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ADIPOQ polymorphism rs182052 is associated with clear cell renal cell carcinoma

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Recent studies have indicated that low circulating adiponectin concentrations are associated with a higher risk of several cancers, including renal cell carcinoma. In this case–control study, we examined the frequency of single nucleotide polymorphisms (rs182052G>A, rs266729C>G, and rs3774262G>A) in the adiponectin gene (*ADIPOQ*) in 1004 patients with clear cell renal cell carcinoma (ccRCC) compared with a group of healthy subjects (n = 1108). Fasting serum adiponectin concentrations were also examined. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). The association of serum adiponectin concentration with genetic variants was calculated using a multivariate linear regression model. A significantly higher ccRCC risk was associated with the rs182052 variant A allele (adjusted OR, 1.36 and 95% CI, 1.07–1.74 for AA *vs* GG, P = 0.013; adjusted OR, 1.27 and 95% CI, 1.04–1.56 for AA *vs* GG+AG, P = 0.019), and this positive association was more evident in overweight subjects. Fasting serum adiponectin was lower in subjects carrying A alleles of rs182052 in both ccRCC patients (β = −0.399, P = 0.018) and healthy controls (β = −0.371, P = 0.024). These results suggest that *ADIPOQ* rs182052 is significantly associated with ccRCC risk.

Renal cell carcinoma is the most common malignancy derived from the kidney, and has been increasing in incidence over recent decades.[1] Both patient genetic background and environmental factors contribute to RCC pathogenesis;[2] indeed, loss of chromosome 3p is the most prevalent genetic alteration in ccRCC,[3] the major pathological type of RCC, while a mutation of the von Hippel–Lindau gene is observed in approximately two-thirds of ccRCC patients.[4] Growing evidence has demonstrated the association of SNPs with RCC risk that is dependent on ethnic origin. For example, vitamin D receptor polymorphisms (BsmI and FokI) were associated with an increased risk and progression of RCC in an Indian population,[5] although this was not observed in studies from Japan or Eastern Europe.[6,7]

The best-known environmental risk factor for RCC is tobacco smoking.[8] Factors with both genetic and environmental influences include male gender, hypertension, and obesity. Obesity is independently associated with increased long-term RCC risk,[9] and Bergstrom *et al.*[10] reported that increased BMI was equally strongly associated with an increased risk of RCC in both men and women. Obesity has also been proven to be associated with unfavorable RCC prognosis.[11]

The molecular basis underlying the contribution of obesity to RCC development is the subject of intensive investigation. Leptin, an adipocyte-derived cytokine that is closely correlated with obesity, was previously shown to be involved in RCC carcinogenesis. Both serum leptin levels and leptin receptor expression in RCC tissue were higher in patients with local progression, and elevated leptin levels were associated with shorter progression-free survival.[12] Moreover, leptin promoted the invasiveness of RCC cells *in vitro*.[13] Adiponectin is another important component of adipokines that is secreted predominantly by white adipose tissue and functions as a mediator between obesity and cancer. Circulating adiponectin concentrations are reduced in obese populations, and are inversely associated with both overall and central obesity independent of age and menopausal status.[14] Additionally, epidemiological studies found that lower serum adiponectin levels were linked with an increased incidence of cancers of the colon, breast, and endometrium.[15–17] Several SNPs in the gene encoding adiponectin (*ADIPOQ*) were associated with increased prostate cancer risk in Caucasians,[18] of which rs266729 was previously shown to be associated with an enhanced risk of lung, colon, and breast

cancers.[19–22] Recently, genetic variants of rs266729 and rs182052 SNPs were found to be associated not only with prostate cancer risk but also with different circulating adiponectin levels.[23] Furthermore, a study carried out in a Chinese population reported that rs3774262 was associated with both reduced cancer risk and obesity measurements.[24] However, no studies have investigated whether genetic variants of *ADIPOQ* contribute to RCC susceptibility.

In the present case–control study carried out in eastern China, we examined *ADIPOQ* polymorphisms in a group of patients with pathologically confirmed ccRCC (n = 1004) and a group of healthy subjects (n = 1108). Fasting serum adiponectin concentrations were also examined and analyzed according to *ADIPOQ* polymorphisms.

Materials and Methods

Subjects. The study included 1012 patients with pathologically confirmed ccRCC from Fudan University Shanghai Cancer Center (Shanghai, China) between January 2006 and December 2010. All cases were classified using the criteria of the American Joint Committee on Cancer's TNM classification. Among the patients, 870 cases received surgical intervention and 142 were diagnosed by percutaneous renal mass biopsy. BMI data of all the RCC patients were collected right after their admission to hospital. Fasting peripheral blood samples were obtained before surgery or biopsy and preserved at −80°C. Ninety-five patients reported a history of cytokine therapy before hospitalization, and no patients received chemotherapy or radiotherapy. A total of 2236 cancer-free individuals seeking physical examination at The Affiliated Hospital of Qingdao University (Qingdao, China) from January 2010 to December 2010 donated 5 mL peripheral blood after informed consent. Among them, 1125 individuals of appropriate age and sex for frequency matching with the cases were recruited as controls. All subjects were genetically unrelated eastern Chinese of Han ethnicity. Data on age, sex, BMI, smoking status, and history of hypertension were obtained from electronic medical records. The study protocols were approved by the Institutional Research Review Boards of Fudan University Shanghai Cancer Center and The Affiliated Hospital of Qingdao University. Written informed consent was obtained from all subjects before participation.

DNA extraction, SNP selection, and genotyping. Fasting blood samples from all subjects were obtained and stored at −80°C until use. Total genomic DNA was acquired using proteinase K digestion and phenol–chloroform extraction.

We selected *ADIPOQ* SNPs based on the following criteria: (i) reported to influence circulating adiponectin concentration; (ii) reported to be associated with cancer risk; (iii) with low linkage disequilibrium for each other ($r^2 < 0.8$); and (iv) with a minor allele frequency >5% in a Chinese population (http://snpinfo.niehs.nih.gov/). From these criteria, we selected three SNPs (rs182052, rs266729, and rs3774262) for further analysis.

The *Taq*Man genotyping master mix and predesigned primers and probes were purchased from Life Technologies (Carlsbad, CA, USA). Amplifications were run on a 7900 HT Real-Time PCR system (Applied Biosystems, Foster City, CA, USA), and allelic discrimination analyses were determined using SDS2.4 software (Applied Biosystems). To check reliability, genotyping was randomly repeated in 10% of samples, with 100% concordance achieved for all results. Eight ccRCC patients and 17 controls were excluded from the study because of unqualified DNA samples.

Serum adiponectin measurements. Serum samples were extracted from 327 ccRCC patients and 358 controls with different SNP genotypes, and adiponectin levels were measured using ELISA kits (Abcam, Cambridge, UK) according to the manufacturer's protocols. All assays were carried out in duplicate and average levels were used for analysis.

Statistical analysis. Differences in selected SNPs between cases and controls, as well as the Hardy–Weinberg equilibrium for the controls, were analyzed using Pearson's χ^2-tests. Unconditional logistic regression analysis was carried out to calculate the crude and adjusted ORs for ccRCC risk and 95% CIs, which were further stratified by demographic and pathological characteristics including age, sex, smoking status ("ever/current" or "never"), BMI, hypertension ("yes" or "no"), tumor staging, and Fuhrman grade. The association of serum adiponectin concentration with genetic variants was calculated using a multivariate linear regression model. All statistical tests were two-sided, and all analyses were carried out using SAS software (version 9.2; SAS Institute, Cary, NC, USA).

Results

Characteristics of study subjects. A total of 1004 ccRCC patients (median age, 57 years; age range, 13–86 years) and 1108 controls (median age, 57 years; age range, 21–86 years) were included in this study. No significant differences in age, sex, or smoking status were observed between groups. Overweight (BMI ≥25 kg/m^2) and hypertension were both positively associated with ccRCC risk. Fuhrman grades I, II, III, and IV were observed in 40, 380, 347, and 175 patients, respectively. A total of 809 ccRCC patients (80.6%) presented with clinical stage I and II disease, and 195 patients (19.4%) had clinical stage III and IV disease. Demographic characteristics are listed in Table 1.

Associations between *ADIPOQ* SNPs and risk of ccRCC. Control genotype distributions were in agreement with the Hardy–Weinberg equilibrium (P = 0.636 for rs182052, P = 0.143 for rs266729, and P = 0.106 for rs3774262). There is no significant association between these three SNPs and BMI. Compared with the GG genotype, the rs182052 variant AA genotype was associated with a significantly increased ccRCC risk (P = 0.013; OR, 1.36; 95% CI, 1.07–1.74) according to multivariate logistic regression analysis. A significant association was also observed in the recessive genetic model regarding rs182052 and ccRCC risk (P = 0.019; OR, 1.27; 95% CI, 1.04–1.56) after adjustment for age, sex, BMI, smoking status, and hypertension. We observed a trend of increased ccRCC risk as the number of A alleles increased. However, rs266729 and rs3774262 SNPs were not associated with ccRCC risk (Table 2).

Following stratified analysis, we found that the increased risk of ccRCC associated with rs182052 under a recessive genetic model was more evident in younger patients (<65 years of age), never smokers, and overweight patients, as well as in subgroups of stage I/II and Fuhrman III/IV. However, further homogeneity tests indicated that there were no significant differences in risk estimates between stratified subgroups, except for those with BMI ≥25 kg/m^2 (Table S1).

Associations between *ADIPOQ* SNPs and serum adiponectin levels. The SNP rs182052 was significantly associated with adiponectin levels after adjusting for potential confounders (Table 3). The A alleles of rs182052 were associated with lower levels of adiponectin (controls, β = −0.371, P = 0.024; cases, β = −0.399, P = 0.018). Neither rs266729 nor rs3774262 was correlated with serum adiponectin levels. Moreover, serum adiponectin concentrations did not differ between cases and controls (Table S2).

Table 1. Clinicopathological characteristics of 1004 patients with clear cell renal cell carcinoma and 1108 cancer-free controls from a Chinese Han population

Variable	Cases, *n* (%) 1004 (100)	Controls, *n* (%) 1108 (100)	*P*-value†
Age, years			
≤44	195 (19.4)	230 (20.8)	0.559
45–64	580 (57.8)	644 (58.1)	
≥65	229 (22.8)	234 (21.1)	
Sex			
Male	711 (70.8)	815 (73.6)	0.160
Female	293 (29.2)	293 (26.4)	
BMI, kg/m^2			
<25	480 (47.8)	589 (53.2)	0.014
≥25	524 (52.2)	519 (46.8)	
Smoking status			
Never	455 (45.3)	529 (47.7)	0.265
Ever/current	549 (54.7)	579 (52.3)	
Hypertension			
No	639 (63.6)	780 (70.4)	0.001
Yes	365 (36.4)	328 (29.6)	
Fuhrman grade			
I	40 (4.0)		
II	380 (37.8)		
III	347 (34.6)		
IV	175 (17.4)		
Missing	62 (6.2)		
Stage at diagnosis			
I	738 (73.5)		
II	71 (7.1)		
III	19 (1.9)		
IV	176 (17.5)		

†Pearson's χ^2-test.

Discussion

The current study revealed a significant association of *ADIPOQ* rs182052 variant genotypes with an increased ccRCC risk. Furthermore, serum adiponectin levels were lower in subjects carrying A alleles of rs182052. To the best of our knowledge, this is the first report of an association between *ADIPOQ* polymorphisms and ccRCC risk.

The incidence of obesity is increasing worldwide, and obesity-associated diseases, including cancers, have become a tremendous challenge for public health. A direct and independent relationship has been ascertained between RCC and obesity.[9] Although the underlying mechanisms of this remain unclear, promising evidence has revealed a critical role for adipokines. Adiponectin is a 30-kDa protein hormone with a collagen-like motif that can stimulate insulin secretion and increase fatty acid combustion and energy consumption.[25,26] Adiponectin levels were previously shown to be inversely correlated with insulin resistance and visceral obesity;[27] low levels of adiponectin may provide a link between obesity and RCC risk.[28] This protective role might be exerted directly on tumor cells by affecting signaling pathways involved in cell proliferation,[29] or indirectly on regulating insulin sensitivity through altering hormone and cytokine levels.[30]

Recent studies exploring the relationship between adiponectin and RCC have shown conflicting results. Spyridopoulos *et al.*[31] reported that adiponectin levels were inversely associated with RCC risk, and that this association remained significant after controlling for BMI. Moreover, lower circulating levels of adiponectin were independently found to be positively associated with larger tumor size and metastasis in patients with ccRCC.[32,33] However, Liao *et al.*[34] found that higher adiponectin levels were associated with increased RCC risk in an African American population, but not among Caucasians. Therefore, it is possible that adiponectin may link obesity and RCC risk with different quantitative effects according to race. In our study, there was no significant difference in circulating adiponectin levels between cases and controls. Apart from ethnic heterogeneity, we ascribe this discrepancy in part to our small sample size. Thus, further research is needed to elucidate the exact relationship between adiponectin and RCC.

Recently, accumulating evidence has implicated *ADIPOQ* polymorphisms in altering the risk of several cancers, although discrepancies exist among different ethnic origins. Kaklamani

Table 2. Association between *ADIPOQ* single nucleotide polymorphisms (SNP) and clear cell renal cell carcinoma risk

SNP	HWE	Cases, *n* (%)	Controls, *n* (%)	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value†
rs182052							
GG	0.636	249 (24.8)	315 (28.4)	1.00		1.00	
AG		485 (48.3)	544 (49.1)	1.13 (0.92–1.39)	0.253	1.11 (0.90–1.37)	0.331
AA		270 (26.9)	249 (22.5)	1.37 (1.08–1.75)	**0.010**	**1.36 (1.07–1.74)**	**0.013**
AG/AA *versus* GG				1.20 (0.99–1.46)	0.060	1.19 (0.98–1.45)	0.086
AA *versus* GG/AG				1.28 (1.04–1.57)	**0.019**	**1.27 (1.04–1.56)**	**0.019**
rs266729							
CC	0.143	502 (50.0)	572 (51.6)	1.00		1.00	
CG		398 (39.6)	434 (39.2)	1.05 (0.88–1.25)	0.635	1.05 (0.87–1.26)	0.633
GG		104 (10.4)	102 (9.2)	1.16 (0.86–1.57)	0.324	1.17 (0.86–1.58)	0.307
CG/*GG versus* CC				1.07 (0.91–1.29)	0.456	1.07 (0.90–1.27)	0.445
GG versus CC/CG				1.19 (0.83–1.59)	0.377	1.15 (0.86–1.54)	0.353
rs3774262							
GG	0.106	482 (48.0)	523 (47.2)	1.00		1.00	
AG		420 (41.8)	459 (41.4)	0.99 (0.83–1.20)	0.938	0.99 (0.82–1.19)	0.905
AA		102 (10.2)	126 (11.4)	0.88 (0.66–1.17)	0.381	0.90 (0.67–1.20)	0.463
AG/*AA versus* GG				0.98 (0.80–1.16)	0.711	0.97 (0.82–1.15)	0.722
AA *versus* GG/AG				0.88 (0.67–1.18)	0.372	0.90 (0.68–1.19)	0.465

Bold values indicate significance. †Adjusted for age, sex, BMI, smoking status, and hypertension. CI, confidence interval; OR, odds ratio; HWE, Hardy–Weinberg equilibrium.

Table 3. Association between *ADIPOQ* single nucleotide polymorphisms (SNP) and serum adiponectin levels

SNP	Cases			Controls		
	Beta	Crude *P*-value	Adjusted *P*-value†	Beta	Crude *P*-value	Adjusted *P*-value†
rs3774262	−0.083	0.587	0.643	−0.134	0.498	0.462
rs266729	0.256	0.174	0.153	0.137	0.483	0.456
rs182052	−0.399	0.015	0.018	−0.371	0.023	0.024

†Adjusted for age, sex, body mass index, smoking status, and hypertension.

et al.[18] examined the associations of five potential functional *ADIPOQ* SNPs with prostate cancer risk in a Caucasian population, and found that four, including rs266729, were risk-associated SNPs. However, two other studies showed no positive associations between rs266729 and rs182052 and prostate cancer risk.[35,36] Similarly, rs3774262 was identified as an endometrial cancer risk-associated SNP in Chinese women,[24] but was not associated with breast cancer risk.[37] Our study is the first to validate the relationship between these three cancer risk-associated SNPs and ccRCC risk. We found that the rs182052 variant AA genotype was associated with an increased ccRCC risk, and observed a trend toward an increased ccRCC risk as the number of A alleles increased, suggesting a cumulative effect of genetic variants on ccRCC risk.

Previous GWAS have identified several SNPs that were associated with RCC susceptibility, such as rs11894252 and rs7579899 on 2p21, and rs718314 and rs1049380 on 12p11.23.[38,39] In these GWAS, no gene polymorphisms in the *ADIPOQ* gene were discovered. However, these GWAS have been carried out mainly in European countries and North America, and most of the subjects were Caucasian. As we know, genetic susceptibility may differ by race, and natural selection may lead to genetic diversity that might be sensitive to local environment. Lack of replication of genetic associations or the observation of different associations may be related to many factors, such as insufficient power, differences in study population characteristics, allelic heterogeneity, allele frequency and/or linkage disequilibrium differences across various ethnic groups, population stratification, differences in effect sizes, and gene–environment interactions.[40] For example, linkage disequilibrium patterns often vary across populations, which might affect the strength of indirect associations. Therefore, further studies combining more anthropometric measurements are necessary to validate our observations in a large-scale population. In our stratified analysis, individuals carrying the *ADIPOQ* rs182052 AA genotype manifested different risks of ccRCC. The increased risk under a recessive genetic model was more evident in patients younger than 65 years of age, those who never smoked, and overweight patients, as well as in subgroups of stage I/II and Fuhrman III/IV, although after homogeneity analyses were carried out for these significant findings, only weight remained a significant factor. Obesity is considered a risk factor in the etiology of RCC, and was shown to accentuate the metabolic machinery in RCC cells through adiponectin deficiency in obese individuals.[28] It was also reported that the association of *ADIPOQ* polymorphisms with increased cancer risk may be limited to obese individuals.[41] Although the cross-talk between obesity, adiponectin, and RCC carcinogenesis has not been well elucidated, our observation provides further evidence that *ADIPOQ* variants may be associated with ccRCC risk through a complicated correlation with obesity.

Our modified results should be interpreted with caution, and some findings may reflect the limited sample sizes of the subgroups. For example, smoking is a well-known risk factor of RCC, and various types of DNA damage may be involved in smoking-related carcinogenesis.[42] However, we did not obtain detailed information about the smoking status of the patients in the present study, such as duration of smoking or number of cigarettes smoked. It is important to note other limitations of the present study. Although it is the first to evaluate the association of *ADIPOQ* variants with ccRCC risk, a limited number of SNPs was included and additional robust replications are lacking. Moreover, cases and controls were not recruited during the same period, so some selection and information biases may exist in this hospital-based case–control study. However, the frequency-matching nature between cases and controls and the adjustment for potential confounding factors during analyses may minimize these biases. Additionally, adiponectin is thought to be an important mediator bridging obesity to RCC, and evidence suggests that waist circumference is more closely related to metabolic changes compared with BMI,[43,44] yet the assessment of obese status was implemented only by BMI in our study. Thus, further studies combining more anthropometric measurements are necessary to validate our observations in a large-scale population.

In conclusion, the current case–control study found that a G to A allelic substitution of the *ADIPOQ* rs182052 SNP was associated with a significantly higher risk of ccRCC, and likewise associated with lower circulating adiponectin levels. Our study provides further evidence for the role of adiponectin in ccRCC development, but requires validation from well-designed prospective studies with larger patient groups from different races.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

BMI	body mass index
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
GWAS	genome-wide association studies
OR	odds ratio
RCC	renal cell carcinoma
SNP	single nucleotide polymorphism

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Stratification analysis for association between *ADIPOQ* single nucleotide polymorphisms and clear cell renal cell carcinoma risk by recessive genetic model in Chinese men.

Table S2. Serum adiponectin levels in cases and controls to assess the clear cell renal cell carcinoma risk.