex								
Male	291	61.8%	389	59.5%	375	60.2%	243	61.7%
Female	209	38.2%	329	40.5%	268	39.8%	200	38.3%
Race								
White	398	81.4%	445	77.3%	408	68.5%	226	68.7%
Black	102	18.6%	273	22.7%	235	31.5%	217	31.3%
Education								
<12 years	70	14.8%	65	7.9%	109	16.9%	89	18.5%
High school graduate	167	33.9%	225	31.1%	230	35.6%	138	31.8%
Some college	127	24.8%	213	27.6%	182	27.5%	127	27.7%
4+ years college	136	26.6%	215	33.5%	122	20.0%	89	21.9%
RCC Histology								
Clear cell	310	62.0%			357	55.6%		
Papillary	52	10.8%			107	16.4%		
Chromophobe	26	5.1%			24	3.9%		
Other/NOS	84	16.2%			112	17.0%		
Missing	28	5.8%			43	7.1%		
Body Mass Index (kg/m^2)								
<25	130	25.4%	270	36.6%	95	14.7%	82	18.4%
25<30	199	40.9%	284	41.7%	207	33.3%	175	40.9%
30<35	100	19.8%	110	15.5%	177	27.8%	99	22.9%
35+	66	12.9%	49	5.9%	157	23.1%	84	17.5%
Don’t know	5	1.0%	5	0.3%	7	1.1%	3	0.4%
Smoking Status								
Never	173	33.9%	292	39.9%	234	36.4%	155	36.3%
Occasional	19	4.0%	38	5.3%	30	4.9%	16	2.3%

	No history of hypertension				History of hypertension			
	Cases n=500		Controls n=718		Cases n=643		Controls n=443	
	No.	%[a]	No.	%[a]	No.	%[a]	No.	%[a]
Former	165	34.0%	232	34.0%	225	36.0%	182	43.4%
Current	143	28.1%	156	20.8%	154	22.7%	90	18.0%
Family History of Cancer								
None with cancer	231	45.4%	328	41.9%	250	37.9%	198	40.1%
Cancer other than kidney cancer	244	49.2%	371	55.7%	361	57.4%	229	55.6%
Kidney cancer	22	4.7%	14	1.8%	24	3.5%	9	2.3%
Don’t know	3	0.7%	5	0.6%	8	1.2%	7	2.1%
Ever Took Ace Inhibitors								
Yes	10	2.1%	12	1.7%	271	41.8%	157	37.2%
No	485	96.8%	701	97.5%	314	49.1%	236	52.5%
Don’t know	5	1.1%	5	0.8%	58	9.1%	50	10.3%
Ever Took Beta Blockers								
Yes	20	4.0%	29	4.9%	288	46.0%	170	42.7%
No	476	95.2%	684	94.2%	304	46.3%	227	48.2%
Don’t know	4	0.8%	5	0.8%	51	7.7%	46	9.1%
Ever Took Calcium Channel Blockers								
Yes	18	3.8%	9	1.5%	279	42.1%	175	35.3%
No	476	94.9%	704	97.7%	309	49.2%	226	55.9%
Don’t know	6	1.3%	5	0.8%	55	8.7%	42	8.8%
Ever Took Diuretics								
Yes	42	8.2%	59	7.6%	380	58.5%	268	58.1%
No	453	90.8%	651	91.2%	223	35.3%	138	33.7%
Don’t know	5	1.0%	8	1.3%	40	6.3%	37	8.2%

[a]Percentages incorporate poststratification sample weights. Some percentages do not sum to 100 due to rounding.

Table 2.

Renal cell cancer risk and use of antihypertensive drugs with a history of hypertension, by histologic subtype

	All Histologies (n=643 ca, 443 co)		Clear Cell (n=357 ca, 443 co)		Papillary (n=107 ca, 443 co)	
	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]
ACE Inhibitors						
Never	314/236	1.0 (ref)	176/236	1.0 (ref)	43/236	1.0 (ref)
Ever	271/157	1.2 (0.9–1.6)	152/157	1.2 (0.9–1.7)	54/157	1.6 (1.02–2.6)
<=5 years	164/90	1.3 (0.97–1.8)	92/90	1.3 (0.9–1.9)	31/90	1.7 (0.98–3.1)
6–15 years	71/48	1.0 (0.6–1.7)	39/48	1.0 (0.6–1.7)	16/48	1.4 (0.6–2.9)
16+ years	18/10	1.3 (0.5–3.2)	12/10	1.5 (0.5–4.5)	2/10	1.0 (0.3–3.9)
p-trend		0.78		0.61		0.51
			p (difference in trends) = 0.80			
Beta Blockers						
Never	304/227	1.0 (ref)	166/227	1.0 (ref)	48/227	1.0 (ref)
Ever	288/170	1.1 (0.8–1.5)	164/170	1.1 (0.8–1.6)	51/170	1.2 (0.7–2.0)
<=5 years	157/86	1.2 (0.8–1.7)	93/86	1.3 (0.9–1.8)	28/86	1.3 (0.7–2.4)
6–15 years	74/49	1.0 (0.6–1.5)	39/49	1.0 (0.6–1.6)	14/49	1.0 (0.4–2.0)
16+ years	34/19	1.3 (0.7–2.6)	17/19	1.1 (0.5–2.3)	7/19	2.2 (0.8–6.1)
p-trend		0.50		0.99		0.25
			p (difference in trends) = 0.27			
Calcium Channel Blockers						
Never	309/226	1.0 (ref)	179/226	1.0 (ref)	43/226	1.0 (ref)
Ever	279/175	1.3 (0.97–1.7)	146/175	1.3 (0.9–1.8)	57/175	1.4 (0.8–2.3)
<=5 years	153/88	1.4 (0.99–2.0)	79/88	1.4 (0.9–2.0)	31/88	1.6 (0.9–2.8)
6–15 years	79/64	0.9 (0.6–1.6)	43/64	1.0 (0.5–1.8)	15/64	1.0 (0.4–2.2)
16+ years	25/14	1.7 (0.8–3.5)	11/14	1.5 (0.6–3.9)	8/14	2.8 (1.1–7.4)
p-trend		0.43		0.54		0.18
			p (difference in trends) = 0.44			
Diuretics						
Never	223/138	1.0 (ref)	132/138	1.0 (ref)	31/138	1.0 (ref)

	All Histologies (n=643 ca, 443 co)		Clear Cell (n=357 ca, 443 co)		Papillary (n=107 ca, 443 co)	
	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]
Ever	380/268	0.9 (0.7–1.3)	203/268	0.8 (0.6–1.2)	70/268	1.3 (0.7–2.4)
<=5 years	164/144	0.7 (0.5–1.1)	97/144	0.8 (0.5–1.2)	24/144	0.8 (0.4–1.7)
6–15 years	102/72	0.8 (0.5–1.3)	57/72	0.8 (0.5–1.3)	18/72	1.1 (0.5–2.5)
16+ years	62/31	1.3 (0.8–2.3)	24/31	0.9 (0.4–1.8)	16/31	3.1 (1.4–6.7)
p-trend		0.24		0.73		0.014
				p (difference in trends) = 0.004		

[a] Counts do not sum to the total population due to issues related to recall of drug type and/or duration of use.

[b] Adjusted for age (20–44, 45–54, 55–64, 65–74, 75+ years), race (white, black), sex, region, education (<12 years, high school graduate, some college, 4+ years of college), smoking status (never, occasional, regular former, regular current), body mass index (<25, 25-<30, 30-<35, 35+ kg/m2, unknown), family history of cancer (none, cancer other than kidney cancer, kidney cancer, unknown), and self-reported extent of hypertension control (always well controlled, usually well controlled, rarely well controlled, almost never controlled, unknown).

Table 3.

Renal cell cancer risk and use of antihypertensive drugs without a history of hypertension, by histologic subtype

	All Histologies (n=500 ca, 718 co)		Clear Cell (n=310 ca, 718 co)		Papillary (n=52 ca, 718 co)	
	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]	Ca/Co[a]	OR 95% CI)[b]
ACE Inhibitors						
Never	485/701	1.0 (ref)	300/701	1.0 (ref)	50/701	1.0 (ref)
Ever	10/12	0.9 (0.3–2.9)	6/12	0.8 (0.2–3.1)	2/12	2.5 (0.3–20.2)
Beta Blockers						
Never	476/684	1.0 (ref)	295/684	1.0 (ref)	50/684	1.0 (ref)
Ever	20/29	0.7 (0.4–1.2)	12/29	0.6 (0.3–1.3)	2/29	0.6 (0.1–4.6)
Calcium Channel Blockers						
Never	476/704	1.0 (ref)	298/704	1.0 (ref)	44/704	1.0 (ref)
Ever	18/9	2.2 (0.9–5.4)	7/9	1.0 (0.3–2.8)	8/9	17.9 (5.9–54.5)
Diuretics						
Never	453/651	1.0 (ref)	280/651	1.0 (ref)	46/651	1.0 (ref)
Ever	42/59	0.8 (0.5–1.4)	26/59	0.7 (0.4–13)	6/59	1.6 (0.6–4.6)

[a]Counts do not sum to the full study population due to issues related to recall of drug type.

[b]Adjusted for age (20–44, 45–54, 55–64, 65–74, 75+ years), race (white, black), sex, region, education (<12 years, high school graduate, some college, 4+ years of college), smoking status (never, occasional, regular former, regular current), body mass index (<25, 25-<30, 30-<35, 35+ kg/m^2, unknown), family history of cancer (none, cancer other than kidney cancer, kidney cancer, unknown)