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Serum leptin and adiponectin levels and risk of renal cell carcinoma

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Abstract

The incidence of renal cell carcinoma (RCC) has increased rapidly in the U.S., particularly among African Americans. Despite a well-established link between obesity and RCC, the mechanism through which obesity increases cancer risk has yet to be established. Adipokines, such as leptin and adiponectin, may link obesity and cancer, with different quantitative effects by race. We evaluated the association between leptin and adiponectin concentrations and RCC risk among Caucasians (581 cases, 558 controls) and African Americans (187 cases, 359 controls) in a case-control study conducted in Detroit and Chicago. Odds ratios(ORs) and 95% confidence intervals(95%CIs) were estimated using unconditional logistic regression. Among controls, Caucasians had higher median adiponectin than African Americans (males: 8.2 vs. 7.0μg/ml, p=0.001; females: 13.4 vs. 8.4μg/ml, p<0.0001), and lower median leptin than African Americans (males: 11.8 vs. 14.1ng/ml, p=0.04; females: 28.3 vs. 45.9ng/ml, p<0.0001). Among Caucasians, the ORs for RCC comparing the highest (Q4) to the lowest (Q1) sex-specific quartile of leptin were 3.2 (95%CI:1.9–5.2) for males and 4.7 (95%CI:2.6–8.6) for females. Serum leptin was not significantly associated with RCC among African American males (OR 1.5, 95%CI:0.7–3.1) or females (OR 2.1, 95%CI:0.8–5.5). Higher adiponectin was associated with RCC risk among African American males (Q4 vs. Q1: OR 2.3, 95%CI:1.1–4.6) and females (OR 2.1, 95%CI:1.2–6.7), but not significantly among Caucasian males (OR 1.6, 95%CI:0.99–2.7) and females (OR 1.6, 95%CI:0.9–3.1). In conclusion, we observed an association between both leptin and adiponectin concentrations and risk of RCC, which may differ by race. Confirmation in further investigations is needed.

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Introduction

Kidney cancer is among the most commonly diagnosed cancers in men and women in the United States (U.S.) with an estimated 58,000 new cases each year (1). In the U.S., there has been a rapid increase in the incidence of renal cell carcinoma (RCC), involving cancer of the renal parenchyma, particularly among African Americans (2–4). Disparities also exist with respect to survival, with poorer prognosis observed in African Americans when compared to Caucasians (3, 5). The reasons for these disparities are unclear.

It has been estimated that about 40% of RCC in the U.S. is attributable to being overweight or obese (6). A large body of epidemiologic research suggests a strong association between obesity and RCC risk (7–9). Despite a well-established link between obesity and kidney cancer, the mechanisms underlying the association have yet to be established. Several potential mechanisms through which obesity may initiate or promote carcinogenesis have been proposed including chronic inflammation from abnormal production of adipokines by adipose tissue, now recognized as an active endocrine organ (6, 10). Adipokines, such as leptin and adiponectin, are biologically active polypeptides produced by adipocytes and are increasingly being investigated as potential mediators of obesity's effect on diseases such as cancer (11). Leptin is a peptide hormone produced predominantly by adipocytes that is elevated in obese individuals (12, 13). The main function of leptin is to regulate body weight, appetite, and energy homeostatsis (14), but studies have strongly suggested that leptin also plays a role in carcinogenesis through cell proliferation, angiogenesis, apoptotic inhibition, and pro-inflammatory effects (10, 15, 16). In contrast, adiponectin is produced exclusively by adipocytes in visceral adipose tissue and levels are reduced in obese individuals (17, 18). Adiponectin is considered an insulin-sensitizing factor based on upregulated insulin signaling when administered,(19) and may have anti-inflammatory effects by inhibiting the production of inflammatory cytokines. There are limited data, however, on the relationship between any of the adipokine markers and risk of RCC.

Given that differences in the prevalence of obesity (20) and levels of adipokines (21, 22) between African Americans and Caucasians have been reported, it is possible that the association between adipokines and RCC may differ by race. To our knowledge, no studies have examined the association between leptin and adiponectin and RCC risk among African Americans. We therefore evaluated whether serum concentrations of leptin and adiponectin were associated with risk of RCC in the Kidney Cancer Study, a population-based case-control study of RCC in African Americans and Caucasians.

Methods and Procedures

Study population

The Kidney Cancer Study recruited cases from the metropolitan areas of Chicago, Illinois (Cook County) and Detroit, Michigan (Wayne, Macomb, and Oakland counties), and has been described in great detail elsewhere (23). Eligibility criteria for cases included: age between 20 and 79 years at the time of diagnosis, and a histologically confirmed first primary diagnosis of RCC (ICD-O Ed.2. codes 64 or 64.9) diagnosed between February 2002 and July 2006 (Caucasians) or July 2007 (African Americans) in Detroit, and between

January 2003 and December 2003 in Chicago. A rapid-reporting system was used to identify all incident cases of kidney cancer. Control participants between the ages of 20 and 64 years were selected from Department of Motor Vehicle records in each city, while controls 65 years of age and older were selected from Medicare beneficiary records. Controls were frequency matched to the age-, race-, and gender-specific distribution of RCC cases at each study center. A case: control matching ratio of 1:1 was used for Caucasians. For African Americans, a 1:2 ratio was used in order to increase the statistical power of analyses within this racial group. Of 1918 potentially eligible cases and 2718 controls identified, 1217 eligible cases and 1235 controls were interviewed. All case interviews were conducted post-diagnosis and post-surgery. Study participants completed a detailed computer-assisted personal interview at their homes with trained interviewers. Data were collected on demographic factors, tobacco and alcohol use, diet, occupational history, height and weight history, family history of cancer, reproductive history (women), medical history, and medication history. All participants provided written informed consent and all participating study centers were approved by their respective human subjects review boards.

Blood collection and laboratory procedures

Of the 2452 cases and controls in the Kidney Cancer Study, 1872 provided a blood sample (952 cases and 920 controls). Non-fasting blood samples were collected at the time of the personal interview in two ethylenediamine tetraacetic acid (EDTA) tubes, a heparin tube and a serum separator tube, processed, and stored at −80°C. Blood samples collected from cases were post-diagnostic (median time from diagnosis: 4.0 months; range: 1.0–45.9). Broken down by sex and race, the median time was similar except that African American male cases appear to have blood collected about a month earlier than other cases (median time: 3.0 months). In this analysis, we selected a subset of RCC cases and controls with available serum, and cases diagnosed with either Stage 1 (n=649) or 2 (n=119) RCC treated solely by surgery in order to avoid the potential effects of chemotherapy or radiation on adipokine levels.

Serum measurements of adipokines were conducted in the Assay Laboratory of Dr. Michael Pollak at the Lady Davis Research Institute of the Jewish General Hospital, Montreal, Quebec, Canada. Both leptin and total adiponectin concentrations were assayed using standard techniques of enzyme-linked immunosorbent assay with commercial reagents from Millipore (Billerica, Massachusetts). Samples were run in duplicate, with cases and their matched controls analyzed in the same batch. Sample concentrations are the average of duplicate measurements. Results from blinded replicate samples placed randomly in each batch provided high reproducibility with overall coefficients of variation for leptin and adiponectin of 5.4% and 6.7%, respectively.

Statistical Analysis

Data were available on 768 cases (Caucasians n=581 and African Americans n=187) and 917 controls (Caucasians n=558 and African Americans n=359). Differences between cases and controls were tested for significance using the chi-squared test for categorical variables and the Wilcoxon signed rank tests for continuous variables. Circulating levels of adipokines were categorized into quartiles by cutpoints determined by the sex-specific distributions

among controls. Analyses using race- and sex-specific cutpoints yielded similar results, and are not presented. We computed odds ratios (OR) and 95% confidence intervals (95% CI) for the association between leptin and adiponectin levels and RCC using unconditional logistic regression models with adjustment for matching factors (age [10-year categories], race, study center) and potential confounders (smoking status, history of hypertension, history of diabetes, hormone replacement therapy [women only] and family history of cancer). Tests for trend were calculated by modeling the median value within each quartile. We also modeled leptin and adiponectin as continuous values. In addition, we combined men and women according to sex-specific quartiles of leptin and adiponectin, and evaluated associations that included adjustment for sex but not hormone replacement therapy. Linear trends for the models including both men and women were calculated by assigning an ordinal value to respective quartiles of adipokines.

To explore whether adipokines could be mediating the association with obesity, we examined whether the associations between adiopkines and RCC varied with further adjustment by body mass index (BMI), as well as the effect of adjusting for an adipokine on the association between BMI and RCC. Unless specified otherwise, BMI was calculated using weight reported 5 years prior to the reference date. Spearman's correlation coefficients of BMI at blood draw with leptin and adiponectin were 0.70 (95%CI: 0.64, 0.75) and −0.23 (95%CI: −0.33, −0.13) respectively among Caucasian male controls; 0.78 (95%CI: 0.72, 0.83) and −0.31 (95%CI: −0.42, −0.17) among Caucasian female controls; 0.59 (95%CI: 0.48, 0.68) and −0.27 (95%CI: −0.40, −0.13) among African American male controls; and 0.73 (95%CI: 0.65, 0.79) and −0.27 (95%CI: −0.40, −0.13) among African American female controls. Analyses stratified by obesity status (e.g. BMI<30 and 30+ kg/m^2), tumor stage at diagnosis (Stage 1 and Stage 2), time between diagnosis and blood draw, and weight loss in the past 5 years were also conducted to evaluate potential effect modification and reverse causation. An analysis adjusted for fasting status (defined as not eating >6 hours prior to blood draw) was also conducted. Tests for statistical interaction were assessed by cross-product terms composed of continuous or categorical adipokines and categorical variables in a multivariate model. Tests for biological interaction were assessed by calculation of the Synergy Index (95% CI), and was considered present if SI > 1.5 (24). All analyses were conducted using SAS version 9.2. (SAS Institute, Cary, NC).

Results

Overall, cases were more likely to be less educated, overweight and have a history of hypertension compared to controls, as reported previously (Table 1) (23). The characteristics of this subset are very similar to the distributions in the entire study, except that African American controls had a larger proportion of females (23). Median concentrations of leptin were higher for cases than controls, and significantly higher in women compared to men. Median concentrations of adiponectin were slightly higher for cases than controls, and were higher in women compared to men except among African American cases. As concentrations of leptin and adiponectin differed by sex, all subsequent analyses are stratified by sex.

As shown in Table 2, increasing leptin concentrations were associated with increased risk of RCC among men (highest quartile: OR 2.57, 95% CI: 1.72–3.85, P trend <0.0001) and women (3.51, 2.16–5.70, P trend <0.0001). There was a statistically significant interaction between race and leptin concentrations among females (p-interaction=0.04) but not males (p-interaction=0.73). Additional adjustment for BMI attenuated estimates slightly, but the positive association between higher leptin concentrations and RCC was still evident among Caucasian males and females. In models evaluating the association with BMI, adjustment for leptin attenuated the obesity association among Caucasians but not among African Americans (Supplementary Table 2).

Case-control comparisons for adiponectin are summarized in Table 3. Higher concentrations of adiponectin were associated with an increased risk of RCC in in men (highest quartile: OR 1.73, 95%CI: 1.17–2.57, P trend=.002) and women (OR 1.82, 95%CI: 1.12–2.97, P trend=0.04). In analyses stratified by race, the association between higher concentrations of adiponectin and risk of RCC were slightly stronger among African Americans compared to Caucasians, although, tests of interaction were not statistically significant (p-interaction=0.98 and 0.15 for males and females, respectively). After further adjustment for BMI, the positive associations with adiponectin remained, and were slightly stronger than previous estimates. In models evaluating the association between BMI and RCC risk, adjustment for adiponectin did not seem to affect the obesity association and may have strengthened some associations (Supplementary Table 2).

We also examined whether the associations of leptin and adiponectin with RCC were modified by obesity status (BMI > 30 kg/m^2; Table 4). When leptin concentrations and obesity were considered jointly, increased risk associated with higher leptin concentrations (above the median) was present among both males and females regardless of obesity status. When adiponectin concentrations and obesity were considered jointly, increased risk associated with higher adiponectin concentrations was much higher among obese males than non-obese males. In contrast, the effect of obesity among females appeared to be associated with an OR of 2–3 regardless of adiponectin concentrations. None of these interactions were statistically significant (p-interaction >0.20).

Leptin and adiponectin levels were not significantly different by tumor stage at diagnosis among cases (Stage 1 and Stage 2; Supplementary Table 3) and the associations between both adipokines and RCC remained when analyses were restricted to Stage 1 tumors (males: n=363; 266 Caucasians and 97 African Americans; females: n=286; 217 Caucasians and 69 African Americans; data not shown). Stratified analyses by time between diagnosis/reference date and blood draw exhibited some variation in effect sizes, but no obvious trends with time (Supplementary Table 4). Further stratification by race suggested that the association with increasing leptin may be stronger the longer the time between diagnosis and blood draw for African American males, although some odds ratio estimates are unstable due to sparse numbers (data not shown). Sensitivity analyses excluding individuals at various levels of weight loss also did not reveal significantly different estimates for either adipokine. An analysis excluding individuals who reported a loss of more than 10% of their current weight over the last 5 years is included in the supplementary data (Supplementary Table 5). When analyses were restricted to clear cell RCC only (n=479), results were similar

for both males and females (data not shown). An analysis with an additional adjustment for fasting status also provided similar results to the original estimates (Supplementary Table 6). Examination of biological interactions using the Synergy Index suggested the presence of synergistic interaction between leptin concentrations and race among females, but no other interactions were significant (Supplementary Table 7).

Discussion

In this study, we observed a statistically significant association between higher leptin concentrations and increased RCC risk among Caucasian males and females. We also observed an unexpected association between higher adiponectin concentrations and increased RCC risk among African American males and females that was not as evident among Caucasians. Adjustment for BMI did not have a significant effect on either adipokine RCC association.

A recent meta-analysis reported a strong association between higher BMI and an increased risk of RCC (25), but data are sparse on the relationship between either adipokine and risk of RCC. We hypothesized that higher concentrations of leptin would be associated with elevated RCC risk because of the strong correlation between leptin and BMI, and its potential involvement in tumor development. The observed association with leptin was only modestly attenuated after adjustment for BMI, suggesting that other factors associated with leptin may at least partially explain this association. Our analyses also suggest a difference by race, where leptin may mediate the association between BMI and RCC risk among Caucasians, but have less of an impact on African Americans. Our findings for Caucasians, however, are in contrast to findings from a case-control study in Greece that reported an inverse association between leptin and RCC risk (26). However, these differing results may partly be explained by small sample size, no adjustment for sex, and the inclusion of 23 advanced-stage RCC cases in the Greek study. The mechanism through which leptin may influence carcinogenesis remains unclear; several studies have demonstrated that leptin stimulates cell proliferation and angiogenesis and inhibits apoptosis in multiple cancer cell lines, including RCC (10, 15, 27, 28). In addition, the leptin receptor is expressed in renal tissue and all six human RCC cell lines (29, 30), supporting a role for leptin signaling in RCC carcinogenesis.

Higher concentrations of adiponectin were associated with risk of RCC in our study. This was an unexpected finding, as we hypothesized that an inverse association would be observed as adiponectin is often reduced in obese individuals and among several obesity-related cancers (31–35). Interestingly, although adiponectin is produced exclusively by adipocytes, adiponectin was not strongly correlated with BMI in our. Further adjustment for adiponectin did not affect the association between BMI and RCC, suggesting that adiponectin may not be a mediator in the association between obesity and RCC. One small case-control study reported an inverse association between adiponectin levels and RCC risk, which was no longer statistically significant after adjustment for other risk factors.(36) However, the role of adiponectin in carcinogenesis is not yet fully understood. Adiponectin is an insulin-sensitizing hormone that also appears to have anti-inflammatory and antiangiogenic properties, so lower levels could have an impact on initiation and growth of a

tumor (19). Both adiponectin receptors, AdipoR1 and R2, are expressed in normal and renal tumor tissue but appear to be downregulated in tumor tissue compared to normal tissue (19, 37). Different multimers of adiponectin appear to have differing effects and evaluating specific multimers may provide a better indicator of effect than the measurement of total adiponectin conducted in this study (38).

To the best of our knowledge, this is the first study to evaluate leptin and adiponectin and risk of RCC in both Caucasians and African Americans. All previous studies of adipokines and cancer have been conducted in Caucasian study populations. Results from our study suggest that there may be racial differences in the associations between adipokines and RCC risk. These differences do not appear to be solely explained by obesity prevalence, as adjustment for BMI does not diminish the observed associations; but could be due to physiological or genetic differences in the production of adipokines by adipose tissue. Previous studies have described differences in the distribution of leptin and adiponectin among Caucasians and African Americans (21, 22). Lower expression of genes regulating adipogenesis and lipogenesis in adipose tissue in African American women compared to Caucasian women has been observed and may be associated with racial differences in insulin resistance (39). The number and the significance of variants in the adiponectin gene with serum adiponectin concentrations also appears to differ between Caucasians and African Americans (40). The underlying mechanisms accounting for racial differences in the associations observed between adipokines and RCC remains unclear but further studies in this area are needed.

The major limitation of this study is that blood specimens were collected after case diagnosis, introducing the potential for disease- or treatment-induced changes in analyte levels. To minimize the potential for such bias, we selected RCC cases treated solely by surgery and conducted several sensitivity analyses including evaluations on whether reported weight loss in the last five years had an effect on risk estimates. Further, our findings across separate analyses by tumor stage and grade did not materially differ, suggesting that disease progression is unlikely to have affected our results. However, we cannot rule out the possibility that the observed findings are a reflection of reverse causation. We also note that data on weight history and BMI were collected retrospectively and based on self-report, and thus may be subject to recall bias.

In conclusion, we observed an association between both leptin and adiponectin concentrations and risk of RCC, which may differ by race. These data suggest a complex association among circulating levels of leptin and adiponectin, race, and obesity. To address these questions, additional studies are needed, particularly those with prospectively collected samples and both Caucasian and African American subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected characteristics of cases and controls in the Kidney Cancer Study

	Overall		Caucasians		African Americans	
	Cases (N=768)	**Controls (N=917)**	**Cases (N=581)**	**Controls (N=558)**	**Cases (N=187)**	**Controls (N=359)**
Categorical Variables, N (%)						
Age						
20–44	97 (12.6)	134 (14.6)	77 (13.3)	72 (12.9)	20 (10.7)	62 (17.3)
45–54	172 (22.4)	204 (22.3)	123 (21.2)	117 (21.0)	49 (26.2)	87 (24.2)
55–64	256 (33.3)	265 (28.9)	187 (32.2)	161 (28.9)	69 (36.9)	104 (29.0)
65–74	181 (23.6)	237 (25.9)	141 (24.3)	153 (27.4)	40 (21.4)	84 (23.4)
75+	62 (44.6)	77 (8.4)	53 (9.1)	55 (9.9)	9 (4.8)	22 (6.1)
Sex						
Male	434 (56.5)	527 (57.5)	322 (55.4)	352 (63.1)	112 (59.9)	175 (48.8)
Female	334 (43.5)	390 (42.5)	259 (44.6)	206 (36.9)	75 (40.1)	184 (51.3)
Region						
Chicago	29 (3.8)	128 (14.0)	18 (3.1)	65 (11.7)	11 (5.9)	63 (17.6)
Detroit	739 (96.2)	789 (86.0)	563 (96.9)	493 (88.4)	176 (94.1)	296 (82.4)
Education						
<High school	118 (15.4)	106 (11.6)	70 (12.1)	48 (8.6)	48 (25.7)	58 (16.2)
High school Grad	268 (34.9)	297 (32.4)	216 (37.2)	172 (30.8)	52 (27.8)	125 (34.8)
Some College (1–3 years)	205 (26.7)	267 (29.1)	144 (24.8)	141 (25.3)	61 (32.6)	126 (35.1)
College Graduate	177 (23.1)	247 (26.9)	151 (26.0)	197 (35.3)	26 (13.9)	50 (13.9)
Smoking status						
Never	288 (37.5)	355 (38.7)	223 (38.4)	227 (40.7)	65 (34.8)	128 (35.7)
Occasional	33 (4.3)	42 (4.6)	22 (3.8)	19 (3.4)	11 (5.9)	23 (6.4)
Regular, Former	260 (33.9)	338 (36.9)	197 (33.9)	223 (40.0)	63 (33.7)	115 (32.0)
Regular, Current	187 (24.4)	182 (19.9)	139 (23.9)	89 (16.0)	48 (25.7)	93 (25.9)
Body mass index (kg/m2)						
<25	140 (18.2)	264 (28.8)	111 (19.1)	163 (29.2)	29 (15.5)	101 (28.1)
25-<30	268 (34.9)	370 (40.4)	202 (34.8)	234 (41.9)	66 (35.3)	136 (37.9)

	Overall		Caucasians		African Americans	
	Cases (N=768)	**Controls (N=917)**	**Cases (N=581)**	**Controls (N=558)**	**Cases (N=187)**	**Controls (N=359)**
30-<35	189 (24.6)	162 (17.7)	148 (25.5)	98 (17.6)	41 (21.9)	64 (17.8)
35+	163 (21.2)	117 (12.8)	115 (19.8)	61 (10.9)	48 (25.7)	56 (15.6)
Hypertension						
No	312 (40.6)	541 (59.0)	264 (45.4)	355 (63.6)	48 (25.7)	186 (51.8)
Yes	446 (58.1)	371 (40.5)	308 (53.0)	201 (36.0)	138 (73.8)	170 (47.4)
Continuous variables, median (IQR) Leptin concentration, ng/ml						
Overall	25.9 (13.2–54.1)	19.1 (9.9–37.0)	25.6 (12.9–50.6)	16.6 (9.0–28.5)	27.2 (14.5–63.1)	26.4 (13.1–48.8)
Males	16.5 (9.8–29.0)	12.5 (7.4–20.4)	16.4 (9.4–29.1)	11.8 (7.4–19.5)	16.6 (11.1–28.3)	14.1 (6.8–24.5)
Females	46.9 (27.0–76.9)	35.0 (20.3–58.5)	43.3 (26.4–71.8)	28.3 (17.3–46.0)	59.7 (30.2–136.9)	45.9 (27.0–72.4)
Adiponectin concentration, μg/ml						
Overall	10.4 (7.0–15.7)	8.9 (6.1–14.0)	10.8 (7.4–15.7)	9.7 (6.8–14.7)	9.2 (5.9–16.0)	7.7 (5.4–12.2)
Males	9.1 (6.3–13.1)	7.8 (5.6–11.6)	9.1 (6.5–12.8)	8.2 (6.0–12.1)	9.3 (5.5–13.8)	7.0 (4.8–10.7)
Females	13.0 (8.5–19.3)	11.1 (7.1–16.0)	13.9 (8.9–19.5)	13.4 (8.4–18.8)	9.2 (6.3–17.3)	8.4 (6.1–13.2)

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Table 2

Risk of RCC associated with Leptin Concentrations

	Quartile of Serum Leptin (ng/mL)				
	Q1	**Q2**	**Q3**	**Q4**	**P trend[c]**
			Males		
Range, ng/mL	(≤7.37)	(>7.37 and ≤12.49)	(>12.49 and ≤20.44)	(>20.44)	
All subjects					
No. of Cases/Controls	67/129	82/128	102/128	173/128	
Adjusted OR (95% CI)[a]	1.00	1.09 (0.71–1.68)	1.44 (0.94–2.18)	2.57 (1.72–3.85)	**<0.0001**
Adjusted OR +BMI (95% CI)[b]	1.00	1.02 (0.66–1.59)	1.30 (0.84–2.02)	2.24 (1.43–3.50)	**<0.0001**
Caucasians					
No. of Cases/Controls	47/86	67/98	78/85	127/74	
Adjusted OR (95% CI)[a]	1.00	1.18 (0.72–1.95)	1.64 (1.00–2.69)	3.15 (1.93–5.15)	**<0.0001**
Adjusted OR +BMI (95% CI)[b]	1.00	1.16 (0.69–1.95)	1.58 (0.93–2.69)	2.99 (1.71–5.25)	**<0.0001**
African Americans					
No. of Cases/Controls	20/43	15/30	24/43	46/54	
Adjusted OR (95% CI)[a]	1.00	0.81 (0.32–2.04)	1.06 (0.46–2.44)	1.48 (0.70–3.11)	0.15
Adjusted OR +BMI (95% CI)[b]	1.00	0.73 (0.28–1.90)	0.97 (0.41–2.29)	1.33 (0.60–2.94)	0.28
			Females		
Range, ng/mL	(≤20.28)	(>20.28 and ≤34.99)	(>34.99 and ≤58.49)	(>58.49)	
All subjects					
No. of Cases/Controls	55/98	64/97	79/98	136/97	
Adjusted OR (95% CI)[a]	1.00	1.26 (0.77–2.08)	1.81 (1.10–2.97)	3.51 (2.16–5.70)	**<0.0001**
Adjusted OR +BMI (95% CI)[b]	1.00	1.25 (0.75–2.08)	1.53 (0.89–2.63)	2.58 (1.48–4.51)	**0.0004**
Caucasians					
No. of Cases/Controls	46/70	49/62	66/42	98/32	
Adjusted OR (95% CI)[a]	1.00	1.11 (0.63–1.95)	2.49 (1.38–4.49)	4.74 (2.62–8.59)	**<0.0001**
Adjusted OR +BMI (95% CI)[b]	1.00	1.12 (0.62–2.02)	2.22 (1.16–4.27)	4.13 (2.06–8.28)	**<0.0001**
African Americans					

	Quartile of Serum Leptin (ng/mL)				
	Q1	**Q2**	**Q3**	**Q4**	**P trend[c]**
No. of Cases/Controls	9/28	15/35	13/56	38/65	
Adjusted OR (95% CI)[a]	1.00	1.74 (0.60–4.99)	0.91 (0.32–2.61)	2.13 (0.82–5.53)	0.11
Adjusted OR +BMI (95% CI)[b]	1.00	1.54 (0.53–4.46)	0.61 (0.20–1.88)	1.12 (0.39–3.25)	0.89

[a] OR adjusted for age, race, center, smoking status, hypertension, diabetes, hormone replacement therapy (women) and family history of cancer. Stratified analyses by race do not include race in the model.

[b] OR adjusted for variables in previous model with additional adjustment for BMI

[c] P trend calculated by modeling median value within each quartile

Table 3

Risk of RCC associated with Adiponectin Concentrations

	Quartile of Serum Adiponectin (μg/ml)				
	Q1	**Q2**	**Q3**	**Q4**	**P trend[c]**
			Males		
Range, μg/ml	(≤5.61)	(>5.61 and ≤7.82)	(>7.82 and ≤11.62)	(>11.62)	
All subjects					
No. of Cases/Controls	84/132	81/132	129/132	140/131	
Adjusted OR (95% CI)[a]	1.00	1.03 (0.68–1.55)	1.68 (1.13–2.49)	1.73 (1.17–2.57)	**0.002**
Adjusted OR +BMI (95% CI)[b]	1.00	1.04 (0.69–1.59)	1.84 (1.23–2.75)	2.05 (1.37–3.08)	**0.0001**
Caucasians					
No. of Cases/Controls	55/70	65/95	101/94	101/93	
Adjusted OR (95% CI)[a]	1.00	1.06 (0.64–1.75)	1.76 (1.08–2.86)	1.62 (0.99–2.65)	**0.03**
Adjusted OR +BMI (95% CI)[b]	1.00	1.11 (0.67–1.84)	1.97 (1.20–3.23)	1.97 (1.18–3.29)	**0.004**
African Americans					
No. of Cases/Controls	29/62	16/37	28/38	39/38	
Adjusted OR (95% CI)[a]	1.00	0.92 (0.41–2.07)	1.49 (0.71–3.13)	2.25 (1.09–4.64)	**0.01**
Adjusted OR +BMI (95% CI)[b]	1.00	0.96 (0.42–2.20)	1.62 (0.76–3.43)	2.71 (1.28–5.76)	**0.004**
			Females		
Range, μg/ml	(≤7.06)	(>7.06 and ≤11.06)	(>11.06 and ≤16.04)	(>16.04)	
All subjects					
No. of Cases/Controls	54/98	86/97	77/98	117/97	
Adjusted OR (95% CI)[a]	1.00	1.52 (0.93–2.49)	1.27 (0.76–2.12)	1.82 (1.12–2.97)	**0.04**
Adjusted OR +BMI (95% CI)[b]	1.00	1.64 (0.99–2.73)	1.47 (0.86–2.52)	2.24 (1.34–3.76)	**0.007**
Caucasians					
No. of Cases/Controls	33/31	62/48	69/55	95/72	
Adjusted OR (95% CI)[a]	1.00	1.45 (0.74–2.85)	1.53 (0.78–2.99)	1.64 (0.87–3.10)	0.23
Adjusted OR +BMI (95% CI)[b]	1.00	1.58 (0.78–3.20)	1.76 (0.87–3.56)	2.03 (1.03–4.01)	0.07
African Americans					

	Quartile of Serum Adiponectin (μg/ml)				
	Q1	**Q2**	**Q3**	**Q4**	**P trend[c]**
No. of Cases/Controls	21/67	24/49	8/43	22/25	
Adjusted OR (95% CI)[a]	1.00	1.72 (0.81–3.65)	0.60 (0.22–1.62)	2.08 (1.16–6.65)	0.08
Adjusted OR +BMI (95% CI)[b]	1.00	1.81 (0.84–3.91)	0.76 (0.27–2.10)	3.22 (1.28–8.11)	**0.04**

[a] OR adjusted for age, race, center, smoking status, hypertension, diabetes, hormone replacement therapy (women) and family history of cancer. Stratified analyses by race do not include race in the model.

[b] OR adjusted for variables in previous model with additional adjustment for BMI

[c] P trend calculated by modeling median value within each quartile

Table 4

Risk of RCC associated with Leptin and Adiponectin Concentrations according to obesity status

	All subjects						Caucasians						African Americans					
	BMI<30			BMI 30+			BMI<30			BMI 30+			BMI<30			BMI 30+		
Median	**Cases**	**Controls**	**OR[a] 95% CI**	**Cases**	**Controls**	**OR[a] 95% CI**	**Cases**	**Controls**	**OR[a] 95% CI**	**Cases**	**Controls**	**OR[a] 95% CI**	**Cases**	**Controls**	**OR[a] 95% CI**	**Cases**	**Controls**	**OR[a] 95% CI**
Leptin																		
Males																		
≤12.49	115	218	1.00	33	38	1.38 0.80–2.39	89	159	1.00	25	25	1.58 0.83–3.02	26	59	1.00	8	13	0.72 0.23–2.26
>12.49	118	136	**1.77 1.23–2.53**	156	119	**2.35 1.64–3.39**	87	80	**2.02 1.33–3.09**	117	79	**2.59 1.69–3.96**	31	56	1.20 0.58–2.47	39	40	1.83 0.86–3.88
Females																		
≤34.99	93	171	1.00	26	22	1.81 0.91–3.62	76	118	1.00	19	12	1.73 0.73–4.06	17	53	1.00	7	10	1.49 0.46–4.86
>34.99	72	95	**1.93 1.23–3.03**	137	100	**2.98 1.95–4.56**	58	31	**3.20 1.82–5.62**	102	43	**3.52 2.11–5.86**	14	64	0.70 0.30–1.66	35	57	1.69 0.77–3.69
Adiponectin																		
Males																		
≤7.82	84	169	1.00	79	94 1.39	0.91–2.14	58	104	1.00	61	61	1.56 0.93–2.61	26	65	1.00	18	33	1.06 0.46–2.46
>7.82	159	199	**1.52 1.06–2.17**	110	63	**3.09 1.99–4.79**	121	144	**1.53 1.00–2.35**	81	43	**3.27 1.93–5.54**	38	55	1.63 0.81–3.28	29	20	**2.79 1.20–6.45**
Females																		
≤11.06	54	125	1.00	86	69	**2.63 1.58–4.38**	38	55	1.00	57	23	**2.72 1.36–5.46**	16	70	1.00	29	46	**2.40 1.09–5.28**
>11.06	111	141	1.50 0.95–2.35	77	53	**2.70 1.58–4.62**	96	94	1.51 0.88–2.60	64	32	**2.92 1.52–5.60**	15	47	1.43 0.59–3.46	13	21	2.12 0.77–5.79

[a]OR adjusted for age, race, center, smoking status, hypertension, diabetes, hormone replacement therapy (women) and family history of cancer. Stratified analyses by race do not include race in the model.