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Chronic kidney disease and risk of renal cell carcinoma: differences by race

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Abstract

Background—The incidence of renal cell carcinoma in the United States differs by race/ethnicity. To better understand these disparities, we conducted a nested case-control study investigating renal cell carcinoma risk factors across racial/ethnic groups within the Kaiser Permanente Northern California health care network.

Methods—Our study included 3,136 renal cell carcinoma cases (2,152 white, 293 black, 425 Hispanic, 255 Asian) diagnosed between 1998 and 2008 and 31,031 individually matched controls (21,478 white, 2,836 black, 4,147 Hispanic, 2,484 Asian). Risk of renal cell carcinoma was assessed in relation to smoking status, body mass index (BMI), hypertension, and chronic kidney disease. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression, and population attributable risk (PAR) to estimate by race the proportion of cases attributable to hypertension and chronic kidney disease.

Results—The association between chronic kidney disease and renal cell carcinoma differed markedly by race ($P_{interaction}$<0.001), with associations observed among blacks (OR=10.4 [95% CI=6.0–17.9]), Asians (5.1 [2.2–11.7]), and Hispanics (2.3 [1.1–4.6]) but not whites (1.1 [0.6–1.9]). Hypertension, high BMI, and smoking were associated with renal cell carcinoma, but findings generally did not differ by race. Relative to other racial/ethnic groups, blacks had the highest proportion of renal cell carcinoma incidence attributable to hypertension and chronic

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kidney disease (combined, PAR=37%; hypertension only, PAR=27%; chronic kidney disease, PAR=10%).

Conclusions—Our findings suggest that hypertension and chronic kidney disease likely have contributed to the observed excess in renal cell carcinoma incidence among blacks compared with whites.

The incidence of renal cell carcinoma is higher among blacks than among whites in the United States, and rates have been increasing more rapidly among blacks in recent decades.[1] According to the NCI Surveillance and Epidemiology End Results (SEER) Cancer Statistics Review,[2] the age-adjusted incidence of kidney cancers (comprised mainly of renal cell carcinoma) for blacks and whites in the United States was, respectively, 18.0 and 15.5 cases per 100,000 persons in 2011, the last year for which rates were available. The reasons for these racial disparities in incidence are unclear, although hypertension and chronic kidney disease may play a role; both of these established risk factors for renal cell carcinoma are more prevalent among blacks than among whites.[3,4] Furthermore, findings from a recent population-based case-control study suggest that hypertension and renal failure may be more strongly associated with RCC among blacks compared with whites.[5,6] As such, these conditions might account for a substantial proportion of the excess risk of renal cell carcinoma among blacks relative to whites. However, issues involving small sample size and self-reporting of medical history limit the interpretation of these findings.

To further investigate differences in these associations between blacks and whites and to extend this work to other racial/ethnic groups, we conducted a large nested case-control study of renal cell carcinoma risk factors among members of Kaiser Permanente Northern California, an integrated health care delivery system that provides comprehensive care to a large and diverse population in the San Francisco Bay Area.

Methods

Study population

Approximately 3.3 million residents of the San Francisco Bay Area are members of Kaiser Permanente Northern California; membership is racially diverse and demographically representative of the regional population.[7] Kaiser Permanente Northern California utilizes an electronic medical record system that has captured inpatient and outpatient diagnoses for visits since 1995; detailed data on blood pressure measurements, height and weight have been routinely collected electronically since 2005. Cancers were identified using the Kaiser Permanente Cancer Registry, which links with the California Cancer Registry and the Surveillance Epidemiology and End Results (SEER) program; we identified patients with a histologically confirmed incident diagnosis of renal cell carcinoma (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] C64.9) between 1998 and 2008. We did not include transitional cell carcinomas (ICD-O-3 morphology codes 8070, 8071, 8120, 8124, and 8130) or cancers diagnosed among persons under 18 years of age (n=2) or over 99 years of age (n=1). Two cases without any matched controls were also excluded, leaving a total of 3,136 cases for analysis. Controls (n=31,031) were selected from among Kaiser Permanente Northern California members who were free of renal cell

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carcinoma as of the date of diagnosis of the corresponding case. Up to 10 controls were individually matched to each case based on age at cancer diagnosis (±1 year), sex, race/ethnicity (black, white, Hispanic, Asian/Pacific Islander), duration of Kaiser membership (±1 year) prior to the index date (for cases, renal cell carcinoma diagnosis date; for controls, diagnosis date of matched case), and medical center of diagnosis.

Study procedures were approved by the Institutional Review Board at Kaiser Permanente Northern California, which did not require informed consent from the subjects.

Characterization of medical history

History of hypertension (ICD-9 401–405) or chronic kidney disease (ICD-9 585) diagnosed between January 1996 and June 2006 was ascertained from Kaiser Permanente Northern California physician-assigned electronic coding associated with inpatient and outpatient visits. We defined subjects as having a history of hypertension or chronic kidney disease if the condition was diagnosed at least two years prior to the index date. History of diabetes (ICD-9 250) and smoking status (smoker, non-smoker), both of which were assessed at least two years prior to the index date, were also ascertained from electronic records.

Direct measurements of blood pressure levels, height, and weight, recorded during later years in the electronic medical record (February 2005 through June 2008), were extracted from selected cases and matched controls for whom these data were available at least 60 days prior to the index date (blood pressure: 563 cases, 3,735 controls; height and weight: 521 cases, 3,250 controls). These measurements were taken an average of 12 months (range 3–36 months) before renal cell carcinoma diagnosis. Subjects with systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg were classified as having high blood pressure; additional analyses were performed using standardized categories of blood pressure (normal: systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg; pre-hypertension: systolic pressure 120–139 mm Hg or diastolic pressure 80/89 mm Hg; stage 1 high blood pressure, systolic pressure 140–159 mm Hg or diastolic pressure 90–99 mm Hg; and stage 2 high blood pressure, systolic pressure ≥160 mm Hg or diastolic pressure ≥100 mm Hg).[8] Body mass index (BMI) was characterized as weight in kilograms divided by height in meters squared and categorized as follows: normal weight, <25 kg/m^2; overweight, 25–29.9 kg/m^2; obese, 30–34.9 kg/m^2; and severely obese, ≥35 kg/m^2.

Statistical analysis

We used conditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of renal cell carcinoma in relation to a history of smoking, hypertension, or chronic kidney disease, both overall and by race. In addition to conditioning on matched sets, regression models for hypertension and chronic kidney disease were adjusted for diabetes and smoking; the smoking model included diabetes and hypertension as covariates. To evaluate the separate effects of diagnosed hypertension and chronic kidney disease on risk of renal cell carcinoma, we created a combined variable for these conditions (neither hypertension or chronic kidney disease, hypertension only, or chronic kidney disease with or without hypertension); there were too few non-hypertensive subjects with chronic kidney disease (1 case, 7 controls) to evaluate renal cell carcinoma risk

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separately for this group. We also evaluated renal cell carcinoma risk in relation to hypertension and chronic kidney disease overall and among whites and blacks after stratifying by sex, age at renal cell carcinoma diagnosis (<65 years, ≥65 years), stage of renal cell carcinoma at diagnosis (localized, non-localized), and history of diabetes.

We performed additional analyses after restricting to cases and matched controls with measurements of blood pressure and height and weight. We assessed renal cell carcinoma risk in relation to high measured blood pressure and BMI as defined above. Analyses of hypertension and chronic kidney disease were repeated after further adjusting for BMI among the subset of cases and matched controls for whom information on height and weight was available. We also conducted sensitivity analyses restricted to non-smokers, clear cell renal cell carcinoma cases, cases diagnosed in later years (2004–2008), and among subjects who were members of Kaiser Permanente Northern California for eight or more years (approximately the mean duration of membership).

ORs and 95% CIs were computed using Stata version 11.0 (StataCorp, College Station, TX). Tests of multiplicative interaction were performed using unconditional models adjusted for matching factors, smoking, and diabetes; statistical significance was assessed globally using likelihood ratio tests, and Wald tests were used to assess the joint significance of specific cross-product terms in the models.

To estimate the portion of renal cell carcinoma incidence potentially attributable to hypertension and chronic kidney disease overall and within each racial/ethnic group in our study population, we calculated the population attributable risk percent (PAR%) for these conditions. Estimates of PAR% were generated using the Interactive Risk Attributable Program (National Cancer Institute, Bethesda, MD) and were based on the same conditional models and adjustment factors as in the main analyses. To evaluate the proportion of the excess incidence of renal cell carcinoma among blacks compared with whites that may be attributable to hypertension and chronic kidney disease, we estimated the incidence of renal cell carcinoma among blacks and whites in our study population using age- and sex-specific rates from the San Francisco-Oakland SEER registry during the study period (1998–2008). Incidence rates were estimated before and after accounting for the proportion of renal cell carcinoma attributable to hypertension and chronic kidney disease among blacks and whites, respectively.

Results

Demographic and other characteristics of cases and controls are reported in Table 1. Cases and controls had similar distributions of matching factors (age, sex, and race). Cases were more likely than controls to have a history of hypertension, chronic kidney disease, diabetes, and smoking; this pattern was generally consistent across all racial/ethnic groups (eTable). Among controls, the prevalence of diabetes was higher among non-whites compared with whites, and blacks had a higher prevalence of hypertension compared with other racial/ethnic groups.

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The overall and race-specific results for renal cell carcinoma risk in relation to diagnosed hypertension, smoking, and chronic kidney disease are reported in Table 2. For the subset of cases and matched controls with measured blood pressure and BMI, the risk estimates for renal cell carcinoma in relation to these measured characteristics are reported in Table 3. As expected, hypertension, high measured blood pressure, smoking, and high BMI were associated with increased renal cell carcinoma risk; these associations generally did not differ by race/ethnicity. We observed strong associations between long-term hypertension (≥5 years) and renal cell carcinoma risk for all racial/ethnic groups, and a monotonic trend of increasing renal cell carcinoma risk in relation to blood pressure categories overall and among whites and blacks.

Having a history of chronic kidney disease was associated with an almost three-fold increased risk of renal cell carcinoma (OR = 2.8 [95% CI = 2.1–3.7]). This association varied substantially across racial/ethnic groups ($P_{\text{interaction}} < 0.001$); it was strongest among blacks (10.4 [6.0–17.9]), somewhat weaker among Asian/Pacific Islanders (5.1 [2.2–11.7]) and Hispanics (2.3 [1.1–4.6]), and absent among whites (1.1 [0.6–1.9]). After further adjustment for measured blood pressure (using clinically defined categories) and time since hypertension diagnosis (no hypertension, <5 years, or ≥5 years prior to the index date), the association between chronic kidney disease and renal cell carcinoma risk was weaker and more imprecise among Hispanics (1.7 [0.6–5.3]), but risk estimates were similar or only modestly attenuated overall and in other racial/ethnic groups (overall, OR = 2.2 [95% CI = 1.4–3.7]; among blacks, 7.5 [2.1–27.3]; among Asian/Pacific Islanders, 5.9 [1.3–26.5]; and among whites, 1.2 [0.5–2.8]). In joint analyses of history of hypertension and chronic kidney disease, with subjects who did not have hypertension or chronic kidney disease as the referent group, those who had hypertension only had an increased risk of renal cell carcinoma (ORs ranging from 1.8 to 2.3 across racial/ethnic groups), and renal cell carcinoma risk was particularly high among non-white subjects who had been diagnosed with chronic kidney disease (ORs of 17.0, 7.4, 4.4, and 1.7 among black, Asian/PI, Hispanic, and white subjects, respectively; $P_{\text{interaction}} < 0.001$).

Associations with renal cell carcinoma for hypertension and chronic kidney disease were essentially unchanged after adjustment for BMI and after restricting to non-smokers, clear cell renal cell carcinoma cases, cases diagnosed after 2003, or subjects who were members of Kaiser Permanente Northern California for eight or more years (data not shown).

For black and white subjects, we repeated the joint analysis of hypertension and chronic kidney disease separately by sex, age at renal cell carcinoma diagnosis (or reference date), tumor stage, and history of diabetes (Table 4). The associations for having a history of hypertension only were generally similar across strata for both blacks and whites. For chronic kidney disease, however, the risk of renal cell carcinoma among blacks was considerably higher for those under age 65 at the index date compared with those who were 65 years or older (ORs of 36 and 8.0, respectively; $P_{\text{interaction}} = 0.04$), and among those without a history of diabetes compared with diabetic patients (ORs of 25 and 2.6, respectively; $P_{\text{interaction}} = 0.02$). The association with chronic kidney disease was also stronger for localized renal cell carcinoma cases compared with those who had regional or distant metastases (ORs of 20 and 14.1, respectively), although the *P* value for a test of OR

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heterogeneity was 0.2. Among black persons, risk of renal cell carcinoma in relation to chronic kidney disease was similar for men and women.

The estimated PARs for hypertension and chronic kidney disease, separately and in combination with one another, are reported overall and by race in Table 5. In our study population, relative to other racial/ethnic groups, blacks had the highest proportion of renal cell carcinoma incidence attributable to hypertension and chronic kidney disease (combined, PAR = 36.7%; hypertension only, PAR = 27.0%; chronic kidney diseasewith or without hypertension, PAR = 9.6%). Based on the age and sex distributions of our study population and renal cell carcinoma incidence rates for the study years (1998–2008) in the San Francisco-Oakland SEER registry, we estimated the incidence of renal cell carcinoma in our population to be 46.6 cases per 100,000 person-years among blacks and 37.2 cases per 100,000 person-years among whites. Assuming that the associations with renal cell carcinoma for hypertension and chronic kidney disease are causal, we estimated that in the absence of these conditions the incidence of renal cell carcinoma would be essentially equivalent for whites and blacks (29.2 and 29.5 cases per 100,000 person-years, respectively).

Discussion

Our findings from this large nested case-control study suggest that the relative risk of renal cell carcinoma for chronic kidney disease differs substantially by race, and is particularly high among black patients. Whereas the estimated proportion of renal cell carcinoma incidence attributable to chronic kidney disease within this population is negligible among whites, it may account for 10% of renal cell carcinoma incidence among blacks. Furthermore, our data suggest that over one-third of the renal cell carcinoma incidence among blacks may be attributable to hypertension and chronic kidney disease, but these conditions account only for one-fifth of renal cell carcinoma among whites. If the observed associations in our study are causal, it is possible that hypertension and chronic kidney disease may account for the entirety of the black-white disparity in renal cell carcinoma incidence in this population.

Previous studies have consistently reported an increased risk of renal cell carcinoma in relation to renal failure.[9–14] However, few studies have investigated whether this association differs by race. In a large, population-based case-control study of blacks and whites in Detroit and Chicago, renal failure was strongly associated with renal cell carcinoma among blacks but not whites.[6] This study was limited by its retrospective assessment of medical history and reliance on self-reported information about past diagnoses. Our confirmation of that finding in the present study, which assessed medical history through electronically linked medical records rather than personal interviews, provides strong evidence that the association between kidney dysfunction and renal cell carcinoma may differ by race. Our findings of differences by race in the association between chronic kidney disease and renal cell carcinoma were also consistent with recent findings among patients in the Transplant Cancer Match Study, in which standardized incidence ratios for kidney cancer risk among kidney transplant candidates and recipients were higher among blacks and Hispanics relative to whites.[10]

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Interestingly, the association between chronic kidney disease and renal cell carcinoma among blacks appears to be specific to those without a history of diabetes, which was also observed in the previous case-control study.[6] This pattern of findings is consistent with a possible role of *APOL1* genetic variation in renal cell carcinoma pathogenesis. Two *APOL1* variants, common among populations of African ancestry and virtually absent among European-ancestry populations, have been shown to profoundly affect the risk of hypertension-associated kidney disease, with odds ratios of 7–10 reported.[15] It is not known whether the *APOL1* risk variants affect risk of renal cell carcinoma in blacks. ApoL1 expression has recently been reported to be downregulated in renal cell carcinoma cell lines and tissue, leading to speculation that ApoL1 may be an important signaling protein that is eliminated by renal cell carcinoma cells for their survival advantage.[16] Alternatively, the *APOL1* variants may affect renal cell carcinoma risk indirectly by causing non-malignant kidney disease, effects of which may contribute to renal carcinogenesis.

Few studies have investigated risk factors for renal cell carcinoma in Asian or Hispanic populations, and none, to our knowledge, have been conducted among Asian-Americans or Hispanic-Americans. In a hospital-based case-control study of subjects of Han Chinese ancestry conducted in Shanghai, China, Wang et al.[17] reported a 2.5-fold increased risk of clear cell renal cell carcinoma in relation to history of hypertension. A prospective study of measured blood pressure and kidney cancer mortality among Korean men found an adjusted relative risk of 2.4 comparing those with and without high blood pressure.[18] Given the paucity of published data available on risk factors for renal cell carcinoma among U.S. Asians and Hispanics, confirmation of our findings for these racial/ethnic groups and further investigation of potential underlying biological mechanisms is needed.

Our investigation had several notable strengths. It is, to our knowledge, the largest study to investigate differences by race/ethnicity in the etiology of renal cell carcinoma, and the first to assess risk factors among Hispanic- and Asian-Americans. Other strengths include the population-based design and use of prospectively collected data on risk factors obtained from medical records (rather than patient interviews), which limits potential recall or reporting biases.

Several limitations of this study should be considered. It is possible that the observed associations with chronic kidney disease may be spuriously high as a result of increased incidental detection of subclinical tumors during examinations to investigate the possible underlying causes of chronic kidney disease (such as hydronephrosis, stones, or renovascular hypertension). The fact that all subjects were enrolled in the same integrated health system may have helped to minimize the potential impact of detection bias on race-specific associations between chronic kidney disease and risk of renal cell carcinoma. Furthermore, as patients with advanced renal cell carcinoma are less likely to have tumors detected incidentally, we performed analyses among cases with non-localized disease to reduce the potential for detection bias. We found that the magnitude of the association with chronic kidney disease was similar among blacks in this analysis; however, because of the small number of non-localized cases with a history of chronic kidney disease (n=12), these findings should be interpreted cautiously. The lack of access to pathological samples for centralized review was also a limitation of our study, as we were unable to characterize the

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aggressiveness of renal cell carcinoma tumors using well-established prognostic scoring systems that incorporate detailed clinicopathologic variables.

We were unable to assess medical history prior to January 1996 or entry into the KPNC health system. As such, there may have been some misclassification of history of hypertension, chronic kidney disease, and other exposures of interest in this investigation. However, medical history was assessed in the same manner regardless of case-control status, and cases and controls were matched on duration of Kaiser Permanente Northern California membership. We observed similar results after restricting to cases (and matched controls) diagnosed between 2004 and 2008 and among subjects who were Kaiser Permanente Northern California members for 8 or more years. Given that we would expect ascertainment of medical history to be relatively complete in these groups, this consistency with our main findings suggests that the impact of any misclassification of medical history is likely to be minimal.

Information on the severity of chronic kidney disease was unavailable, and therefore we relied on a binary classification of disease. It is possible that differences in the severity of chronic kidney disease by race might explain in part the stronger association with renal cell carcinoma among blacks compared with whites; future studies are needed to assess whether the race-specific associations differ by stage of chronic kidney disease. We also lacked information on antihypertensive medication use or other indicators of hypertension control; as such, it is possible that differences in hypertension control across racial/ethnic groups could contribute to the racial differences in the observed associations between chronic kidney disease and risk of renal cell carcinoma. Among the controls with measured blood pressure, the proportion with stage 2 high blood pressure was highest among blacks (13.7% compared with 7.0–7.6% for other racial/ethnic groups). However, we note that our findings for the overall and race-specific associations between chronic kidney disease and renal cell carcinoma risk were mostly unchanged after adjusting for measured blood pressure and time since hypertension diagnosis, which suggests that the observed associations are not driven solely by poorly controlled hypertension.

Because chronic kidney disease is a relatively rare condition, we had limited statistical power for some race-specific analyses. For example, we did not have a sufficient number of renal cell carcinoma cases with chronic kidney disease to perform stratified analyses among Hispanics ($n_{\text{exposed cases}}=11$) or Asian/Pacific Islanders ($n_{\text{exposed cases}}=9$). BMI data were available for only a limited number of subjects, and data on smoking history were limited. Consistent with previous reports (reviewed in Chow et al.[1]), both high BMI and smoking were associated with renal cell carcinoma in our investigation. However, given the lack of more detailed information on smoking duration or intensity, our findings for the overall and race-specific associations between smoking and renal cell carcinoma risk should be interpreted cautiously. Neither adjustment for BMI and smoking nor restriction to non-smokers materially affected our key findings, suggesting that these factors were unlikely to be important confounders in our analyses of renal cell carcinoma risk in relation to hypertension or chronic kidney disease. Although alcohol consumption has been consistently associated with a reduced risk of RCC,[19,20] we did not have information on

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alcohol intake in this investigation and were thus unable to control for confounding or assess differences by race/ethnicity in the magnitude of its association with renal cell carcinoma.

In conclusion, the findings of this study provide strong evidence of differences by race for renal cell carcinoma risk in relation to history of chronic kidney disease. We also found that hypertension and chronic kidney disease account for a large proportion of renal cell carcinoma incidence among blacks, and are likely to be important contributors to the higher renal cell carcinoma incidence rates among blacks compared with whites. Additional studies are needed to evaluate possible factors that underlie the strong association between chronic kidney disease and risk of renal cell carcinoma among blacks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of renal cell carcinoma cases and matched controls[a]

Characteristic	Cases (n=3136) No. (%)	Controls (n=31031) No. (%)
Age at index date (years)		
18–54	742 (24)	7401 (24)
55–64	860 (27)	8537 (28)
65–74	864 (28)	8577 (38)
75–99	670 (21)	6516 (21)
Sex		
Female	1132 (36)	11225 (36)
Male	2004 (63)	19806 (64)
Race/ethnicity		
White, non-Hispanic	2152 (69)	21478 (69)
Black, non-Hispanic	293 (9)	2836 (9)
Hispanic	425 (14)	4147 (13)
Asian/Pacific Islander	255 (8)	2484 (8)
Other/missing	11	86
History of hypertension		
No	1530 (49)	19003 (61)
Yes	1606 (51)	12028 (39)
History of chronic kidney disease		
No	3070 (98)	30821 (99)
Yes	66 (2)	210 (1)
History of diabetes		
No	2583 (82)	26899 (87)
Yes	553 (18)	4132 (13)
History of smoking		
No	2393 (76)	24818 (80)
Yes	743 (24)	6213 (20)
Measured blood pressure[b, c]		
Normal or pre-hypertension	376 (67)	2748 (74)
High blood pressure	187 (33)	987 (26)
Body mass index (kg/m^2)[c]		
<25	101 (19)	797 (25)
25–29.9	185 (36)	1263 (39)
30–34.9	125 (24)	768 (24)
35+	110 (21)	422 (13)
Renal cell carcinoma histologic subtype		
Clear cell	2642 (84)	
Papillary	165 (5)	
Chromophobe	95 (3)	
Other	234 (8)	

[a] Missing values were excluded from percentages.

[b] High measured blood pressure was defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg.[8]

[c] These data were available in the electronic medical record only for the years 2005–2008.

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Table 2

Risk of renal cell carcinoma in relation to diagnosed hypertension, chronic kidney disease, and smoking status, overall and by race, 1998–2008[a]

	Overall		White		Black		Hispanic		Asian/Pacific Islander		
	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	P_{int}[b]
Hypertension											
No[c]	1530/19003	1.0	1075/13297	1.0	103/1400	1.0	214/2693	1.0	134/1572	1.0	
Yes	1606/12028	1.9 (1.7–2.0)	1077/8181	1.8 (1.6–2.0)	190/1436	2.3 (1.7–3.1)	211/1454	2.3 (1.8–2.9)	121/912	1.8 (1.3–2.5)	0.6
						P_{int} = 0.4[d]		P_{int} = 0.3[d]		P_{int} = 0.8[d]	
Time from hypertension diagnosis to index date											
No hypertension[c]	1530/19003	1.0	1075/13297	1.0	103/1400	1.0	214/2693	1.0	134/1572	1.0	
<5y since hypertension diagnosis	657/5316	1.6 (1.5–1.8)	458/3779	1.6 (1.4–1.8)	50/487	1.5 (1.1–2.3)	92/630	2.2 (1.6–2.9)	54/401	1.7 (1.2–2.5)	
≥5y since hypertension diagnosis	949/6712	2.2 (1.9–2.4)	619/4402	2.0 (1.8–2.3)	140/949	3.2 (2.2–4.5)	119/824	2.5 (1.8–3.4)	67/511	1.9 (1.3–2.8)	0.6
						P_{int} = 0.4[d]		P_{int} = 0.4[d]		P_{int} = 0.7[d]	
Chronic kidney disease											
No[c]	3070/30821	1.0	2137/21360	1.0	263/2803	1.0	414/4107	1.0	246/2466	1.0	
Yes	66/210	2.8 (2.1–3.7)	15/118	1.1 (0.6–1.9)	30/33	10.4 (6.0–17.9)	11/40	2.3 (1.1–4.6)	9/18	5.1 (2.2–11.7)	<0.001
						P_{int} < 0.001[d]		P_{int} = 0.1[d]		P_{int} = 0.007[d]	
Hypertension and chronic kidney disease combined											
Neither[c]	1529/18996	1.0	1075/13291	1.0	103/1400	1.0	214/2693	1.0	133/1571	1.0	
Hypertension only	1541/11825	1.8 (1.7–2.0)	1062/8069	1.8 (1.6–2.0)	160/1403	2.0 (1.5–2.7)	200/1414	2.3 (1.8–2.9)	113/895	1.8 (1.3–2.4)	
Chronic kidney disease[e]	66/210	4.4 (3.2–5.8)	15/118	1.7 (1.0–2.9)	30/33	17.0 (9.4–30.9)	11/40	4.4 (2.1–9.2)	9/18	7.4 (3.1–17.5)	<0.001
						P_{int} < 0.001[d]		P_{int} = 0.2[d]		P_{int} = 0.03[d]	
Smoking status											
Non-smoker[c]	2393/24818	1.0	1622/16995	1.0	212/2182	1.0	339/3419	1.0	217/2157	1.0	
Smoker	743/6213	1.2 (1.1–1.3)	530/4483	1.2 (1.1–1.3)	81/654	1.3 (0.9–1.7)	86/728	1.1 (0.9–1.5)	38/327	1.1 (0.8–1.7)	>0.9
						P_{int} = 0.8[d]		P_{int} = 0.8[d]		P_{int} = 0.7[d]	

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[a] Odds ratios and 95% confidence intervals were estimated using conditional logistic regression models. Analyses of hypertension and chronic kidney disease were adjusted for smoking and diabetes. Analyses of smoking were adjusted for diabetes and hypertension.

[b] *P*-value for an overall test of interaction by race.

[c] Reference category.

[d] *P*-value for a test of interaction compared with whites.

[e] With or without a history of hypertension.

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Table 3

Risk of renal cell carcinoma in relation to measured blood pressure and body mass index, overall and by race, 2005–2008[a]

	Overall		White		Black		Hispanic		Asian/Pacific Islander		
	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	No. Cases/No. Controls	OR (95% CI)	P_{int}[b]
Measured blood pressure[c]											
Normal or pre-hypertension[d]	376/2748	1.0	261/1867	1.0	26/203	1.0	48/421	1.0	37/239	1.0	
High blood pressure	187/987	1.4 (1.1–1.7)	117/676	1.2 (1.0–1.5)	22/106	1.9 (1.0–3.6)	36/131	2.3 (1.4–3.7)	11/67	1.1 (0.5–2.4)	0.08
						P_{int} = 0.4[e]		P_{int} = 0.02[e]		P_{int} = 0.7[e]	
Measured blood pressure (categorical)[f]											
Normal[d]	107/853	1.0	69/586	1.0	7/51	1.0	19/141	1.0	12/67	1.0	
Pre-hypertension	269/1895	1.1 (0.8–1.4)	192/1281	1.2 (0.9–1.6)	19/152	0.8 (0.3–2.2)	29/280	0.7 (0.4–1.3)	25/172	0.8 (0.4–1.7)	
High blood pressure, stage 1	131/693	1.4 (1.1–1.9)	82/485	1.3 (0.9–1.9)	12/62	1.5 (0.5–4.4)	31/93	2.1 (1.1–4.2)	5/47	0.6 (0.2–2.0)	
High blood pressure, stage 2	56/294	1.5 (1.0–2.1)	35/191	1.5 (1.0–2.4)	10/44	1.7 (0.6–5.1)	5/38	0.8 (0.2–2.5)	6/20	1.6 (0.5–5.0)	0.07
						P_{int} = 0.8[e]		P_{int} = 0.01[e]		P_{int} = 0.4[e]	
Body mass index (kg/m^2)											
<25[d]	101/797	1.0	67/552	1.0	4/37	1.0	12/79	1.0	16/121	1.0	
25–29.9	185/1263	1.1 (0.8–1.4)	127/883	1.1 (0.8–1.5)	16/85	1.7 (0.5–5.8)	24/193	0.8 (0.4–1.8)	16/92	1.4 (0.6–3.2)	
30–34.9	125/768	1.2 (0.9–1.6)	88/518	1.2 (0.9–1.8)	10/78	1.4 (0.4–5.2)	21/135	1.0 (0.5–2.3)	6/35	1.8 (0.6–5.4)	
35+	110/422	1.7 (1.2–2.3)	69/269	1.6 (1.1–2.4)	13/56	2.0 (0.6–7.5)	21/78	1.5 (0.7–3.6)	6/14	4.2 (1.1–15.9)	>0.9
						P_{int} = 0.8[e]		P_{int} = 0.9[e]		P_{int} = 0.9[e]	

[a] Odds ratios and 95% confidence intervals were estimated using conditional logistic regression models. Analyses of measured blood pressure were adjusted for smoking and diabetes, and analyses of body mass index were adjusted for hypertension, smoking, and diabetes.

[b] *P*-value for an overall test of interaction by race.

[c] High measured blood pressure was defined as systolic pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg (8).

[d] Reference category.

[e] *P*-value for a test of interaction compared with whites.

[f] Measured blood pressure was defined as follows: normal, systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg; pre-hypertension, systolic pressure 120–139 mm Hg or diastolic pressure 80/89 mm Hg; stage 1 high blood pressure, systolic pressure 140–159 mm Hg or diastolic pressure 90–99 mm Hg; stage 2 high blood pressure, systolic pressure ≥160 mm Hg or diastolic pressure ≥100 mm Hg (8).

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Table 4

Stratified analyses of renal cell carcinoma risk in relation to hypertension and chronic kidney disease, overall and among whites and blacks, 1998–2008[a]

	Overall		White		Black	
	No. Cases	OR (95% CI)	No. Cases	OR (95% CI)	No. Cases	OR (95% CI)
Stratified by sex						
Male						
Neither[b]	1001	1.0	721	1.0	59	1.0
Hypertension only	956	1.7 (1.6–1.9)	658	1.6 (1.4–1.9)	87	1.8 (1.2–2.7)
Chronic kidney disease	47	4.0 (2.8–5.6)	13	2.0 (1.1–3.6)	20	16.8 (8.1–35)
Female						
Neither[b]	528	1.0	354	1.0	44	1.0
Hypertension only	585	2.0 (1.8–2.4)	404	2.0 (1.7–2.4)	73	2.2 (1.4–3.7)
Chronic kidney disease	19	5.6 (3.2–9.8)	2	0.9 (0.2–3.7)	10	17.2 (6.2–48)
Stratified by age at renal cell carcinoma diagnosis						
<=64 years						
Neither[b]	966	1.0	624	1.0	74	1.0
Hypertension only	600	2.1 (1.8–2.3)	367	2.0 (1.7–2.3)	76	2.2 (1.5–3.2)
Chronic kidney disease	36	10.1 (6.4–15.9)	6	3.2 (1.3–8.1)	18	36 (13.9–92)
65+ years						
Neither[b]	563	1.0	451	1.0	29	1.0
Hypertension only	941	1.6 (1.4–1.8)	695	1.6 (1.4–1.8)	84	1.6 (1.0–2.6)
Chronic kidney disease	30	2.4 (1.6–3.6)	9	1.2 (0.6–2.5)	12	8.0 (3.4–19.0)
Stratified by renal cell carcinoma stage at diagnosis						
Localized						
Neither[b]	970	1.0	658	1.0	73	1.0
Hypertension only	944	1.9 (1.7–2.1)	639	1.8 (1.6–2.1)	105	1.9 (1.3–2.7)
Chronic kidney disease	54	5.8 (4.2–8.2)	13	2.5 (1.4–4.6)	26	20 (10.3–40)
Non-localized						
Neither[b]	538	1.0	404	1.0	28	1.0

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	Overall		White		Black	
	No. Cases	**OR (95% CI)**	**No. Cases**	**OR (95% CI)**	**No. Cases**	**OR (95% CI)**
Hypertension only	568	1.8 (1.5–2.0)	403	1.7 (1.4–2.0)	52	2.4 (1.3–4.3)
Chronic kidney disease	12	2.2 (1.2–4.2)	2	0.6 (0.1–2.5)	4	14.1 (3.5–57)
Stratified by history of diabetes						
No history of diabetes						
Neither[b]	1444	1.0	1022	1.0	93	1.0
Hypertension only	1100	1.8 (1.6–1.9)	779	1.7 (1.5–1.9)	121	1.9 (1.4–2.7)
Chronic kidney disease	39	5.1 (3.5–7.6)	8	1.5 (0.7–3.2)	21	25 (10.5–58)
History of diabetes						
Neither[b]	85	1.0	53	1.0	10	1.0
Hypertension only	441	1.4 (1.0–1.9)	283	1.4 (0.9–2.3)	39	1.0 (0.4–2.4)
Chronic kidney disease	27	2.4 (1.2–4.8)	7	1.9 (0.4–8.5)	9	2.6 (0.6–12.2)

[a] Odds ratios and 95% confidence intervals were estimated using conditional logistic regression models adjusted for smoking and diabetes (except for analyses stratified by history of diabetes, which were only adjusted for smoking).

[b] Neither hypertension nor chronic kidney disease. Reference category.

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Table 5

Population attributable risk percent (PAR%) of renal cell carcinoma for hypertension and chronic kidney disease, overall and by race

	PAR % (95% CI)[a]				
	Overall	**White**	**Black**	**Hispanic**	**Asian/Pacific Islander**
Hypertension and chronic kidney disease combined	24.0 (21.0–27.2)	21.6 (18.0–25.6)	36.7 (26.2–48.5)	28.3 (21.4–36.4)	22.1 (13.4–34.1)
Hypertension only	22.4 (19.5–25.6)	21.3 (17.8–25.3)	27.0 (17.6–39.2)	26.3 (19.6–34.3)	19.0 (10.9–31.1)
Chronic kidney disease[b]	1.6 (1.2–2.2)	0.3 (0.1–1.0)	9.6 (6.7–13.8)	2.0 (0.9–4.3)	3.1 (1.4–6.4)

[a] The reported 95% confidence intervals are based on logit transformation.

[b] With or without a history of hypertension.