Original Contribution

Joint Association of Genome-Wide Association Study–Identified Susceptibility Loci and Dietary Patterns in Risk of Renal Cell Carcinoma Among Non-Hispanic Whites

Stephanie C. Melkonian, Carrie R. Daniel, Michelle A. T. Hildebrandt, Nizar M. Tannir, Yuanqing Ye, Wong-Ho Chow, Christopher G. Wood, and Xifeng Wu*

* Correspondence to Dr. Xifeng Wu, Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Unit 1340, 1155 Pressler Boulevard, Houston, TX 77030 (e-mail: xwu@mdanderson.org).

Initially submitted March 7, 2014; accepted for publication May 22, 2014.

Dietary factors may affect risk of renal cell carcinoma (RCC). In an ongoing case-control study of RCC initiated in Houston, Texas, in 2002, we identified 3 empirically derived dietary patterns: “fruits and vegetables,” “American/Western,” and “Tex-Mex.” Among 659 RCC cases and 699 controls, we evaluated associations of these dietary patterns with RCC risk and whether the associations varied by obesity status, smoking status, physical activity level, history of hypertension, and genetic variants previously identified via genome-wide association studies. Among persons in the highest categories of adherence versus the lowest, the “fruits and vegetables” dietary pattern was associated with an approximately 50% lower RCC risk ($P_{\text{trend}} < 0.001$), while “American/Western” dietary pattern scores were positively associated with a 2-fold higher risk ($P_{\text{trend}} < 0.001$). We observed synergistic interaction between the American/Western pattern and hypertension status: The odds ratio (highest tertile vs. lowest) among persons with hypertension was 2.23 (95% confidence interval: 1.43, 3.45), as compared with 1.76 (95% confidence interval: 1.16, 2.70) among persons without hypertension (additive $P_{\text{interaction}} = 0.01$). A variant (rs718314) in the inositol 1,4,5-trisphosphate receptor, type 2 gene (*ITPR2*) was found to interact with the American/Western dietary pattern in relation to RCC risk (additive $P_{\text{interaction}} = 0.03$). *ITPR2* has been shown to affect nutrient metabolism and central obesity. Dietary patterns, genetic variants, and host characteristics may individually and jointly influence susceptibility to RCC.

case-control studies; dietary patterns; gene-diet interaction; renal cell carcinoma

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; GWAS, genome-wide association study; *ITPR2*, inositol 1,4,5-trisphosphate receptor, type 2 gene; MET, metabolic equivalent; OR, odds ratio; RCC, renal cell carcinoma; SNP, single-nucleotide polymorphism.

In 2013, kidney cancer accounted for approximately 5% of new cancer cases in the United States, 85% of which were classified as renal cell carcinomas (RCCs) (1). Smoking, obesity, and hypertension have been linked to RCC; however, the etiology of RCC remains poorly described. Previous studies have suggested that various foods and nutrients may play a role in RCC risk (2, 3). Dietary intake of fiber and fiber-rich foods (4), vitamins (5, 6), fat (7), proteins (8), fruits (9), vegetables (10, 11), and red meat (6, 11) have been associated with RCC etiology in some studies but not in others (12–14). Therefore, associations between dietary intake and RCC etiology remain inconclusive.

Diets consist of correlated intakes of many foods and nutrients that can potentially interact to influence disease outcomes and risk. Measuring dietary patterns, rather than specific nutrient or food intakes, may be an alternative methodology for estimating diet-related disease risks (15). Data are available to suggest that dietary patterns derived from factor analysis can predict disease risk and mortality, including risk of various cancers (16–18). However, few studies have utilized factor analysis to evaluate associations between dietary intake patterns and RCC risk (19, 20).

Recently, genome-wide association studies (GWAS) have identified 6 common genetic variants associated with RCC

etiology (21–23). Some of these single-nucleotide polymorphism (SNPs) are located near genes related to nutrient uptake, metabolism, and obesity, such as the inositol 1,4,5-trisphosphate receptor, type 2 gene (*ITPR2*) and the scavenger receptor class B, member 1 gene (*SCARB1*)—a receptor for high-density lipoprotein cholesterol (22, 23). Therefore, genetic variation may potentially modify the association between dietary intake and RCC risk.

In a large study of newly diagnosed RCC patients and healthy controls, we investigated whether empirically derived dietary patterns were associated with RCC risk and whether these associations varied according to known and suspected RCC risk factors, including smoking, hypertension, and obesity. To our knowledge, this is the first study to have investigated potential interactions between genetic predisposition to RCC, as defined by previously GWAS-identified genetic variations, and dietary patterns in relation to RCC risk in a case-control study of newly diagnosed RCC patients and healthy controls.

METHODS

Study population and recruitment

RCC patients were drawn from an ongoing case-control study of RCC initiated in Houston, Texas, in 2002 (24). The study was approved by the M. D. Anderson Institutional Review Board. The procedures for subject recruitment and eligibility criteria have been previously described (24). All case subjects were newly diagnosed with histologically confirmed RCC. Healthy control subjects without a history of cancer, except nonmelanoma skin cancer, were identified and recruited via random-digit dialing (25). Control subjects were frequency-matched to case subjects according to age (± 5 years), sex, ethnicity, and county of residence. All participants provided written informed consent prior to participation in the study. Epidemiologic data were collected by M. D. Anderson staff interviewers in an in-person interview. After the interview, a 40-mL blood sample was collected from each participant and delivered to the laboratory for molecular analysis.

Data collection

We used a previously validated modified version of the National Cancer Institute Health Habits and History Questionnaire (26). This food frequency questionnaire (FFQ) asks participants about their consumption of 165 food and beverage items, including ethnic foods commonly consumed in the Houston area, and contains an open-ended section regarding dietary behaviors such as dining in restaurants and food preparation methods. For each item consumed, the participant was also queried about portion size. Total energy intake and amount consumed (g/day) were estimated for each food item using the US Department of Agriculture Food and Nutrient Database for Dietary Studies (27).

Covariate data included history of hypertension prior to diagnosis or recruitment, alcohol use, physical activity level, and smoking status. Alcohol use was adjusted for total caloric intake using the residual method and divided into tertiles based on the distribution in the controls for males and females separately.

A person who had never smoked or had smoked fewer than 100 cigarettes in his or her lifetime was defined as a never smoker. A person who had smoked at least 100 cigarettes in his or her lifetime but had quit at least 12 months prior to diagnosis (for cases) or interview (for controls) was classified as a former smoker. Current smokers were defined as persons who were currently smoking or had quit less than 12 months before diagnosis (for cases) or interview (for controls).

Weight and height at diagnosis (for cases) or recruitment (for control subjects) was recorded. Body mass index (weight (kg)/height (m)²) was derived from weight and adult height. Body mass index was categorized according to the standard classification of the World Health Organization (normal = <25 ; overweight = 25 – 29.9 ; obese = ≥ 30).

Participants also reported the average number of times they had undertaken activities in each of 5 broad groups during the year before the interview. Individual activities included active sports, physical exercises, swimming, walking (including walking for golf), cycling, gardening or yard work, hunting, housework, and other strenuous exercises. A metabolic equivalent (MET) value was assigned on the basis of the energy cost of each activity group (28). Energy expenditure from physical activity was calculated as the MET value of each activity multiplied by the frequency of each activity; data were then summed across all activities. Weekly METs of total activity were categorized into tertiles based on the distribution in control subjects.

Exclusions and eligibility

Exclusion and inclusion criteria for the parent case-control study have been described in detail elsewhere (24). We additionally excluded persons with outlying total energy intake by removing men ($n = 33$) and women ($n = 34$) with values that fell outside the interval delimited by the 25th percentile minus 1.5 times the interquartile range and the 75th percentile plus 1.5 times the interquartile range. Because of the small number of minority participants ($n = 91$), we limited the analysis to non-Hispanic whites only, leaving 1,358 persons (659 cases and 699 controls) for inclusion in the present study.

Food grouping and dietary pattern analysis

Of the 165 food and beverage items queried about using the FFQ, 125 items were included in the present analysis. We excluded alcoholic beverages (due to potential independent associations with RCC risk) and foods with low levels of consumption in the study population (mole, meat substitute, ham hocks, and boudain). We also excluded food additions that were considered to contribute minimally to total dietary intake, including milk used on cereal, butter used on toast, soy sauce, and mayonnaise.

Several foods were grouped into predefined food groups according to current US Department of Agriculture food-group guidelines. Vegetables were categorized as deep yellow (squash, carrots, sweet potatoes, green and red peppers), cruciferous (beets, broccoli, cauliflower, red and green cabbage), or dark leafy (raw/cooked spinach, collard greens, salad). Berries (strawberries, blueberries, other berries) and low-fat dairy items (low-fat yogurt, cottage cheese, and low-fat cream

cheese) were grouped into separate categories. We evaluated the correlation matrix of the foods to determine whether it was factorable through both visual inspection of the matrix and statistical measures such as the Kaiser-Meyer-Olkin measure (29).

For each of the 125 remaining food items (measured in g/day) we added 1 g/day (to avoid food intake values of zero) and then log-transformed data for each of the 125 food items to obtain an approximately normal distribution. All nutrient intakes were adjusted for total energy intake using the residual method (30).

We then applied exploratory factor analysis to reduce the food groups into a small number of factors that explained the maximum fraction of variance in the data. We used a varimax rotation, an orthogonal rotation procedure, to create uncorrelated and normally distributed factors (31). The number of factors that best represented the data (3 factors) was chosen on the basis of eigenvalues greater than 1, identification of a break point in the scree plot, and interpretability. Foods or food groups with an absolute loading greater than 0.25 on a given factor were considered as contributing to that factor.

Factors were subsequently interpreted as dietary patterns and named after the foods or food groups with the highest loadings. Estimated factor scores were computed for each individual as a linear combination of the standardized intake values multiplied by their respective factor loadings. Tertiles of dietary pattern factor scores were created using the distribution of intake in the controls, by sex, with the first tertile corresponding to the lowest factor score or level of adherence to that dietary pattern. Dietary pattern analysis was carried out with the FACTOR command in Stata 10.0 (StataCorp LP, College Station, Texas). Dietary patterns were subsequently assessed for controls only, as well as for males and females separately. Resulting dietary patterns were similar and are not shown here.

Genotyping and selection of SNPs

We selected 6 SNPs previously identified through recent GWAS as showing significant or marginally significant associations ($P < 10^{-6}$) with RCC risk: rs12105918, rs10054504, rs718314, rs7579899, rs7105934, and rs4765623 (21–23). Genomic DNA was extracted from peripheral blood using a QIAmp DNA extraction kit (Qiagen, Inc., Valencia, California) and genotyped by means of TaqMan genotyping assays (Applied Biosystems, Inc., Foster City, California) on the 7900HT Sequence Detection System (Life Technologies, Grand Island, New York) according to the manufacturer's protocol. Each run included negative controls (water) and 5% of samples as replicates. Concordance was 100%. All SNPs were in Hardy-Weinberg equilibrium ($P > 0.05$).

Statistical analysis

Comparisons of case-control characteristics were performed using Pearson's χ^2 test for categorical variables and Student *t* tests for continuous variables. Unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals for the associations between tertiles of dietary pattern scores and RCC risk. Associations for dietary

pattern tertiles were adjusted for sex and age. Multivariable models included further adjustment for factors selected a priori on the basis of hypothesized associations with RCC risk and/or dietary intake patterns, including age (years; continuous), sex, smoking status (ever smoker/never smoker), alcohol intake (energy-adjusted tertiles), history of hypertension (yes/no), and total energy intake (kcal/day; continuous). Obesity (body mass index ≥ 30) was significantly associated with case-control status in this data set (not shown). Therefore, covariate adjustment included a dichotomous indicator for obesity (obese (body mass index ≥ 30) vs. overweight/normal-weight (body mass index < 30)). Tests for trend were conducted by including an ordinal exposure variable in the model.

We also examined how known RCC risk factors and GWAS-identified genetic variants may modify the association between dietary intake patterns and RCC risk. The association between each previously identified SNP and RCC risk was initially tested in this study sample via unconditional logistic regression adjusted for sex and age, using the homozygous major genotype as the reference category. We subsequently carried out multivariable-adjusted stratified analyses of risk according to known and suspected RCC risk factors, including sex, age (< 60 years, ≥ 60 years), obesity, smoking, hypertension, alcohol use, and physical activity level, in addition to 6 previously identified genetic variants using the dominant model. We tested for multiplicative interaction by including the cross-product term of the dichotomous risk-factor variables and ordinal dietary pattern variables in the logistic regression model. The statistical significance of the interactions was determined using the Wald statistic for the cross-product term. Additive interaction was assessed by means of the relative excess risk due to interaction (32). *P* values and 95% confidence intervals (bias-corrected and accelerated) were determined using 1,000 bootstrap samples (33).

RESULTS

The Kaiser-Meyer-Olkin statistic was equal to 0.76, suggesting an adequate sample size (relative to the number of food items) for conducting dietary pattern analysis. Factor analysis of the FFQ-derived food items resulted in 3 factor dietary patterns (Table 1). These patterns—designated the “fruits and vegetables,” “American/Western,” and “Tex-Mex” patterns—were assigned names based on the foods that loaded heavily (factor loadings of 0.25 or higher) on that factor. Together these factors accounted for 40% of the total variance.

Characteristics of the RCC cases and controls for the overall population are shown in Table 2. We observed significant differences between cases and controls with regard to age, smoking, obesity, hypertension, physical activity level, and tertiles of the 3 dietary patterns.

Age- and sex-adjusted and multivariable-adjusted results for the association between dietary pattern scores and RCC risk are summarized in Table 3. Factor scores for the “fruits and vegetables” pattern showed a strong inverse association with RCC risk in both the age- and sex-adjusted model and the multivariable-adjusted models. Greater adherence to the fruits and vegetables pattern was inversely related to RCC

Table 1. Rotated Factor Pattern Loadings^a for 125 Food Items Assessed at Recruitment in a Case-Control Study of Renal Cell Carcinoma, Houston, Texas, 2002–2013

Food Item	Dietary Pattern		
	Fruits and Vegetables (Factor 1)	American/Western (Factor 2)	Tex-Mex (Factor 3)
Deep yellow vegetables	0.65		
Cruciferous vegetables	0.57		
Dark leafy green vegetables	0.54		
Berries	0.49		
Apples	0.48		
Tomatoes	0.47		
Oranges	0.47		
Grapes	0.43		
Celery	0.42		
Other fish ^b	0.41		
Low-fat dairy food (not milk)	0.36		
Melons	0.36		
Green beans	0.34	0.27	
Snow peas	0.33		
Vegetable soup	0.32		
Rolls		0.40	
Roast beef		0.36	
Pork		0.35	
Spaghetti		0.33	
Chili (with and without meat)		0.33	
Macaroni and cheese/casseroles		0.33	
Steak		0.32	
Potatoes		0.32	
Biscuits		0.31	
Pizza		0.31	
Barbecued beef ^c		0.31	
Corn		0.27	
Ham		0.27	
Chicken		0.27	
Hot dogs		0.27	
Corn bread		0.26	
Tacos			0.54
Flour tortillas			0.51
Salsa			0.49
Corn tortillas			0.47
Enchiladas			0.45
Refried beans			0.44
Green chilies			0.42
Tamales			0.34
Menudo			0.31

^a The table shows any food item with a factor loading greater than 0.25. For Factor 1, only the top 15 factor loadings are displayed.

^b Any type of fish other than canned tuna.

^c Not including hamburgers or steak.

Table 2. Characteristics of Renal Cell Carcinoma Cases and Controls and Distribution of Their Dietary Intake Patterns, Houston, Texas, 2002–2013^a

Characteristic	Cases (n = 659)		Controls (n = 699)		χ^2 P Value
	No.	%	No.	%	
Age, years ^b	59.27 (10.4)		60.7 (10.5)		0.01 ^c
Sex					
Male	439	66.6	462	66.1	0.83
Female	220	33.4	237	33.9	
Smoking status					
Never smoker	341	51.8	353	50.5	0.65
Ever smoker	318	48.3	346	49.5	
History of hypertension					
Yes	388	58.9	299	42.8	<0.001
No	271	41.1	400	57.2	
Body mass index ^d					
<30 (normal/overweight)	411	62.4	500	71.5	<0.001
≥30 (obese)	248	37.6	199	28.5	
Alcohol use ^e					
Tertile 1 (low)	325	49.3	225	32.2	<0.001
Tertile 2 (medium)	155	23.5	238	34.1	
Tertile 3 (high)	179	27.2	236	33.8	
Physical activity level, METs/week ^f					
<30 (low)	332	53.4	206	30.3	<0.001
30–47 (medium)	196	31.5	253	37.2	
≥48 (high)	94	15.1	221	32.5	
Dietary intake pattern and tertile of factor score					
Fruit and vegetables pattern					
Tertile 1 (low)	312	47.3	231	33.1	<0.001
Tertile 2	192	29.1	234	33.5	
Tertile 3 (high)	155	23.5	234	33.5	
American/Western pattern					
Tertile 1 (low)	133	20.2	228	32.6	<0.001
Tertile 2	216	32.8	234	33.5	
Tertile 3 (high)	310	47.0	237	33.9	
Tex-Mex pattern					
Tertile 1 (low)	250	37.9	223	31.9	0.001
Tertile 2	165	25.0	237	33.9	
Tertile 3 (high)	244	37.0	239	34.2	

Abbreviation: MET, metabolic equivalent.

^a Tertiles were based on the distribution of dietary intake patterns in controls.

^b Values are expressed as mean (standard deviation).

^c *t* test *P* value.

^d Weight (kg)/height (m)².

^e Tertiles of sex-specific, energy-adjusted gram equivalents.

^f Patients with an “unknown” level of physical activity were not included.

Table 3. Odds Ratios for the Association Between Tertile of Dietary Intake Pattern Factor Score and Renal Cell Carcinoma Risk,^{a,b} Houston, Texas, 2002–2013

Dietary Intake Pattern and Tertile of Factor Score	Age- and Sex-Adjusted Results				Multivariable-Adjusted Results			
	No. of Cases	No. of Controls	OR	95% CI	No. of Cases	No. of Controls	OR	95% CI
Fruits and vegetables pattern								
Tertile 1 (low)	312	231	1.00	Referent	299	226	1.00	Referent
Tertile 2	192	234	0.62	0.48, 0.81	178	223	0.66	0.49, 0.88
Tertile 3 (high)	155	234	0.50	0.38, 0.65	145	231	0.54	0.40, 0.73
<i>P</i> for trend				<0.001				<0.001
American/Western pattern								
Tertile 1 (low)	133	228	1.00	Referent	125	226	1.00	Referent
Tertile 2	216	234	1.58	1.19, 2.10	205	227	1.53	1.12, 2.09
Tertile 3 (high)	310	237	2.23	1.70, 2.94	292	227	1.98	1.47, 2.67
<i>P</i> for trend				<0.001				<0.001
Tex-Mex pattern								
Tertile 1 (low)	250	223	1.00	Referent	236	216	1.00	Referent
Tertile 2	165	237	0.60	0.46, 0.78	155	229	0.61	0.46, 0.83
Tertile 3 (high)	244	239	0.83	0.64, 1.07	231	235	0.87	0.65, 1.15
<i>P</i> for trend				0.13				0.33

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Missing data on physical activity level were coded as “unknown.”

^b Multivariable models were adjusted for age (years; continuous), smoking status (ever/never), sex, body mass index (weight (kg)/height (m)²; obese vs. normal/overweight), physical activity level (tertiles), alcohol intake (tertiles), and total energy intake (kcal/day; continuous).

risk in the multivariable-adjusted model (across tertiles, odds ratio (OR) = 1.00 (referent), OR = 0.66 (95% confidence interval (CI): 0.49, 0.88), and OR = 0.54 (95% CI: 0.40, 0.73), respectively; *P* for trend < 0.001), while a higher pattern score for the “American/Western” dietary pattern was significantly associated with a higher risk of RCC in both models (multivariable-adjusted model: OR = 1.00 (referent), OR = 1.53 (95% CI: 1.12, 2.09), and OR = 1.98 (95% CI: 1.47, 2.67), respectively; *P* for trend < 0.001). No significant associations were observed for the “Tex-Mex” dietary pattern.

The associations between dietary pattern scores and RCC risk according to history of hypertension are presented in Table 4. Results suggested a significant synergistic interaction between the American/Western pattern and history of hypertension (highest tertile vs. lowest: OR = 1.76 (95% CI: 1.16, 2.70) among persons with no history of hypertension and OR = 2.23 (95% CI: 1.43, 3.45) among persons with a history of hypertension; additive *P* for interaction = 0.01). Models stratified according to smoking, body mass index, alcohol use, and physical activity level yielded no meaningful differences by stratum, with findings qualitatively similar to those of the overall analyses (data not shown).

Age- and sex-adjusted associations between the selected GWAS SNPs and RCC risk in this study are shown in Table 5. In this selected case-control population, 3 of the 6 SNPs yielded significant associations with RCC risk: rs10054504, rs718314, and rs7579899 (*P* < 0.05). Only 1 SNP, rs718314

(located near *ITPR2*), showed evidence of a synergistic interaction with the American/Western dietary pattern (Table 6). The association with the American/Western dietary pattern was stronger for persons with at least 1 copy of the minor allele in this variant (highest tertile vs. lowest: OR = 1.74 (95% CI: 1.15, 2.83) among persons with no minor alleles and OR = 2.39 (95% CI: 1.52, 3.77) among persons with at least 1 copy of the minor allele; additive *P* for interaction = 0.03). Analyses for the remaining SNPs showed no interaction with dietary pattern scores, and results are not shown.

DISCUSSION

Three empirically derived dietary patterns, termed the “fruits and vegetables,” “American/Western,” and “Tex-Mex” patterns, were generated in this study. High scores for the fruits and vegetables pattern were inversely associated with RCC risk, while higher scores for the American/Western dietary pattern were associated with an higher risk of RCC. These associations were consistent across results stratified according to known and suspected RCC risk factors. We found significant interactions between the American/Western dietary pattern and history of hypertension and rs718314 (located downstream of *ITPR2*), an established genetic variant related to RCC risk.

Two studies have previously utilized factor analysis to identify dietary intake patterns associated with RCC risk (19, 20). In a large prospective cohort study of Swedish

Table 4. Odds Ratios for the Association Between Tertile of Dietary Intake Pattern Factor Score and Renal Cell Carcinoma Risk, by History of Hypertension,^{a,b} Houston, Texas, 2002–2013

Dietary Intake Pattern and Tertile of Factor Score	History of Hypertension								Multiplicative <i>P</i> for Interaction	Additive <i>P</i> for Interaction
	No				Yes					
	No. of Cases	No. of Controls	OR	95% CI	No. of Cases	No. of Controls	OR	95% CI		
Fruits and vegetables pattern										
Tertile 1 (low)	126	134	1.00	Referent	173	92	1.00	Referent	0.75	0.36
Tertile 2	73	109	0.82	0.54, 1.24	105	114	0.53	0.36, 0.80		
Tertile 3 (high)	58	144	0.49	0.32, 0.76	87	87	0.51	0.34, 0.78		
<i>P</i> for trend				0.002				0.005		
American/Western pattern										
Tertile 1 (low)	58	139	1.00	Referent	67	87	1.00	Referent	0.36	0.01
Tertile 2	84	116	1.56	1.00, 2.42	121	111	1.55	1.00, 2.41		
Tertile 3 (high)	115	132	1.76	1.16, 2.70	177	95	2.23	1.43, 3.45		
<i>P</i> for trend				0.01				0.005		
Tex-Mex pattern										
Tertile 1 (low)	84	123	1.00	Referent	152	93	1.00	Referent	0.2	0.1
Tertile 2	65	123	0.78	0.51, 1.19	90	106	0.51	0.34, 0.75		
Tertile 3 (high)	108	141	1.05	0.70, 1.56	123	94	0.70	0.46, 1.03		
<i>P</i> for trend				0.71				0.08		

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Missing data on physical activity level were coded as “unknown.”

^b Multivariable models were adjusted for age (years; continuous), smoking status (ever vs. never), sex, body mass index (weight (kg)/height (m)²; obese vs. normal/overweight), physical activity level (tertiles), alcohol intake (tertiles), and total energy intake (kcal/day; continuous).

women, Rashidkhani et al. (20) identified 3 dietary patterns: “healthy,” “Western,” and “drinker.” A case-control study by Handa and Kreiger (19) suggested that dietary patterns high in fat and protein may be risk factors for RCC. However, the dietary patterns and identified associations were not consistent with findings in our study population. These inconsistencies

can potentially be attributed to low incidence, small sample sizes, varying populations, differing criteria for inclusion in the factor analysis, and inadequate adjustment for total energy intake. To our knowledge, this is the largest case-control study of dietary patterns and RCC risk to date, and the first to have been conducted in a US population.

Table 5. Marginal Associations Between Selected Single-Nucleotide Polymorphisms^a and Renal Cell Carcinoma Risk, Houston, Texas, 2002–2013

Gene	Variant	Distance to Gene, kilobases	Minor Allele	Minor Allele Frequency		Odds Ratio ^b	95% Confidence Interval	<i>P</i> Value
				Cases	Controls			
<i>ZEB2</i>	rs10054504	110.6	T	0.27	0.20	1.46	1.13, 1.87	0.003
<i>SCARB1</i>	rs4765623	27.7	T	0.40	0.40	1.01	0.80, 1.25	0.96
<i>LOC390218//CCND1</i>	rs12105918	69.7	C	0.13	0.11	1.18	0.85, 1.62	0.32
<i>LOC390218//CCND1</i>	rs7105934	216.1	A	0.12	0.14	0.87	0.64, 1.20	0.39
<i>ITPR2</i>	rs718314	28.4	G	0.49	0.40	1.54	1.24, 1.91	<0.001
<i>EPAS1</i>	rs7579899	13	A	0.39	0.34	1.31	1.05, 1.63	0.02

Abbreviations: *CCND1*, cyclin D1 gene; *EPAS1*, endothelial PAS domain-containing protein 1 gene; *ITPR2*, inositol 1,4,5-trisphosphate receptor, type 2 gene; LOC, locus number; MAF, minor allele frequency; *SCARB1*, scavenger receptor class B, member 1 gene; *ZEB2*, zinc finger E-box-binding homeobox 2 gene.

^a Assumes dominant model (0 = no minor alleles, 1 = at least 1 minor allele).

^b Adjusted for age and sex.

Table 6. Odds Ratios for the Association Between Tertile of Dietary Intake Pattern Factor Score and Renal Cell Carcinoma Risk, According to Genotype of the Risk-Associated Single-Nucleotide Polymorphism rs718314 (*ITPR2*),^{a,b} Houston, Texas, 2002–2013

Dietary Intake Pattern and Tertile of Factor Score	rs718314 Genotype								Multiplicative <i>P</i> for Interaction	Additive <i>P</i> for Interaction
	AA (<i>n</i> = 736)				AG/GG (<i>n</i> = 622)					
	No. of Cases	No. of Controls	OR	95% CI	No. of Cases	No. of Controls	OR	95% CI		
Fruits and vegetables pattern										
Tertile 1	153	126	1.00	Referent	159	105	1.00	Referent	1.00	0.64
Tertile 2	85	145	0.52	0.34, 0.78	107	89	0.82	0.54, 1.24		
Tertile 3	82	145	0.50	0.32, 0.76	73	89	0.58	0.36, 0.91		
<i>P</i> for trend				0.01				0.02		
American/Western pattern										
Tertile 1	68	137	1.00	Referent	65	91	1.00	Referent	1.00	0.03
Tertile 2	100	131	1.44	0.93, 2.24	116	103	1.65	1.05, 2.60		
Tertile 3	152	148	1.74	1.15, 2.83	158	89	2.39	1.52, 3.77		
<i>P</i> for trend				0.01				<0.001		
Tex-Mex pattern										
Tertile 1	143	140	1.00	Referent	107	83	1.00	Referent	1.00	0.23
Tertile 2	83	135	0.57	0.38, 0.85	82	102	0.60	0.38, 0.96		
Tertile 3	94	141	0.88	0.56, 1.24	150	98	1.06	0.68, 1.66		
<i>P</i> for trend				0.23				0.64		

Abbreviations: CI, confidence interval; *ITPR2*, inositol 1,4,5-trisphosphate receptor, type 2 gene; OR, odds ratio.

^a Missing data on physical activity level were coded as “unknown.”

^b Multivariable models were adjusted for age (years; continuous), smoking status (ever vs. never), sex, body mass index (weight (kg)/height (m)²; obese vs. normal/overweight), physical activity level (tertiles), alcohol intake (tertiles), and total energy intake (kcal/day; continuous).

We identified a synergistic interaction between history of hypertension and the American/Western dietary pattern. Western diets (consisting of red meats, processed meats, and starches) and hypertension are associated with high levels of serum insulin and insulin-like growth factors, which have been found to affect tumor growth and to inhibit apoptosis (34–36).

We found higher scores for the fruits and vegetables pattern to be associated with a lower risk of RCC, which is consistent with previous findings (37–39). In a recent meta-analysis of 13 prospective studies and 1,478 incident RCC cases, Lee et al. (38) found fruit and vegetable intake to be jointly and separately associated with a lower risk of RCC. Results suggested that components of fruits and vegetables, such as carotenoids, may play a role in the prevention of RCC. Carotenoids such as carotene, β -carotene, and lutein inhibit oxidative damage to DNA, mutagenesis, tumor growth, and malignant transformation and enhance cell-to-cell communication (38, 40).

Our data suggest that the effects of an American or Western diet are not homogeneous in people with different genetic backgrounds. Previous studies have shown that *ITPR2*, which encodes for an inositol 1,4,5-trisphosphate receptor, is associated with severe obesity (41), waist:hip ratio (42), nutrient metabolism (41), and lipid metabolism (43). Metabolism of foods comprising the American/Western dietary pattern, and their corresponding nutrients, may be affected by variation in the *ITPR2* gene. The rs718314 variant is located 28 kilobases from *ITPR2* in the 3'-flanking region of the

gene. Interestingly, this variant is located near several potential regulatory elements identified by the Encyclopedia of DNA Elements (ENCODE) Consortium, including a DNase I hypersensitivity region, H3K27Ac histone marks representing active regulatory elements, and a cluster of transcription factor binding sites (44). rs718314 is the first common SNP to be associated with both waist:hip ratio and cancer (23). Results of the present study suggest that persons with genetic susceptibility to RCC may further increase their risk via adherence to an American/Western diet. Further research is necessary to replicate these findings and explore the biological mechanisms through which variation in this gene can affect the association between dietary intake and RCC risk.

The present study had several strengths, including the detailed measurement of genetic variants and dietary intake. To our knowledge, it is the first study to have evaluated the association between empirically derived dietary patterns and RCC risk in a US population. It is also the first study to have evaluated the potential impact of established genetic variants on the association between dietary patterns and RCC risk. Additionally, we assessed both multiplicative and synergistic interactions of the derived dietary patterns with RCC risk factors and established genetic variants in relation to RCC risk. The 2 patterns that explained the greatest variation in our data have been consistently identified in the literature (16, 45–48) and have been shown to be stable over time in prospective analyses (16).

Despite these strengths, however, one potential limitation is recall bias. Healthy controls are more likely to recall healthy dietary habits or food intakes (such as fruits and vegetables) than are diseased patients, potentially leading to biased results. However, we conducted a factor analysis in the control group separately which yielded dietary patterns consistent with those of the overall population. Therefore, it is unlikely that recall bias was differential between cases and controls. Utilization of FFQ data is also a potential limitation, since it is not an appropriate tool with which to accurately estimate nutrient or food intakes. However, the FFQ used here was validated in this study population and ranks participants reasonably well with regard to food intake. Finally, the present study included only non-Hispanic whites. It is possible that these dietary patterns are unique to this population. Similar analyses should be conducted to determine whether these associations are consistent in other population subgroups.

This study provides additional support for the hypothesis that diet plays a critical role in RCC etiology—specifically, the protective role of fruits and vegetables and the deleterious role of westernized diets in cancer risk. While limiting dietary consumption of red meats, processed foods, and starches may aid in reducing overall RCC risk, this risk may be further modified by genotypic variations. This study suggests that the effects of dietary intake on RCC risk are likely to be complex, and further research is required to understand the biological mechanisms underlying these associations.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas (Stephanie C. Melkonian, Carrie R. Daniel, Michelle A. T. Hildebrandt, Yuanqing Ye, Wong-Ho Chow, Xifeng Wu); Department of Genitourinary Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas (Nizar M. Tannir); and Department of Urology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas (Christopher G. Wood).

This work was supported in part by the National Institutes of Health (grant R01 CA170298), the Center for Translational and Public Health Genomics, Duncan Family Institute for Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, and a National Cancer Institute R25T Postdoctoral Fellowship in Cancer Prevention.

Conflicts of interest: none declared.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63(1):11–30.
2. Kroenke CH, Fung TT, Hu FB, et al. Dietary patterns and survival after breast cancer diagnosis. *J Clin Oncol*. 2005; 23(36):9295–9303.
3. Fung TT, Stampfer MJ, Manson JE, et al. Prospective study of major dietary patterns and stroke risk in women. *Stroke*. 2004; 35(9):2014–2019.
4. Gao X, Chen H, Fung TT, et al. Prospective study of dietary pattern and risk of Parkinson disease. *Am J Clin Nutr*. 2007; 86(5):1486–1494.
5. Aballay LR, Eynard AR, Díaz Mdel P, et al. Overweight and obesity: a review of their relationship to metabolic syndrome, cardiovascular disease, and cancer in South America. *Nutr Rev*. 2013;71(3):168–179.
6. Mesías M, Seiquer I, Navarro MP. Is the Mediterranean diet adequate to satisfy zinc requirements during adolescence? *Public Health Nutr*. 2012;15(8):1429–1436.
7. Andreatta MM, Del Campo ML, Carbonetti A, et al. Food preferences and their “decision contexts” as predictors of dietary pattern. *Rev Fac Cien Med Univ Nac Cordoba*. 2011; 68(1):14–19.
8. Mesías M, Seiquer I, Muñoz-Hoyos A, et al. The beneficial effect of Mediterranean dietary patterns on dietary iron utilization in male adolescents aged 11–14 years. *Int J Food Sci Nutr*. 2009;60(suppl 7):355–368.
9. Saadatian-Elahi M, Slimani N, Chajès V, et al. Plasma phospholipid fatty acid profiles and their association with food intakes: results from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr*. 2009;89(1):331–346.
10. Keinan BL, Peeters PH, Mulligan AA, et al. Consumption of soy products among European consumers of a health-conscious diet. *IARC Sci Publ*. 2002;156:109–112.
11. Romieu I, Ferrari P, Rinaldi S, et al. Dietary glycemic index and glycemic load and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Clin Nutr*. 2012;96(2):345–355.
12. Agudo A, Slimani N, Ocké MC, et al. Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. *Public Health Nutr*. 2002;5(6B):1179–1196.
13. Andreatta MM, Navarro A, Muñoz SE, et al. Dietary patterns and food groups are linked to the risk of urinary tract tumors in Argentina. *Eur J Cancer Prev*. 2010;19(6):478–484.
14. Bertoia M, Albanes D, Mayne ST, et al. No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma. *Int J Cancer*. 2010;126(6):1504–1512.
15. Reedy J, Wirfalt E, Flood A, et al. Comparing 3 dietary pattern methods—cluster analysis, factor analysis, and index analysis—with colorectal cancer risk: the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2010;171(4):479–487.
16. Flood A, Rastogi T, Wirfalt E, et al. Dietary patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. *Am J Clin Nutr*. 2008;88(1): 176–184.
17. Dixon LB, Balder HF, Virtanen MJ, et al. Dietary patterns associated with colon and rectal cancer: results from the Dietary Patterns and Cancer (DIETSCAN) Project. *Am J Clin Nutr*. 2004;80(4):1003–1011.
18. Malik VS, Fung TT, van Dam RM, et al. Dietary patterns during adolescence and risk of type 2 diabetes in middle-aged women. *Diabetes Care*. 2012;35(1):12–18.
19. Handa K, Kreiger N. Diet patterns and the risk of renal cell carcinoma. *Public Health Nutr*. 2002;5(6):757–767.
20. Rashidkhani B, Akesson A, Lindblad P, et al. Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. *J Nutr*. 2005;135(7):1757–1762.
21. Henrion M, Frampton M, Scelo G, et al. Common variation at 2q22.3 (ZEB2) influences the risk of renal cancer. *Hum Mol Genet*. 2013;22(4):825–831.
22. Purdue MP, Johansson M, Zelenika D, et al. Genome-wide association study of renal cell carcinoma identifies two

- susceptibility loci on 2p21 and 11q13.3. *Nat Genet.* 2011; 43(1):60–65.
23. Wu X, Scelo G, Purdue MP, et al. A genome-wide association study identifies a novel susceptibility locus for renal cell carcinoma on 12p11.23. *Hum Mol Genet.* 2012;21(2):456–462.
  24. Clague J, Lin J, Cassidy A, et al. Family history and risk of renal cell carcinoma: results from a case-control study and systematic meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(3):801–807.
  25. Olson SH, Kelsey JL, Pearson TA, et al. Evaluation of random digit dialing as a method of control selection in case-control studies. *Am J Epidemiol.* 1992;135(2):210–222.
  26. Block G, Coyle LM, Hartman AM, et al. Revision of dietary analysis software for the Health Habits and History Questionnaire. *Am J Epidemiol.* 1994;139(12):1190–1196.
  27. Food Surveys Research Group, Agricultural Research Service, US Department of Agriculture. *USDA Food and Nutrient Database for Dietary Studies, 4.1.* Beltsville, MD: US Department of Agriculture; 2010.
  28. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of Physical Activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc.* 2000;32(9 suppl): S498–S504.
  29. Bertuccio P, Edefonti V, Bravi F, et al. Nutrient dietary patterns and gastric cancer risk in Italy. *Cancer Epidemiol Biomarkers Prev.* 2009;18(11):2882–2886.
  30. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986;124(1):17–27.
  31. Newby PK, Tucker KL. Empirically derived eating patterns using factor or cluster analysis: a review. *Nutr Rev.* 2004;62(5): 177–203.
  32. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology.* 1992;3(5):452–456.
  33. Knol MJ, van der Tweel I, Grobbee DE, et al. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *Int J Epidemiol.* 2007;36(5):1111–1118.
  34. Melnik BC, John SM, Schmitz G. Over-stimulation of insulin/IGF-1 signaling by Western diet may promote diseases of civilization: lessons learnt from Laron syndrome. *Nutr Metab (Lond).* 2011;8:41.
  35. Dunn SE, Kari FW, French J, et al. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res.* 1997;57(21):4667–4672.
  36. Bianchi S, Bigazzi R, Valtriani C, et al. Elevated serum insulin levels in patients with essential hypertension and microalbuminuria. *Hypertension.* 1994;23(6):681–687.
  37. Rashidkhani B, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer.* 2005;113(3):451–455.
  38. Lee JE, Männistö S, Spiegelman D, et al. Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1730–1739.
  39. Zhao J, Zhao L. Cruciferous vegetables intake is associated with lower risk of renal cell carcinoma: evidence from a meta-analysis of observational studies. *PLoS One.* 2013;8(10): e75732.
  40. Krinsky NI. Carotenoids and cancer: basic research studies. In: Frei B, ed. *Natural Antioxidants in Human Health and Disease.* San Diego, CA: Academic Press, Inc.; 1994: 239–261.
  41. Cotsapas C, Speliotes EK, Hatoum IJ, et al. Common body mass index-associated variants confer risk of extreme obesity. *Hum Mol Genet.* 2009;18(18):3502–3507.
  42. Heid IM, Jackson AU, Randall JC, et al. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet.* 2010;42(11):949–960.
  43. Greenawalt DM, Dobrin R, Chudin E, et al. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. *Genome Res.* 2011;21(7): 1008–1016.
  44. ENCODE Project Consortium. A user's guide to the Encyclopedia of DNA Elements (ENCODE). *PLoS Biol.* 2011; 9(4):e1001046.
  45. Fung T, Hu FB, Fuchs C, et al. Major dietary patterns and the risk of colorectal cancer in women. *Arch Intern Med.* 2003; 163(3):309–314.
  46. Kim MK, Sasaki S, Otani T, et al. Dietary patterns and subsequent colorectal cancer risk by subsite: a prospective cohort study. *Int J Cancer.* 2005;115(5):790–798.
  47. Navarro Silvera SA, Mayne ST, Risch H, et al. Food group intake and risk of subtypes of esophageal and gastric cancer. *Int J Cancer.* 2008;123(4):852–860.
  48. Ambrosini GL, Fritschi L, de Klerk NH, et al. Dietary patterns identified using factor analysis and prostate cancer risk: a case control study in Western Australia. *Ann Epidemiol.* 2008;18(5): 364–370.