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Research paper

Insulin resistance and risk of renal cell cancer: a case-control study

Themistoklis N. Spyridopoulos,[1] Nick Dessypris,[1] Antonis G. Antoniadis,[1] Spyros Gialamas,[1] Constantine N. Antonopoulos,[1] Konstantina Katsifoti,[2] Hans-Olov Adami,[3,4] George P. Chrousos,[5] Eleni Th. Petridou,[1] and the Obesity and Cancer Oncology Group*

[1]Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, [2]1st Department of Internal Medicine, General Hospital of Athens "G. Gennimatas", Athens, Greece, [3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, [4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA, [5]1st Department of Pediatrics, Athens University Medical School, Athens, Greece

*Members of the Obesity and Cancer Oncology Group in the Renal Cancer Study: a) Giannopoulos Aris, 1st Department of Urology, Athens University Medical School, Athens, Greece, b) Alivizatos Gerasimos, 2nd Department of Urology, Athens University Medical School, "Sismanoglion Hospital", Athens, Greece, c) Vassilakis George, Department of Urology, General Hospital of Athens "G. Gennimatas", Athens, Greece, d) Kalogeropoulos Theodore, Department of Urology, "Saint Savvas" Anticancer Hospital, Athens, Greece

ABSTRACT

OBJECTIVE: Obesity and diabetes are considered risk factors for Renal Cell Carcinoma (RCC). We aimed to explore whether insulin resistance (IR) plays an independent role in the development of RCC. DESIGN: In a hospital-based case-control study, we analyzed serum glucose, insulin, leptin and adiponectin levels among 60 incident RCC patients and 236 age- and gender-matched healthy controls. We assessed insulin resistance according to insulin levels, alone or controlled for diabetes mellitus (DM). An alternative measure of insulin resistance, such as the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) index, was also assessed with and without controlling for history of DM. We used logistic regression to estimate odds ratios (ORs) adjusted for possible confounders. RESULTS: The positive association of DM and waist to hip ratio as a measure of obesity with RCC was evident in the data set. Insulin levels controlled or not controlled for DM, however, were inversely associated with the risk for RCC; notably, an approximately 40% higher risk was observed in the 1st tertile when compared with the 2nd and 3rd tertile levels of insulin resistance. Similar results were obtained when HOMA-IR was alternatively used. The inverse associations persisted and were even strengthened after controlling for potential confounding factors in multivariate analyses. CONCLUSIONS: Our

Address for correspondence:
Eleni Th. Petridou MD, MPH, Professor of Preventive Medicine and Epidemiology, Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 75 Mikras Asias Str., Goudi, Athens 11527, Greece, Tel.: +30 210 7462187, Fax: +30 210 7462105, E-mail: epetrid@med.uoa.gr

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data suggest that insulin resistance may be inversely associated with RCC risk, independently of obesity, DM, lifestyle and hormonal confounding variables. Given the close interconnections among metabolic, inflammatory and immune pathways in RCC causation, it is difficult to infer which process actually initiates a pathologic cascade. The findings should be considered as preliminary data that need to be further confirmed in more appropriate study designs.

Key words: Renal Cell Carcinoma, Obesity, Insulin resistance, HOMA-IR, Leptin, Adiponectin

INTRODUCTION

The etiology of renal cell cancer (RCC) is still rather obscure, with obesity and diabetes mellitus (DM) being the most widely accepted risk factors among men and women.[1,2] Epidemiological studies have indeed suggested that the increasing prevalence of obesity may, at least partly, explain the rising incidence of RCC worldwide.[3,4] Insulin resistance (IR), which has been linked with the development and progression of cancer,[5] usually coexists with obesity, central body fat distribution, DM and subclinical inflammation.

Adipose tissue is considered an active endocrine organ, secreting numerous cytokines, chemokines and adipokines such as leptin and adiponectin; these hormones seem to play a central role in energy regulation and homeostasis of the immune system.[6] By inducing chronic activation of the innate immune response, obesity is also associated with chronic low-grade inflammation of adipose tissue, which can lead to insulin resistance and impaired glucose tolerance.[7,8]

In the past few years research findings have linked obesity, adipokines and carcinogenesis via pathways orchestrated by the complex network of soluble mediators derived from immune cells and adipocytes.[9] We previously reported the inverse association of RCC risk with adiponectin and leptin levels.[10,11] Given the positive association between obesity and RCC risk and the interactions of adipokines with IR, we aimed to further explore the potential relation of IR with RCC risk in a case-control study.

MATERIALS AND METHODS

Study population

The design, the sample collection and the methodology of the current study have been previously reported in detail.[10,11] Briefly, we included 60 consecutive patients aged 24 to 83 years (mean= 61.5, SD= 13.9), with newly diagnosed, histologically confirmed RCC, derived from four collaborating general hospitals in the Athens metropolitan area. Ten patients with other than RCC tumors (seven patients with transitional epithelium cancer and three with other renal malignancies) that were diagnosed during the study period were excluded from the study population because they may have a different etiology than RCC. None of the recruited patients had ever been previously diagnosed with any other type of cancer. In addition to the overall tumor staging, we used the TNM (Tumor-Node-Metastasis) system and the Fuhrman scale for tumor grading and we also classified tumors according to their histological subtype.[12-14]

Each case-patient was matched for age (±5 years), gender and county of residence to four healthy controls, who self-referred to participate in health screening examination at the collaborating hospitals. Controls had a negative self-reported medical history for cancer, hepatic disease, major hormonal or hematological disorders, asthma, autoimmune disease, HIV infection, advanced heart failure and recent myocardial infarction, chronic renal failure, acute pancreatitis, bone fracture or stroke. The same exclusion criteria applied for both patients and controls. Refusal rate was minimal among controls (<2%), whereas all patients agreed to participate in this study. Finally, 60 cases and 236 controls aged 23 to 87 years (mean= 61.4, SD= 14.2) comprised the study population.

Based on a pre-coded questionnaire, information concerning sociodemographics: age, gender, education (years), somatometrics: Body Mass Index (BMI, kg/m^2), Waist to Hip Ratio (WHR, %), lifestyle: cur-

rent smoking status, alcohol and coffee consumption and physical exercise (min/day) and medical history variables, including DM status (self-reported history of DM or glucose level higher than 125mg/dl), were recorded for each individual. Data was collected by personal interview performed by one of four trained interviewers, who were blinded to study hypothesis; each interview lasted about 30 minutes for both cases and controls and each interviewer interviewed about the same proportion of cases and controls. Somatometric variables were measured by specially trained health professionals using standard techniques (height, with subjects wearing no shoes; waist and hip circumference, with subjects wearing no clothes).[10,11]

The study protocol was approved by the University of Athens Medical School Ethics Committee, conformed to the Helsinki Declaration of 1975, and written informed consent was obtained from subjects prior to study enrolment.

Biochemical measurements

Fasting morning venous blood samples were obtained, properly stored in a deep freezer at -70°C. Blinded to case-control status they were air shipped with dry ice in one batch to the Beth Israel Deaconess Medical Center, Boston, MA, USA, for measurements of serum leptin and adiponectin levels, as previously described.[10,11] Human insulin levels were also measured via Radio-Assay (Millipore; Billerica, MA) with inter-assay CV of 2.9 - 6.0%, intra-assay CV of 2.2 - 4.4% and a sensitivity of 2 μU/mL. Average preservation time was similar for cases and controls and all samples were analyzed by the same technician. Insulin resistance was also estimated by calculating the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index, based on the equation HOMA-IR = Insulin (mU/L)* Glucose (mg/dL)/405.[15]

Statistical analysis

We calculated the mean value and standard deviation (SD) of insulin among the 60 RCC patients by tumor staging, grading and histological type. We then assessed differences among cases and controls with respect to socio-demographic, somatometric and lifestyle variables, as well as insulin, glucose, serum adiponectin and leptin, using the Wilcoxon, t-test or chi-square test, as appropriate. Spearman's correlation coefficients were also calculated to evaluate the association of insulin and HOMA-IR with age, BMI, WHR, physical activity, leptin, adiponectin and glucose. We used conditional logistic regression models to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of RCC. The main exposure variable was insulin and HOMA-IR analyzed in tertiles based on the distribution among the control-subjects (3.47-143.46mU/L and 0.83-33.30, respectively). We considered as potential confounders and adjusted in multivariate models for DM (categorical: yes vs no), education (ordered: 3 levels), physical activity (ordered: 30 min more), coffee consumption (categorical: yes vs rare or not), smoking status (categorical: yes/ex-smoker vs no smoker), alcohol consumption (categorical: 0, 1-31 and 32+ glasses/month), WHR (ordered: with increment of 5% more), BMI (ordered: with increment of 2kg/m^2), leptin and adiponectin (both ordered with increments of 1 SD among controls). The same models were run with insulin or HOMA-IR (both alone or controlled for DM). Statistical analyses were performed using the SAS statistical package (SAS v9, SAS Institute, Carry, NC version).

RESULTS

Insulin levels by tumor characteristics are displayed in Table 1. Stage I RCC comprised 42% of the cases and they presented with the highest levels of insulin. Apart from a decreasing trend of insulin levels with increased tumor stage, however, no statistically significant differences of insulin levels were observed among cases with respect to tumor staging ($p = 0.15$), grading ($p = 0.73$) and histological type ($p = 0.41$).

Table 2 shows the distribution of anthropometric, demographic, medical and lifestyle variables, as well as serum adiponectin, leptin and glucose for cases and controls. The results of this table serve mainly descriptive purposes as they may not be directly interpretable due to mutual confounding. Table 3 shows that among controls insulin levels were significantly positively correlated with BMI ($\rho = 0.36$, $p < 0.0001$), WHR ($\rho = 0.21$, $p = 0.001$), leptin ($\rho = 0.24$, $p = 0.0002$), glucose ($\rho = 0.32$, $p < 0.0001$) and negatively with adiponectin ($\rho = -0.21$, $p = 0.0001$) but not with physical activity. Similar results derived

Table 1. Mean values and standard deviations (SDs) of insulin by tumor staging, grading and histological type among 60 RCC patients

		Insulin		
Variable		**N**	**Mean**	**SD**
Stage				
I	$T_1N_0M_0$	25	17.63	26.9
II	$T_2N_0M_0$	14	16.08	9.44
III	$T_{3a}N_0M_0$ (N=8), $T_{3b}N_0M_0$ (N=3), $T_{3b}N_1M_0$ (N=4)	14	10.03	3.80
IV	$T_1N_0M_1$ (N=1), $T_1N_1M_1$ (N=1), $T_2N_1M_1$ (N=1), $T_{3b}N_2M_1$ (N=1), $T_{3c}N_2M_1$ (N=1), $T_4N_2M_1$ (N=3)	7	7.76	2.28
Grade				
1		5	16.02	15.54
2		22	12.96	5.65
3		20	17.48	30.30
4		9	12.52	5.33
Non-available		4	8.25	1.61
Histological type				
Clear cell		42	15.38	21.52
Papillary		8	15.50	7.80
Chromophobe		6	9.76	2.36
Collecting duct		1	8.16	-
Unclassified		3	7.94	1.02

when HOMA-IR levels were taken into account, respectively.

Results derived from the conditional logistic regression analyses are shown in Table 4. The positive association of WHR (OR = 2.24, 95%CI = 1.42-3.53) and DM (OR = 2.32, 95%CI = 0.95-5.66) with RCC risk was evident in our dataset (data not shown), as previously reported.[1,3,4] Insulin levels were inversely associated with the risk for RCC in the univariate model with an approximately 40% reduced risk in 2nd and 3rd tertiles compared with 1st tertile (Model 1). This association was even strengthened when DM and potential confounders were introduced in the full model 3 ($OR_{2nd\ tertile}$ = 0.24, 95%CI = 0.09-0.63, p = 0.0038; $OR_{3rd\ tertile}$ = 0.27, 95%CI = 0.09-0.82, p = 0.02). Likewise, when HOMA-IR, alone or controlled for DM, was introduced as an alternative measure of insulin resistance, the results were practically unchanged (Models 2 and 4, respectively).

DISCUSSION

In this hospital-based case-control study we found that two insulin resistance measures (insulin levels and HOMA) seem to be inversely associated with RCC risk. Adjustment for possible confounders, namely DM, WHR, education, smoking, coffee and alcohol consumption, physical activity, leptin and adiponectin serum levels, practically replicated the results.

Our study has important strengths and limitations. Strengths include high participation rates among eligible case-patients and control-subjects as well as strictly standardized procedures for personal interview, blood sampling and laboratory analyses. The number of participants was limited but large enough to refute the null hypothesis with confidence. Our most fundamental concern is selection bias among controls. Because population-based sampling is not feasible in our setting, we used a secondary source, namely individuals attending health screening procedures. We cannot provide proof that their exposure prevalence adequately reflects in the person-time that gave rise to our cases. As a corollary, our study should be considered hypothesis-generating for a malignancy with an incompletely understood etiology. Inherent limitations of our study design were the lack of the

Table 2. Distribution of 60 RCC patients and 236 age- and gender-matched controls by anthropometric, demographic, lifestyle, hormonal and medical history variables

Variable	**Cases**		**Controls**		**p-value**
Continuous variables	**Mean (SD)**		**Mean (SD)**		**Wilcoxon*/Student's t** test**
Age (years)	61.5 (13.90)		60.7 (14.37)		matched variable
BMI (kg/m^2)	27.3 (3.28)		27.7 (4.39)		0.60*
WHR (%)	100.4 (13.22)		93.4 (10.18)		0.0002*
Adiponectin (μg/ml)	9.43 (3.71)		10.15 (3.23)		0.14**
Leptin (ng/ml)	7.43 (7.12)		9.89 (9.90)		0.10*
Physical activity (min/day)	4.20 (7.47)		6.43 (6.52)		0.0001*
Glucose (mg/dL)	114.13 (45.06)		104.81 (39.64)		0.04*
	Cases		**Controls**		
Categorical/ ordinal variables	**N**	**%**	**N**	**%**	**p-value of x^2 for trend*/contrast****
Insulin (mU/L)					0.09
1st tertile (< 9.47)	26	43.4	72	30.5	
2nd (9.47- 13.96)	17	28.3	81	34.3	
3rd (> 13.97)	17	28.3	81	35.2	
HOMA-IR					0.54
1st tertile (< 2.25)	23	38.3	75	31.8	
2nd (2.25- 3.60)	17	28.3	81	34.3	
3rd (> 3.61)	20	33.4	80	33.9	
Diabetes Mellitus					0.001**
Yes	21	35	39	16.5	
No	39	65	197	83.5	
Gender					matched variable
Male	38	63.3	149	63.1	
Female	22	36.7	87	36.9	
Education (years)					0.07*
<6	7	11.6	27	11.4	
6-11	40	66.7	119	50.5	
12+	13	21.7	90	38.1	
Smoking					0.20**
yes/ex-smoker	39	65.0	132	55.9	
no	21	35.0	104	44.1	
Coffee					0.27**
Yes	55	91.7	204	86.4	
No	5	8.3	32	13.6	
Alcohol (glasses/month)					0.006**
0	17	28.3	38	16.1	
1-31	24	40.0	148	62.7	
32+	19	31.7	50	21.2	

time sequence criterion for causality, and the fact that no measurement of IGFs or other insulin resistance associated hormones and metabolites or their receptors were available. Despite its limitations, to our knowledge, this is the first study that investigated the association of insulin resistance with RCC risk.

Table 3. Spearman correlation coefficient ρ (p-values) of insulin and HOMA-IR with age, obesity indices, physical activity, serum leptin, adiponectin and glucose among controls

Variable	Age	BMI	WHR	Leptin	Adiponectin	Glucose	Physical activity
Insulin							
ρ (p-values)	-0.004 (0.95)	0.36 (<0.0001)	0.21 (0.001)	0.24 (0.0002)	-0.38 (<0.0001)	0.32 (<0.0001)	-0.10 (0.15)
HOMA-IR							
ρ (p-values)	0.12 (0.07)	0.36 (<0.0001)	0.27 (<0.0001)	0.22 (0.001)	-0.37 (<0.0001)	0.66 (<0.0001)	-0.10 (0.16)

Table 4. Conditional logistic regression-derived crude and mutually adjusted Odds Ratios and 95% Confidence Intervals (95% CIs) for RCC by Insulin and HOMA-IR (in tertiles) and study covariates

Variable	Category	ORs[1] (95% CIs)	ORs[2] (95% CIs)	ORs[3] (95% CIs)	ORs[4] (95% CIs)
Insulin	1st tertile	baseline		baseline	
	2nd	0.57 (0.28- 1.14)		0.24 (0.09-0.63)	
	3rd	0.56 (0.28- 1.11)		0.27 (0.09-0.82)	
Homa-IR	1st tertile		baseline		baseline
	2nd		0.68 (0.34-1.37)		0.24 (0.09-0.64)
	3rd		0.79 (0.40-1.59)		0.10 (0.02-0.40)

[1]Model 1: Unadjusted odds ratios for Insulin, [2]Model 2: Unadjusted odds ratios for HOMA-IR, [3]Model 3: Odds ratios for Insulin, adjusted also for Diabetes Mellitus, Leptin, Adiponectin, WHR, BMI, education, physical activity, coffee, smoking and alcohol consumption, [4]Model 4: Odds ratios for HOMA-IR, adjusted also for Diabetes Mellitus, Leptin, Adiponectin, WHR, BMI, education, physical activity, coffee, smoking and alcohol consumption

Previous studies have demonstrated not only the association of body fat mass with RCC risk, but also implied a role of adipose tissue distribution.[10,11,16] Adipose tissue is not an inert energy storage compartment, but an active endocrine organ. Obesity, as measured by BMI or WHR indices, is considered one of the main risk factors for RCC.[3] Moreover, obesity may lead to hyperinsulinemia and activation of the insulin-like growth factor 1 (IGF-1) pathway, which has been implicated in several types of cancer;[17] elevated IGF-1 levels have been reported, for example, among patients with cancer of the prostate, breast, colon and lung, as well as with leukemia.[18-22]

Insulin resistance, an underlying mechanism of the metabolic syndrome, is interrelated with obesity and adipokines.[23] Given the increasing trends of obesity worldwide and the association of adiposity with various cancer types, the current study aimed to investigate the association of IR as an independent risk factor with RCC risk and was part of a series of studies focusing on different cancer sites, e.g. lung,[24] melanoma.[25] The study findings confirmed the positive correlation of insulin and HOMA-IR with BMI, WHR, leptin and glucose, along with the negative correlation with adiponectin.[16,26]

With regard to the association of insulin resistance to RCC, the findings of the present study are in contrast to those derived from already studied cancer types. Of note, however, a recent study reported that IGF-1 levels were inversely associated with renal cancer risk.[27] Indeed, the IGF-1 receptor (IGF-1R) may be an important mediator of RCC chemoresistance, and RCC chemosensitivity is enhanced by IGF-1R depletion.[28] Previous studies have also shown that IGF-1R positivity on immunohistochemistry correlated with higher tumor grade and poor prognosis,[29,30] whereas another study demonstrated that IGF-1R expression predisposes to increased risk for RCC and correlates significantly with RCC grading and survival.[31]

We have previously reported an inverse association of leptin levels with RCC risk.[11] Leptin is known to be positively correlated with IR and this was also the case in the current investigation, as well as with IGF-1 levels. Leptin also plays a significant role in alerting immune system, since its congenital

deficiency as well as negative energy balance may alter the nature and vigor of the immune response by leptin-dependent mechanisms.[32] Since there is an overlap between signal-transducing pathways of leptin and insulin, a common pathogenesis of leptin and IR has also been suggested.[33] Thus, our findings may imply the preponderance of leptin's anti-tumor immunity effect on RCC.

In conclusion, this case-control study shows preliminary results of an inverse association of insulin resistance with RCC risk, independently of potential studied somatometric, lifestyle and hormonal confounding parameters. Given the close interconnections among metabolic, inflammatory and immune pathways, it is difficult to explicitly infer which process actually initiates a pathologic cascade. It is more likely that more than one pathogenetic mechanism is implicated to fit all the above parameters. This should be further explored, as the accumulating evidence in the field of RCC etiology needs to be confirmed by more appropriate study designs.

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