

Prediagnostic circulating adipokine concentrations and risk of renal cell carcinoma in male smokers

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Despite a well-established link between obesity and renal cell carcinoma (RCC), the mechanism through which obesity acts to increase cancer risk is unclear. Adiponectin, leptin and resistin are adipocyte-secreted peptide hormones that may influence RCC development through their demonstrated effects on inflammation, insulin resistance and cell growth and proliferation. We conducted a nested case-control study to evaluate whether prediagnostic serum adiponectin, leptin and resistin levels are associated with RCC risk. This case-control study (273 cases and 273 controls) was nested within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of Finnish male smokers. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using conditional logistic regression models, with analyte levels modeled continuously and categorically (defined using quartiles among controls). High adiponectin levels were significantly associated with reduced RCC risk (Quartile 4 versus Quartile 1: OR = 0.52, 95% CI = 0.30–0.88; *P* trend = 0.01). This association remained upon additional adjustment for body mass index at blood collection and exclusion of cases diagnosed within the first 2 years of follow-up. In addition, model adjustment for adiponectin resulted in a substantial attenuation of the association between BMI and RCC (OR per 5 kg/m² changed from 1.19 to 1.05). No clear associations with RCC were observed for leptin or resistin. Our results suggest that elevated levels of circulating adiponectin are associated with decreased subsequent risk of RCC. These findings provide the strongest evidence to date, suggesting that the association between obesity and RCC is mediated at least in part through the effects of low adiponectin.

Introduction

The incidence of renal cell carcinoma (RCC), the predominant form of kidney cancer involving cancer of the renal parenchyma, varies worldwide, but is generally high in the USA and Europe (1,2). Obesity has consistently been associated with risk of RCC in a number of epidemiologic studies (3–9). Despite this well-established link between obesity and RCC, the mechanism through which obesity acts to increase cancer risk is unclear (10). Recently, several obesity-related biomarkers have been identified and proposed as the potential link between obesity and cancer (11). Of particular interest among these biomarkers are adipokines, peptide hormones secreted by adipocytes that influence a variety of proneoplastic mechanisms such as inflammation, insulin resistance and cell growth and proliferation (11–13). The adipokines adiponectin, leptin and resistin have demonstrated

particularly promising results as predictors of risk and progression in several other obesity-related cancers (14–16).

Adiponectin is produced exclusively by adipocytes and levels are reduced in obese individuals (17,18). Adiponectin is considered an insulin-sensitizing factor based on upregulated insulin signaling in certain tissues when adiponectin is administered (19), and may have antiinflammatory effects by inhibiting the production of inflammatory cytokines. Importantly, adiponectin activates adenosine monophosphate kinase, which results in inhibition of fatty acid synthesis, protein synthesis and proliferation, actions which might be expected to reduce cancer risk (20–22). Leptin is a peptide hormone produced predominantly by adipocytes that is elevated in obese individuals (23,24). The main function of leptin is to regulate body weight and appetite (25), but studies have strongly suggested that leptin plays a role in carcinogenesis through cell proliferation, angiogenesis, apoptotic inhibition and proinflammatory effects (13,26,27). In humans, resistin is predominantly the product of macrophages infiltrating the adipose tissue (28) and has been linked to inflammation, adiposity and insulin resistance (29–31). A proinflammatory role of resistin is suggested by the increased stimulation in the synthesis of several cytokines and proliferative properties (32).

There are limited epidemiologic data regarding the relationship of adipokines to RCC risk. A few case-control studies have observed postdiagnostic serum/plasma levels of adiponectin and leptin to be associated with RCC; however, the potential for reverse causation limits the interpretation of these findings (L.M. Liao, unpublished manuscript) (33–34). Prospective investigations are necessary to investigate the etiologic significance of circulating adipokine levels for RCC. To that end, we conducted a case-control study nested within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of Finnish male smokers to evaluate whether prediagnostic serum leptin, adiponectin and resistin levels were associated with future RCC risk.

Materials and methods

Study population

The ATBC study is a randomized intervention trial that tested whether α -tocopherol and/or β -carotene supplementation reduced the incidence of cancer in Finnish male smokers. The study rationale, design and methods have been described in detail previously (35). Briefly, the ATBC cohort consists of 29 133 eligible men aged 50–69 years in southwestern Finland who smoked at least five cigarettes per day at study entry (between 1985 and 1988). Men were excluded from the study if they had a history of cancer. At baseline, participants completed a questionnaire on background characteristics, lifestyle behaviors and medical history. Height, weight and blood pressure were measured using standard methods. Body mass index (BMI) was calculated from measured height and weight (kg/m²). All study participants provided written informed consent prior to study enrollment, and the study protocol was approved by the institutional review boards of both the National Public Health Institute in Finland and the US National Cancer Institute.

Included in this nested case-control study are 273 incident RCC cases and 273 matched controls that provided a blood sample at the baseline visit. Incident RCC cases (ICD-9 code 189.0) diagnosed through April 2006 were identified through the Finnish Cancer Registry, which provides almost complete case ascertainment in Finland (36). Controls were randomly selected from ATBC cohort members and individually matched to cases (1:1 ratio) by age at randomization (± 5 years) and date of baseline blood collection (± 30 days). Controls were also alive and free of RCC at the time of cancer diagnosis for their corresponding case.

Blood collection and laboratory procedures

At baseline visit, fasting blood samples were collected and stored frozen at -70°C until analyzed (35). Serum measurements of adipokines were conducted in the laboratory of Dr Michael Pollak at Jewish General Hospital, Montreal, Canada (14). Leptin, total adiponectin and resistin concentrations were assayed using standard techniques of enzyme-linked immunosorbent assay with commercial reagents from Millipore (Billerica, MA). Samples

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI, body mass index; CI, confidence interval; OR, odds ratio; RCC, renal cell carcinoma.

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 48 blinded replicate samples placed randomly in each batch demonstrated high assay reproducibility with overall coefficients of variation for leptin, adiponectin and resistin of 6.8, 6.6 and 12.1%, respectively.

Statistical analysis

Differences between paired cases and controls were tested for statistical significance using the McNemar's or Bowker's test for categorical variables and the Wilcoxon signed-rank tests for continuous variables. Spearman correlations were calculated between each adipokine and BMI at blood collection. Circulating levels of leptin, adiponectin and resistin were categorized into quartiles by cutpoints determined by the distributions among controls. To investigate associations across a broader range of analyte concentration, the highest quartile was further split in half based on the distributions among controls. We computed odds ratios (OR) and 95% confidence intervals (CI) for the association between leptin, adiponectin and resistin levels and RCC using conditional logistic regression models with adjustment for the following potential confounders: number of years smoking, presence of hypertension (indicated history of hypertension through questionnaire or had measured blood pressure readings at baseline of systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg), history of diabetes and physical activity level [(i) light/sedentary (e.g. reading, watching television), (ii) moderate (e.g. walking, hunting, gardening fairly regularly) or (iii) heavy (e.g. running, skiing, swimming fairly regularly)]. Tests for trend were calculated by modeling the median value within each category. Continuous ORs were standardized to the average size of the two central quartiles, such that the OR for an analyte corresponded to a 25% increase in serum concentration. Analyses excluding cases diagnosed within 2 years of blood collection ($n = 29$) were conducted to minimize the potential influence of undiagnosed disease. We also considered a separate model with an adjustment for BMI at the time of blood collection in order to explore whether adipokines could be mediating the association with obesity or vice versa. In addition, analyses stratified by BMI (BMI < 25, 25–30 and 30+ kg/m²) and number of cigarettes smoked per day (≤ 20 and >20) were conducted, using unconditional logistic regression and adjusting for matching factors and potential confounders, to evaluate potential effect modification. Effect modification was assessed by cross-product terms composed of continuous adipokines and categorical variables in a multivariate model. All statistical tests in the analysis were two-sided and all analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Some selected characteristics of study cases and controls are summarized in Table I. Compared with controls, cases had a higher BMI ($P = 0.07$), a longer smoking duration ($P = 0.03$) and were more likely to have been diagnosed with hypertension ($P = 0.005$). The median length of follow-up from blood collection to case diagnosis was

9.0 years (range, 0.1–19.9 years). Median concentrations of adiponectin were higher for controls (7923.5 ng/ml) than cases (7800.4 ng/ml; $P = 0.05$). Leptin and resistin concentrations were not significantly different between cases and controls. Among the controls, the Spearman correlations with BMI at blood collection for adiponectin, leptin and resistin were -0.49 (95% CI: $-0.58, -0.40$), 0.73 (95% CI: $0.67, 0.78$) and -0.07 (95% CI: $-0.18, 0.05$), respectively.

The highest category of adiponectin concentration was statistically significantly associated with a reduced risk of RCC [fourth quartile (Q4) versus Q1: OR = 0.52, 95% CI: 0.30–0.88; Table III]. When we subdivided Q4 using the intracategory median, the inverse association with RCC for the higher subcategory (Q4b) was even stronger (OR = 0.33, 95% CI: 0.16–0.69). When modeled continuously, each 25% increase in adiponectin was associated with a 13% decreased risk of RCC (OR = 0.87, 95% CI: 0.78–0.97; $P = 0.009$). The association between serum adiponectin and RCC did not materially change when we additionally adjusted for BMI at blood collection (Q4b: OR = 0.36, 95% CI: 0.16–0.78; P trend = 0.03) and excluded cases diagnosed within the first 2 years of follow-up (Q4b: OR = 0.40, 95% CI: 0.19–0.82; P trend = 0.04).

Results from analyses of serum leptin and resistin are summarized in Table II. We did not observe a clear relationship between leptin levels and RCC; the second quartile was associated with increased risk compared with the lowest quartile (OR = 2.17, 95% CI: 1.25–3.76), but the highest quartile was not (OR = 1.45, 95% CI: 0.82–2.56). A continuous association between leptin and RCC risk was not evident (OR = 0.93, 95% CI: 0.84–1.03). No association was observed between resistin concentrations and RCC risk.

We conducted analyses of BMI with adjustment for each adipokine to evaluate whether adipokine effects mediate the established relationship between obesity and RCC. In models evaluating the association between BMI and RCC risk, adjustment for adiponectin attenuated the BMI association, with the OR per 5 kg/m² increase changing from 1.19 (95% CI: 0.93–1.53) to 1.05 (95% CI: 0.80–1.39). Adjustment for leptin or resistin did not appear to have any noticeable effects on the BMI association (data not shown). We did not observe evidence of effect modification with BMI or number of cigarettes smoked per day for any of the adipokines (data not shown). We also did not observe any statistically significant changes in adipokine levels by the number of cigarettes smoked per day among controls (data not shown).

Discussion

In this prospective study, higher prediagnostic serum levels of adiponectin were statistically significantly associated with a reduced

Table I. Selected baseline characteristics of RCC cases and controls in the ATBC study

Characteristic	Cases ^a	Controls ^a	P value*
	($n = 273$)	($n = 273$)	
Age at randomization (years)	57 (53–61)	57 (53–61)	0.43
BMI (kg/m ²)	26.6 (24.5–28.7)	25.9 (23.8–28.2)	0.07
Alcohol intake (g/d)	9.7 (2.0–21.3)	10.6 (2.8–25.1)	0.37
Smoking history			
Cigarettes smoked/day	20 (15–25)	20 (15–25)	0.57
Years of smoking	37 (32–42)	36 (30–42)	0.03
Primary school education or less (%)	213 (78.0)	214 (78.4)	0.92
Physical activity leisure			
Light	122 (44.7)	111 (40.7)	
Moderate	146 (53.5)	146 (53.5)	
Heavy	5 (1.8)	16 (5.9)	0.08
Presence of hypertension	194 (71.1)	162 (59.3)	0.005
History of diabetes	10 (3.7)	11 (4.0)	0.83
Adiponectin concentration (ng/ml)	7800 (5921–9809)	7924 (6306–11 117)	0.05
Leptin concentration (ng/ml)	4.56 (2.47–7.87)	4.23 (1.91–7.84)	0.36
Resistin concentration (ng/ml)	9.27 (7.54–11.23)	9.28 (7.31–11.13)	0.90

^a n (%) or median (interquartile range) are presented.

* P value for continuous variables were based on Wilcoxon signed-rank test. P value for categorical values were based on the McNemar's or Bowker's test.

Table II. Associations between serum levels of adiponectin, leptin and resistin and RCC

Concentration (ng/ml)	Leptin				Resistin				
	Cases	Controls	OR ^a	95% CI	Concentration (ng/ml)	Cases	Controls	OR ^a	95% CI
Continuous OR ^b			0.87	0.78–0.97	Continuous OR ^b			0.93	0.84–1.03
Q1 (≤6306)	84	69	1.00		Q1 (≤7.31)	43	69	1.00	
Q2 (>6306 and ≤7923)	59	68	0.71	0.44–1.15	Q2 (>1.91 and ≤4.23)	84	69	2.17	1.25–3.76
Q3 (>7923 and ≤11117)	82	68	0.93	0.58–1.48	Q3 (>4.23 and ≤7.84)	77	67	1.72	0.99–2.97
Q4 (>11117)	48	68	0.52	0.30–0.88	Q4 (>7.84)	69	68	1.45	0.82–2.56
Q4a (>11117 and ≤14246)	32	34	0.72	0.38–1.35	Q4a (>7.84 and ≤11.93)	50	34	2.06	1.10–3.87
Q4b (>14246)	16	34	0.33	0.16–0.69	Q4b (>11.93)	19	34	0.73	0.34–1.57
<i>P</i> trend*				0.01	<i>P</i> trend*				0.44
									0.45

^aConditional logistic regression adjusted for number of years smoking, presence of hypertension, history of diabetes and physical activity.

^bContinuous variables were standardized to the average size of the two central quartiles. Therefore, OR change of one unit corresponds to a 25% increase in serum concentration relative to the control distribution.

**P* trend calculated by modeling median of each category (Q1, Q2, Q3, Q4a and Q4b).

future risk of RCC. This association persisted even after adjustment for BMI and among cases diagnosed 2 years or longer from the date of blood collection. Further, model adjustment for adiponectin resulted in a substantial attenuation of the association between BMI and RCC, suggesting that adiponectin effects may act along the obesity–RCC causal pathway. No clear associations with RCC risk were observed for leptin or resistin levels.

Adiponectin, an insulin-sensitizing hormone, is produced specifically by adipose tissue and has antiinflammatory and antiangiogenic properties (27,37,38). Experimental studies suggest that adiponectin exerts its effects on carcinogenesis mainly through binding to adiponectin receptors and the subsequent activation of the adenosine monophosphate kinase signaling pathway (20–22). Adiponectin has also been associated with binding to T-cadherin, a receptor in endothelial and smooth muscle cells, which plays a role in cell adhesion and calcium-mediated cell signaling (39). T-cadherin may serve as a coreceptor for adiponectin and compete with binding to adiponectin receptors; however, its role in adiponectin signaling is still not fully characterized. Adiponectin levels have been reported to be significantly decreased with obesity (17,18) and were inversely associated with BMI in our controls ($r = -0.49$). In our study, the adiponectin association did not disappear when adjusted for BMI, and adjustment for adiponectin appeared to substantially attenuate the BMI association with RCC risk. This would suggest that the established association between obesity and RCC may be partly mediated through the effects of adiponectin. The BMI association with RCC risk observed in our nested case–control study is slightly lower than what was reported in a recent meta-analysis (1.19 versus 1.24 per 5 kg/m² (40)); this may be a reflection of the composition of the ATBC cohort, comprised entirely of Finnish male smokers. Adiponectin may inhibit RCC development through antiinflammatory or antiangiogenic pathway. Adiponectin receptors, AdipoR1 and R2, are expressed in normal and renal tumor tissue but appear to be downregulated in tumor tissue compared with normal tissue (19,41). Elevated adiponectin levels have been associated with a reduced risk of several different cancer sites (14,42–47). Previous case–control studies evaluating adiponectin levels and RCC risk have yielded mixed results and observed associations might be due to reverse causality (L.M.Liao, unpublished manuscript) (34). Although leptin is a more well-established indicator of total adiposity than adiponectin, we suspect that the effects of adiponectin are only in part due to its association with obesity and adiposity.

We did not observe a clear association with RCC for circulating levels of leptin or resistin. Previous case–control studies of RCC evaluating leptin and resistin have also generated inconsistent results (L.M.Liao, unpublished manuscript) (33). The collective evidence to date does not support a role in RCC pathogenesis for these analytes.

To our knowledge, this is the first study to evaluate the relationship between leptin, adiponectin and resistin and RCC risk using prospectively collected serum samples. The prospective nature of the study reduces the possibility of reverse causality on our observed associations. Our study benefited from the use of prediagnostic serum samples, but we are limited to a single measurement that may not accurately capture adipokine levels over time. Additionally, all participants were male smokers and results may not be generalizable to populations that include women and non-smokers.

In conclusion, in this prospective study, we observed an association between higher serum levels of adiponectin and reduced risk of RCC. Our findings offer the strongest evidence to date suggesting that adiponectin effects may at least partly mediate association between obesity on RCC risk. Although the adiponectin association is promising, further research in other prospective studies is needed to confirm this finding. If confirmed, the potential benefit of higher adiponectin levels may lead to an increased interest in evaluating adiponectin as a therapeutic target (48), with studies focused on the upregulation of adiponectin production through pharmacological interventions. Given the presence of adiponectin receptors in renal tissue, a therapeutic application for adiponectin in RCC treatment is possible (48,49).

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