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Obesity and renal cell carcinoma risk by histologic subtype: a nested case-control study and meta-analysis

Catherine L. Callahan^a, Jonathan N. Hofmann^a, Douglas A. Corley^b, Wei K. Zhao^b, Brian Shuch^c, Wong-Ho Chow^d, and Mark P. Purdue^{a,*}

^aDivision of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

^bDivision of Research, Kaiser Permanente Northern California, Oakland, California, United States of America

^cDepartment of Urology, Yale School of Medicine, New Haven, Connecticut, United States of America

^dDepartment of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Abstract

Background: Although obesity is an established risk factor for renal cell carcinoma (RCC), it is unclear whether this relationship varies across histologic subtypes.

Methods: We conducted a nested case-control study within the Kaiser Permanente Northern California (KPNC) health care network, and meta-analysis combining our results with those of previously published studies. Our KPNC study included 685 RCC cases [421 clear cell; 65 papillary; 24 chromophobe; 35 other; 141 not otherwise specified (NOS)] and 4,266 controls. Subtype-specific odds ratios (ORs) and 95% confidence intervals (CIs) for categories of body mass index (BMI) and were computed from the case-control data using polytomous logistic regression. Findings from this and other relevant studies were combined by meta-analysis using a random effects model.

Results: In the KPNC study, obesity (BMI $\geq 30\text{kg/m}^2$) was associated with clear cell RCC (OR 1.5, 95% CI 1.1–2.1) and chromophobe RCC (OR 2.5, 95% CI 0.8–8.1), but not with papillary RCC (OR 1.0, 95% CI 0.5–1.9). In meta-analysis including two additional studies, a similar pattern of summary relative risks (SRR) for obesity was observed across subtypes (clear cell: SRR 1.8, 95% CI 1.4–2.2; chromophobe: SRR 2.2, 95% CI 1.3–3.8; papillary, SRR 1.1, 95% CI 0.6–1.8).

Conclusions: These findings support the hypothesis that histologic subtypes of RCC possess distinct etiologic pathways, with obesity important for the development of clear cell and, possibly, chromophobe RCC, but not papillary RCC.

*Corresponding author: purduem@mail.nih.gov, 9609 Medical Center Drive, Rockville, MD 20850.

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Keywords

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1. Introduction

Kidney cancer is estimated to account for over 60,000 new cancer diagnoses and over 14,000 deaths annually in the United States [1]. Over 90% of kidney cancers represent renal cell carcinoma (RCC) [2], the incidence of which has been increasing over the past several decades. While rising incidental detection of RCC through abdominal imaging is a likely contributor to this trend, increases in the prevalence of established risk factors such as obesity and hypertension may also play a role. Other established risk factors for RCC include male sex, African American and American Indian race, a family history of kidney cancer, and tobacco smoking (reviewed by: [2]).

RCC includes several histologic subtypes with varying genetic characteristics and prognosis [3, 4]. The most commonly diagnosed subtypes are clear cell (70–75% of all cases), papillary (10–15%) and chromophobe (5%) RCC [5]. In an analysis of RCC cases in the U.S. Surveillance, Epidemiology and End Results (SEER) program, both papillary and chromophobe RCC had better cancer-specific survival than clear cell RCC (hazard ratios 0.7 and 0.4 vs. clear cell respectively) [6]. As RCC histologic subtypes have been reported to differ in frequency by age, sex and race [7–12], it has been speculated that RCC subtypes may possess distinct etiologies. A growing body of evidence suggests that the association between obesity and risk of RCC may also be subtype-specific. Specifically, in some studies [13–18] but not others [15, 19] the association between obesity and risk of RCC was limited to clear cell and chromophobe histology. Most of these investigations have had limited power to detect statistically significant differences in obesity associations across subtypes owing to small sample sizes. To clarify whether the relationship between overweight or obesity and RCC risk differs by subtype, we analyzed data from a large case-control study nested within the Kaiser Permanente Northern California (KPNC) integrative healthcare system, and conducted a meta-analysis of findings from the published literature.

2. Methods

2.1 Kaiser Permanente Northern California nested case-control study of RCC

Our study methods have been described in detail elsewhere [20]. Briefly, we identified 3,136 patients with a histologically confirmed incident diagnosis of RCC using the Kaiser Permanente Cancer Registry. Controls (n=31,031) were selected from KPNC members who were free of RCC on the date of diagnosis of the corresponding case. Up to ten controls were individually matched to each case on age at cancer diagnosis (± 1 year), sex, race/ethnicity (black, white, Hispanic, Asian/Pacific Islander), duration of prior KPNC membership (± 1 year), and medical center of diagnosis. Six cases and 29 controls were excluded because they did not have information on race. KPNC began systematically recording height and weight measured by health professionals at medical visits in patients'

electronic medical records in 2005. There were 2,445 cases and 26,736 controls who did not have information on measured height and weight and were excluded.

The three most common subtypes of RCC were classified in accordance with the World Health Organization 2016 tumor classification [4]; these include clear cell [International Classification of Diseases for Oncology Third Edition (ICD-O-3) histology code 8310, n = 421], papillary (ICD-O-3 histology code 8260, n = 65), and chromophobe (ICD-O-3 histology codes 8317 and 8270, n = 24). Other, rarer, subtypes (n = 35; listed in Supplemental Table 1) could not be individually analyzed due to sparse data, and were grouped together. RCC tumors of not otherwise specified histology (NOS, ICD-O-3 histology code 8312, n = 141) were categorized separately.

Demographic information and medical history were obtained from subjects' electronic medical records. Subjects were classified as having a history of hypertension, diabetes, smoking, or chronic kidney disease if the condition was diagnosed at least two years prior to the index date, using ICD-9 codes associated with outpatient and inpatient medical visits. Height and weight measurements were taken an average of 12 months (range 3–36 months) before RCC diagnosis. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared and categorized as: normal weight, $<25 \text{ kg/m}^2$; overweight, $25\text{--}29.9 \text{ kg/m}^2$; or obese, $\geq 30 \text{ kg/m}^2$. Study procedures were approved by the Institutional Review Board at KPNC, which did not require informed consent from the subjects given the low likelihood of patient harm from data disclosure and the high likelihood that requiring individual-level consent would introduce bias into the analyses.

2.2 Meta-analysis of BMI and RCC subtypes

We searched PubMed MEDLINE (<http://www.ncbi.nlm.nih.gov/sites/entrez>) using the search terms “kidney cancer subtype body mass index” and “renal cancer subtype obesity”, and reviewed the references and citing articles in the identified reports for additional studies. All studies that were published in English before 06/1/2017 that reported frequencies of histologic subtypes by World Health Organization categories of BMI were included. We identified nine potentially eligible studies [13–19, 21, 22]. Of these, two were excluded because they did not report frequencies of subtypes by BMI or relative risk estimates [19, 21]; an additional study was excluded because the categorizations of BMI were not explained in enough detail [22]; and two studies were excluded because they were case-series that only reported frequencies of clear cell RCC [16, 17]. One study reported results only for clear cell RCC and was thus only included in clear cell-specific analyses [14]. The remaining four studies reported results for clear cell, chromophobe, and papillary RCC; two of these studies were case-series [15, 18] and two were case-control studies [13]. A PRISMA flowchart of study selection is presented in Supplemental Figure 1. We conducted a meta-analysis of BMI and subtype specific case-control odds ratios (ORs) for the two prior case-control studies and our KPNC study. We also calculated case-only meta-analyses using the four prior studies and KPNC [23]. One study reported those with a BMI greater than 30 kg/m^2 vs. those with a BMI less than 30 kg/m^2 [18] and was only included in the obesity meta-analysis. Lowrance et al. did not report the ORs of interest for either the papillary or chromophobe case-only meta-analysis [18] and Lipworth et al. did not report the ORs of

interest for the chromophobe meta-analysis [15]. In these instances, we calculated unadjusted ORs and corresponding confidence intervals from the frequencies provided. The methods and results of the meta-analysis are reported following the PRISMA guidelines (Supplemental Figure 2) [24].

2.3 Statistical analysis

Within the KPNC analytic dataset (685 cases and 4,266 controls) we conducted analyses across five case subgroups: clear cell, papillary, chromophobe, other, and NOS RCC. Case-control analyses using polytomous logistic regression models were performed to estimate subtype-specific ORs and 95% CIs in relation to BMI and histories of smoking, hypertension, diabetes, and chronic kidney disease, with adjustment for the matching factors. We performed case-only analyses (involving pair-wise comparisons of papillary, chromophobe, other, or NOS RCC vs. clear cell RCC) to compare subtype distributions in relation to age, race and sex using unconditional logistic regression modeling adjusted for these and other matching factors. Case-only analyses of smoking, hypertension, diabetes, and chronic kidney disease were also conducted to test for heterogeneity in the ORs of individual histologic subgroups vs. clear cell RCC. We also conducted case-only analyses using polytomous logistic regression models to assess the association between BMI and tumor stage adjusting for covariates.

To assess potential bias from incidental diagnoses from abdominal imaging, case-control analyses were repeated restricted to cases diagnosed at stage II or greater. We repeated case-only analyses of papillary vs. clear cell RCC stratifying on sex and race (white and black only) to assess potential effect modification by these covariates. Tests for interaction on the multiplicative scale were assessed via the inclusion of an interaction term in the fully adjusted models. We also performed analyses of BMI and smoking restricted to individuals without a diagnosis of hypertension, diabetes, or chronic kidney disease. All of the aforementioned analyses were conducted using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

For the meta-analysis, we used random effects models to calculate summary relative risk (SRR) estimates of case-only and case-control analyses comparing odds of having clear cell RCC vs. papillary RCC and chromophobe RCC vs. papillary RCC across categories of BMI (25–29.9 and 30 kg/m² vs. <25 kg/m²) using the metafor package in R 3.0.1 [25]. We used the Higgin's I² statistic to evaluate heterogeneity across studies [26].

3. Results

3.1 KPNC nested case-control study of RCC

Descriptive characteristics of KPNC subjects are presented in Table 1. Cases and controls were similar with regards to matching factors (age, race, and sex). Compared to controls, cases were more likely to have a history of smoking, hypertension and chronic kidney disease. The subset of subjects who had medical records after 2005 and thus had measured height and weight available were more likely to have a history of smoking, hypertension,

and chronic kidney disease, however these differences were consistent across case/control status.

Findings from case-control analyses of risk factors across RCC subtypes in the KPNC dataset are summarized in Table 2. Obesity was associated with clear cell RCC (BMI ≥30 vs. <25: OR 1.5, 95% CI 1.1–2.1) and, though not at a level of statistical significance, chromophobe RCC (OR 2.5, 95% CI 0.8–8.1), while no evidence of an association with papillary RCC was observed (OR 1.0, 95% CI 0.5–1.9). We did not observe significant differences across RCC subtypes for associations with smoking, hypertension, or chronic kidney disease. Results of analyses restricted to cases diagnosed at stage II or greater are presented in Supplemental Table 2. The association between obesity and clear cell RCC persisted when cases were restricted to stage II or greater (OR 1.7, 95% CI 0.9–3.0), although no longer at a level of statistical significance, obesity was not associated with papillary RCC (OR 0.9, 95% CI 0.3–2.7) or chromophobe RCC (OR 1.3, 95% CI 0.7–2.5).

In case-only analyses of the KPNC dataset, the age, sex, and racial patterns of RCC cases were observed to vary by histologic subtype (Table 3). Compared to clear cell RCC, papillary RCC cases were less likely to be female (OR 0.4, 95% CI 0.2–0.8). Among racial groups, papillary cases were more likely than clear cell cases to be black (OR 8.4, 95% CI 3.7–19.4) and less likely to be Hispanic (OR 0.3, 95% CI 0.1–1.0) relative to non-Hispanic whites. The proportion of papillary RCC cases with BMI ≥30 was non-significantly smaller than that of clear cell RCC (BMI ≥30 vs. <25: OR 0.7, 95% CI 0.3–1.6). We did not observe any evidence of effect modification across strata of sex (Supplemental Table 3) or race (Supplemental Table 4). Findings from analyses of smoking and BMI restricted to subjects without a history of chronic kidney disease, hypertension, or diabetes were similar (Supplemental Table 5). BMI was not associated with tumor stage (results not shown).

3.2 Meta-analysis of BMI and RCC subtypes

Details of the studies included in the meta-analysis are presented in Supplemental Table 6. Findings from the meta-analysis combining our KPNC case-control results for BMI with those from the two prior case-control studies are presented in Figure 1. Compared to BMI <25 kg/m², overweight and obesity were associated with increased risks of clear cell (SRR overweight 1.3, 95% CI 1.1–1.5; SRR obesity 1.8, 95% CI 1.5–2.2) and chromophobe RCC (SRR overweight 1.9, 95% CI 1.1–3.4; SRR obesity 2.2, 95% CI 1.3–3.8), but not papillary RCC (SRR overweight 0.9, 95% CI 0.7–1.3; SRR obesity 1.1, 95% CI 0.8–1.6) or other/NOS subtypes (SRR overweight 0.9, 95% CI 0.6–1.4; SRR obesity 1.1, 95% CI 0.6–1.8).

We conducted a meta-analysis to combine our KPNC case-only findings (clear cell vs. papillary RCC and chromophobe vs. papillary RCC) for overweight and obesity with those reported from four previous studies [13, 15, 18]. As shown in Figure 2, statistically significant summary case-only clear cell vs. papillary RCC associations were observed for overweight (SRR 1.3, 95% CI 1.0–1.7, *p* = 0.02) and obesity (SRR 1.5, 95% CI 1.3–1.9, *p* < 0.001), suggesting that the case-control association with high BMI is significantly stronger for clear cell RCC than for papillary cases. Excluding the study that required calculated crude ORs for the obesity analyses did not materially change the results (SRR 1.5, 95% CI 1.2–2.0). The case-only association between high BMI and RCC did not

significantly differ between chromophobe and papillary RCC (SRR overweight 1.2, 95% CI 0.5–2.9; SRR obese 1.2, 95% CI 0.8–1.6). When we considered only the three studies for which adjusted measures were available, the summary estimates were statistically non-significant but suggested the case-control association was non-significantly stronger for chromophobe RCC than papillary (SRR overweight 2.0, 95% CI 1.0, 4.3; SRR obese 1.8, 95% CI 0.8–3.9). There was no evidence of heterogeneity in effect measures between studies ($I^2 = 0\%$ for each analysis).

4. Discussion

Our findings from this investigation of 685 RCC cases and 4,266 controls in the KPNC integrative health care network and the meta-analysis of previous studies provide the strongest evidence to date that excess weight is associated more strongly with elevated risk of clear cell RCC than papillary RCC. Furthermore, we observed distinct age, racial, and sex distributions across RCC subtypes in KPNC that were consistent with previous findings.

Compared to clear cell RCC cases within the KPNC study, papillary cases were more likely to be male and African American and less likely to be Hispanic. These findings are consistent with previous studies, including an analysis of 84,255 cases from the SEER Program [5], although that study only evaluated cases and could not look at underlying risks compared to the general population. The reasons for these differences by subtype are currently unknown. Genetic evidence suggests that these subtypes are distinct disease entities, perhaps arising from different cells of origin in the nephron [27], and may develop through dysregulation of different biologic pathways, as evidenced by their heterogeneity in somatic mutations [27]. It is possible that sex- and race-related variation in genetic, hormonal and other biologic characteristics could differentially modulate the risk of development of RCC subtypes.

There is abundant epidemiologic evidence establishing excess weight as a risk factor for RCC. Adult weight gain has also been associated with increased risk of RCC, suggesting that avoiding excess weight gain or losing weight may reduce an individual's risk of RCC [28]. However, only a small number of studies have investigated associations with BMI or other anthropometric measures for individual subtypes. As shown by our meta-analysis, the case-control evidence from three studies suggests that BMI is associated with increased risk of clear cell and, possibly, chromophobe RCC, but is unrelated to papillary RCC risk. Similarly, our meta-analysis of case-only results from five studies also suggests that the association with BMI is significantly stronger for clear cell vs. papillary RCC. These findings suggest that the underlying biological mechanisms through which obesity drives RCC development may operate through subtype-specific pathways. This is plausible in the case of clear cell RCC, the hallmark of which is constitutive upregulation of oncogenic hypoxia-inducible factors (HIFs) due to inactivation of the tumor suppressor VHL; obesity-induced kidney injury can lead to chronic renal hypoxia, potentially inducing persistent upregulated expression of HIFs contributing to clear cell RCC development [29]. Chronic low-grade inflammation is a feature of obesity [30] and may contribute to the development of clear cell RCC via the upregulation of inflammatory genes [31]. Further, obesity has been associated with molecular differences within clear cell RCC. In a recent study, obese

patients were significantly more likely to have the “ccA” ccRCC tumors [32]. Excess weight has also been associated with differences in expression of metabolic and fatty acid synthesis genes in analyses of clear cell RCC tumors [33].

It is unclear what, if any, obesity-related mechanisms potentially influence chromophobe RCC development, as the pathogenesis of sporadic forms of this RCC subtype is poorly understood [34]. It is possible that obesity-related influences on *TERT* expression and mitochondrial activity, commonly dysregulated in chromophobe RCC, may play a role [35]. Targeted interventions to reduce obesity may have a beneficial impact on the incidence of clear cell and possibly chromophobe RCC.

Our KPNC study has several important strengths. We utilized medical records that were collected prior to diagnosis of RCC as opposed to self-reported exposures after case identification. Additionally, we had a relatively large sample size, which allowed us to assess the association between known risk factors of RCC and rarer histologic subtypes. Height and weight information was measured by trained health professionals prior to RCC diagnosis.

Inferences from our study should be made in the context of several limitations. Our KPNC data on medical history were limited, lacking information on duration and severity of hypertension and chronic kidney disease and detailed smoking history. For some cases the time between measurement of height and weight and diagnosis of RCC was relatively short (e.g. <12 months) and weight loss from undiagnosed RCC may have attenuated our results. BMI does not account for body fat percentage or distribution of adipose tissue [36], which may also contribute to development of RCC. The number of cases with less common RCC subtypes (e.g. collecting duct carcinoma or tubular adenocarcinoma) was small and we were unable to evaluate them individually. The statistical power for subgroup analyses and tests for interaction was limited. Additionally, we did not have information on abdominal imaging, which is a potential confounding factor since most RCC tumors are detected incidentally [37]. When we restricted to cases diagnosed at stage II or greater, obesity-related odds ratios for clear cell and papillary RCC from the sensitivity analysis did not materially differ from the overall analysis, suggesting that incidental detection does not account for these differences in findings across these subtypes. The originally observed association for chromophobe RCC was not apparent in the sensitivity analysis (ORs 2.5 and 1.3 respectively), although there were only five chromophobe cases diagnosed at stage II or greater. We did not centrally adjudicate the pathology of tumors, although we used a SEER-associated registry. Furthermore, our results are largely consistent with previous studies that included a central histopathologic review of cases, which provides reassurance that outcome misclassification is not an alternative explanation for our results. Our meta-analysis is also limited by the small number of studies eligible for inclusion. Additionally, we relied on crude case-only OR calculations from based on frequencies in two instances, although our summary estimates did not materially change after excluding these studies.

5. Conclusions

Our results provide support for the hypothesis that histologic subtypes of RCC represent distinct etiologic pathways, and that obesity is more strongly associated with risk of clear

cell RCC. Additional research to elucidate the underlying biology of specific subtypes of RCC is warranted. More generally, our findings underscore the importance of accounting for histologic subtype in investigations of RCC etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

OR	odds ratio
CI	confidence interval
RCC	renal cell carcinoma
KPNC	Kaiser Permanente Northern California
BMI	body mass index
SRR	summary relative risk
NOS	not otherwise specified

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Figure 1.

Summary of meta-analyses of case-control RCC subtype specific odds ratios for overweight and obesity vs. BMI<25kg/m². Abbreviations: BMI, body mass index; RCC, renal cell carcinoma; Summary Relative Risk; USKC, US Kidney Cancer Study; CEERC, Central and Eastern European Renal Cell Cancer Study; KPNC, Kaiser Permanente Northern California.

Figure 2.

Summary of meta-analyses of case-only odds ratios (clear cell vs. papillary RCC) for overweight and obesity vs. BMI < 25 kg/m². Abbreviations: BMI, body mass index; RCC, renal cell carcinoma; Summary Relative Risk; USKC, US Kidney Cancer Study; CEERC, Central and Eastern European Renal Cell Cancer Study; KPNC, Kaiser Permanente Northern California; SRR, summary relative risk. *Compared BMI > 30 kg/m² with BMI < 30 kg/m²

Table 1.

Descriptive characteristics of Kaiser Permanente Northern California (KPNC) renal cell carcinoma cases and controls

	All KPNC subjects		KPNC subjects 2005–2008	
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>
Age in years	N (%)	N (%)	N (%)	N (%)
18–54	739 (24)	7374 (24)	160 (23)	927 (22)
55–64	856 (27)	8510 (28)	220 (32)	1331 (31)
65–75	862 (28)	8557 (28)	171 (25)	1086 (25)
75–99	668 (21)	6504 (21)	134 (20)	922 (22)
Race				
White, non-Hispanic	2152 (69)	21478 (69)	457 (67)	2923 (69)
Black, non-Hispanic	293 (9)	2836 (9)	60 (9)	353 (8)
Hispanic	425 (14)	4147 (13)	107 (16)	626 (15)
Asian/Pacific Islander	255 (8)	2484 (8)	61 (9)	364 (9)
Sex				
Male	1997 (64)	19760 (64)	451 (66)	2774 (65)
Female	1128 (36)	11185 (36)	234 (34)	1492 (35)
History of smoking				
No	2390 (76)	24753 (80)	441 (64)	2884 (68)
Yes	735 (24)	6192 (20)	244 (36)	1382 (32)
Hypertension				
No	1526 (49)	18962 (61)	248 (36)	2045 (48)
Yes	1599 (51)	11983 (39)	437 (64)	2221 (52)
Chronic kidney disease				
No	3060 (98)	30736 (99)	656 (96)	4196 (98)
Yes	65 (2)	209 (1)	29 (4)	70 (2)
Body mass index (kg/m ²)				
<25			136 (20)	1074 (25)
25–30			245 (36)	1661 (39)
30			304 (44)	1531 (36)

Table 2.

Case-control comparisons of smoking, hypertension, diabetes, chronic kidney disease, and body mass index (BMI) for histologic subtypes of renal cell carcinoma, within the Kaiser Permanente Northern California integrative healthcare system, 2005–2008

	Controls		Clear Cell		Papillary		Chromophobe		Other		NOS		Phet
	N (%)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)
History of smoking													
No	2884 (68)	270 (64)	1.0		39 (60)	1.0		18 (75)	1.0		27 (77)	1.0	
Yes	1382 (32)	150 (36)	1.2	(0.9–1.5)	26 (40)	1.1	(0.7–1.9)	6 (25)	1.2	(0.9–1.5)	8 (23)	0.6	(0.3–1.4)
Hypertension													
No	2045 (48)	151 (36)	1.0		21 (32)	1.0		15 (63)	1.0		14 (40)	1.0	
Yes	2221 (52)	270 (64)	1.9	(1.5–2.5)	44 (68)	1.9	(1.0–3.4)	9 (38)	0.7	(0.3–1.9)	21 (60)	2.1	(0.9–4.8)
Diabetes													
No	3488 (82)	327 (78)	1.0		53 (82)	1.0		20 (83)	1.0		30 (86)	1.0	
Yes	778 (18)	94 (22)	0.9	(0.7–1.2)	12 (18)	0.8	(0.4–1.6)	4 (17)	1.0	(0.3–3.3)	5 (14)	0.6	(0.3–1.4)
Chronic kidney disease													
No	4196 (98)	401 (95)	1.0		60 (92)	1.0		24 (100)	1.0		35 (100)	1.0	
Yes	70 (2)	20 (5)	2.9	(1.7–4.9)	5 (8)	3.7	(1.4–10.0)	0			0	1.3	(0.5–3.8)
BMI (kg/m ²)													
<25	1074 (25)	74 (18)	1.0		14 (22)	1.0		4 (17)	1.0		10 (29)	1.0	
25–29.9	1661 (39)	152 (36)	1.2	(0.9–1.7)	27 (42)	1.0	(0.5–2.0)	8 (33)	1.7	(0.5–5.9)	9 (26)	0.5	(0.2–1.3)
30	1531 (36)	195 (46)	1.5	(1.1–2.1)	24 (37)	1.0	(0.5–1.9)	12 (50)	2.5	(0.8–8.1)	16 (46)	0.9	(0.4–2.1)
Per 5kg/m ²			1.2	(1.1–1.3)		0.9	(0.7–1.2)		1.5	(1.1–2.0)		1.0	(0.8–1.4)

Abbreviations: OR, odds ratio; CI, confidence interval; NOS, not otherwise specified.

^a Adjusted for age, race, sex, duration of Kaiser membership, membership category, smoking history, hypertension, diabetes, chronic kidney disease.

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	Clear Cell		Papillary		Chromophobe			Other		NOS			
	N (%)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)
Age in years													
18–54	109 (26)	10 (15)	1.0		10 (42)	1.0		10 (29)	1.0		21 (15)	1.0	
55–64	141 (33)	24 (37)	1.6	(0.7–3.8)	7 (29)	0.8	(0.2–2.3)	12 (34)	1.0	(0.4–2.6)	36 (26)	1.3	(0.7–2.5)
65–75	108 (26)	17 (26)	1.4	(0.6–3.6)	5 (21)	0.7	(0.2–2.7)	6 (17)	0.6	(0.2–2.1)	35 (25)	1.8	(0.9–3.5)
75–99	63 (15)	14 (22)	2.0	(0.7–5.5)	2 (8)	0.6	(0.1–3.8)	7 (20)	1.2	(0.4–4.1)	48 (34)	4.1	(2.0–8.6)
Per 5-year increase			1.2	(1.0–1.4)		0.9	(0.7–1.1)		1.0	(0.9–1.2)		1.3	(1.2–1.4)
Race													
White, non-Hispanic	275 (65)	42 (65)	1.0		13 (54)	1.0		21 (60)	1.0		106 (76)	1.0	
Black, non-Hispanic	24 (6)	18 (28)	8.4	(3.7–19.4)	0 (0)			5 (14)	4.1	(1.3–12.9)	13 (9)	2.2	(1.0–4.8)
Hispanic	79 (9)	3 (5)	0.3	(0.1–1.0)	4 (17)	1.0	(0.3–3.3)	8 (23)	1.4	(0.6–3.4)	13 (9)	0.5	(0.3–1.0)
Asian/Pacific Islander	43 (10)	2 (3)	0.3	(0.1–1.3)	7 (29)	3.5	(1.2–9.8)	1 (3)	0.3	(0.0–2.1)	8 (6)	0.5	(0.2–1.2)
Sex													
Male	275 (65)	53 (82)	1.0		10 (42)	1.0		25 (71)	1.0		88 (63)	1.0	
Female	146 (35)	12 (18)	0.4	(0.2–0.8)	14 (58)	2.7	(1.1–6.5)	10 (29)	0.7	(0.3–1.6)	52 (37)	1.0	(0.7–1.6)
History of smoking													
No	270 (64)	39 (60)	1.0		18 (75)	1.0		27 (77)	1.0		87 (62)	1.0	
Yes	151 (36)	26 (40)	0.8	(0.5–1.5)	6 (25)	0.8	(0.3–2.2)	8 (23)	0.5	(0.2–1.2)	53 (38)	1.0	(0.6–1.5)
Hypertension													
No	151 (36)	21 (32)	1.0		15 (63)	1.0		14 (40)	1.0		47 (34)	1.0	
Yes	270 (64)	44 (68)	1.0	(0.5–2.0)	9 (38)	0.4	(0.1–1.1)	21 (60)	1.2	(0.5–2.8)	93 (66)	0.8	(0.5–1.3)
Chronic kidney disease													
No	401 (95)	60 (92)	1.0		24 (100)	1.0		35 (100)	1.0		136 (97)	1.0	
Yes	20 (5)	5 (8)	0.9	(0.3–3.0)	0 (0)			0 (0)			4 (3)	0.5	(0.2–1.6)
BMI (kg/m ²)													
<25	74 (18)	14 (22)	1.0		4 (17)	1.0		10 (29)	1.0		34 (24)	1.0	
25–29.9	152 (36)	27 (42)	0.8	(0.4–1.6)	8 (33)	1.9	(0.5–7.2)	9 (26)	0.3	(0.1–0.9)	49 (35)	0.7	(0.4–1.3)

	Clear Cell		Papillary		Chromophobe		Other		NOS	
	N (%)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)	N (%)	OR ^a	(95%CI)
30	195 (46)	24 (37)	0.7	(0.3–1.6)	12 (50)	1.8	(0.5–6.7)	16 (46)	0.5	(0.2–1.3)
per 5kg/m ² increase			0.8	(0.6–1.1)		1.1	(0.8–1.6)		0.9	(0.6–1.3)
									0.8	(0.7–1.0)

Abbreviations: OR, odds ratio; CI, confidence interval; NOS, not otherwise specified.

^aOdds ratios calculated using logistic regression models, adjusted for age in years, race, sex, duration of Kaiser Permanente membership, membership category, smoking history, hypertension, diabetes, and chronic kidney disease.