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Family history and risk of Renal Cell Carcinoma: results from a case-control study and systematic meta-analysis

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Abstract

We conducted a case-control analysis, a family-based population analysis and a meta-analysis to assess the role of family history of cancer and kidney cancer in association with the risk of renal cell carcinoma (RCC). A total of 325 cases and 329 controls were identified from an on-going case-control study of RCC. Study variables were assessed through 45-minute structured, face-to-face interviews. In the case-control analysis, a family history of any cancer (in first-degree relatives) was associated with a non-significant 1.2-fold increase in RCC risk [95% confidence interval (95% CI), 0.8–1.6]. The risk increased to 1.7 and became significant when the relative was a sibling (95% CI 1.1–2.5). A family history of kidney cancer (kidney cancer in first-degree relatives) was associated with a 4.3-fold significantly increased risk of RCC (95% CI, 1.6–11.9). The cases reported a total of 2,536 first-degree relatives of which 21 (0.8%) had kidney cancer and the controls reported a total of 2,333 first-degree relatives of which 5 (0.2%) had kidney cancer ($P = 0.003$). In the family-based population analysis, a family history of kidney cancer was associated with a 2.8-fold increased risk of RCC (95% CI, 1.0–7.8). The meta-analysis further confirmed this significant association with a 2.2-fold increased risk of RCC (95% CI, 1.6–2.9). To our knowledge, this is the first study to use three analytic strategies to investigate the association between a family history of kidney cancer and risk of RCC, and the first systematic evaluation of the relative risk for developing RCC associated with family history.

Keywords

Renal Cell Carcinoma; Family History; Meta-analysis

INTRODUCTION

Malignant tumors of the kidney account for approximately 4% of all new primary cancer cases diagnosed in the United States, with an estimated 54,390 cases occurring in 2008 (1). RCC accounts for 85% of all renal cancers(2). Numerous epidemiological studies have identified

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cigarette smoking, obesity and hypertension as the main risk factors for RCC, potentially accounting for 50% of all U.S. cases (3,4).

Family history of kidney cancer was first associated with the risk of developing RCC through a series of early case reports (5,6). Research since has reported associations ranging from none to a five-fold increase in risk (7–15). Results from a relatively large Icelandic study indicated that almost 60% of RCC cases had a first- or second-degree relative with kidney cancer (9), suggesting a strong genetic component to risk. Among previous population-based case-control studies, a Canadian study including 518 cases and 1,381 controls did not identify an association between family history and RCC (11), whereas others reported significant increases in risk (7,12,15). Among the hospital-based case-control studies, one observed a significantly increased risk of RCC (particularly when the affected relative was a sibling) (13), whilst two further studies reported a non-significant increased risk for subjects with at least one first-degree relative with kidney cancer (10,14).

To date, however a systematic evaluation of the relative risk for developing RCC associated with family history has not been reported. In this study, we aim to address the inconsistent results reported in previous studies, thereby improving the estimate of the familial component of RCC risk. In the first instance, a case-control approach was applied to compare self-reported family history of kidney cancer in first-degree relatives of RCC cases and their matched controls. Next, a family-based population analysis was applied to investigate the familial risk of renal cell carcinoma after controlling for confounding effects among the relatives. Lastly, to address the heterogeneity of previous studies, we conducted a meta-analysis (including our own data) to provide an overall estimate of effect.

MATERIALS and METHODS

Study Population

Incident RCC cases were recruited from The University of Texas M. D. Anderson Cancer Center in Houston, Texas. M. D. Anderson Cancer Center staff interviewers identified RCC cases through a daily review of computerized appointment schedules for the Departments of Urology and Genitourinary Medical Oncology. All cases were individuals with newly diagnosed, histologically confirmed RCC. There were no age, gender, ethnicity or cancer stage restrictions on recruitment. However, to be eligible, the cases must have been residents of Texas. Healthy control subjects without a history of cancer, except non-melanoma skin cancer, were identified and recruited using the random digit dialing (RDD) method. In RDD, randomly selected phone numbers from households were used to contact potential control volunteers in the same residency of cases accordingly to the telephone directory listings. To be eligible, controls must have lived for at least one year in the same county or socio-economically matched surrounding counties that the case resided. The controls were frequency matched to the cases by age (±5 years), sex, ethnicity and county of residence. We examined the comparability of case and control characteristics within and outside of the immediate geographic areas of the study center and no significant differences were observed (data not shown), suggesting that case and control characteristics within and outside of the immediate geographic areas of M.D. Anderson are comparable.

The overall response rate for RDD screening was 51% and among those who agreed to participate, the response rate was 88%. The response rate for the eligible cases was 87%. This RCC case-control study started subject recruitment in 2002 and is currently on going.

Data Collection

After written informed consent was obtained, study participants completed a 45-minute structured, in person interview conducted by trained M. D. Anderson staff interviewers. Data was collected on demographic characteristics, tobacco use history, alcohol consumption and family history of cancer. Family history data included cancer history for all first-degree relatives (biologic parents, siblings, and offspring). Specifically, information collected included whether the relative ever had cancer (yes or no), the type of cancer (site), age at diagnosis, current age or age of death, vital status (dead or alive), smoking status (yes or no), years smoked, number of cigarettes smoked and whether the relative ever had high blood pressure (yes or no). An individual who had never smoked at least 100 cigarettes in his or her lifetime was defined as a never smoker. An individual who had smoked at least 100 cigarettes in his or her lifetime but had quit at least 12 months before diagnosis (for cases) or before the interview (for controls) was coded as a former smoker. Current smokers were those who were currently smoking or had quit less than 12 months before diagnosis (for cases) or before the interview (for controls). Both former and current smoker were also defined as ever smoker. Body mass index (BMI, kg/m^2) was calculated through self-reported height and weight. High blood pressure was assessed by whether a subject answered yes or no to ever having been told by a doctor if they had hypertension or high blood pressure. The study protocol was approved by the M. D. Anderson Institutional Review Board.

Selection of studies included in the meta-analysis

A comprehensive literature review was carried out to identify studies on risks for RCC associated with a family history of kidney cancer. We conducted a computerized search of PubMed for literature published in any language between 1950 and April 2008 and was expanded by a review of previously cited references. To limit publication bias, search criteria were not limited to “kidney cancer” and “family history,” but included “renal cell carcinoma” and all suspected risk factors. In this meta-analysis, we included studies that fulfilled the following criteria: 1) presented original data from either case-control or cohort studies; 2) had family history of cancer or kidney cancer among first-degree relatives as the exposure of interest; 3) had RCC as the outcome of interest; 4) provided relative risk (RR) estimates with confidence intervals or enough data to calculate them. We extracted the following information from each publications: the author’s last name; publication year; study design; type of control (among case-controls studies); study location; sample size; family history assessment (type of first-degree relative); variables controlled for in the analysis; and RR estimates with confidence intervals for RCC associated with a family history of cancer and kidney cancer.

We identified eleven studies: seven case-controls studies and four cohort studies (7–17). One cohort study (17) was excluded because the outcome of interest was defined as familial papillary renal cell carcinoma and one case-control study (12) was excluded because the participants were included in an international study (15). Including the current case-control and family-based population studies, a total of eleven met our inclusion criteria. The seven case-control studies were published between 1993 and 2007. Including data from the current case-control study, the number of cases and controls in the meta analysis were 5,470 and 9,126 respectively. The four cohort studies were published between 1994 and 2002. The total number of subjects included in the cohort studies was 29,771.

Statistical Analysis

Descriptive analyses were conducted to characterize the study population of RCC cases, controls, and their first-degree relatives. The Pearson χ^2 test was used to test for differences between cases and controls in the distribution of gender, ethnicity, smoking status and history of hypertension. The Student’s t-test was used to test for differences between subjects for continuous variables including age, smoking pack-years and body mass index.

To study familial aggregation, two analytic approaches were utilized. First, a case-control analysis was performed using unconditional logistic regression to estimate the odds ratio (OR) associated with family history while adjusting for age, gender, ethnicity, smoking status, BMI, and history of hypertension. However, an inherent limitation in studying family history through a case-control analysis is that the family clustering may be explained by shared exposures among relatives and probands, including smoking habits(18). Subsequently, a family-based population analysis was applied to determine whether there was an excess of kidney cancer among first-degree relatives of case probands as compared to control probands after controlling for confounding effects, including shared exposures, among the relatives. Probands themselves were excluded from this analysis. Instead, each first-degree relative was treated as a study subject and his/her cancer status was treated as the outcome variable in the model. The family history variable was defined as positive if the study subject was related to a case proband, and the variable was defined as negative if the study subject was a relative of a control proband. Odds ratios (ORs) and 95% CIs associated with a family history of kidney cancer were calculated by fitting a generalized estimating equations (GEEs) model (19,20) with binomial link function (logit) and exchangeable correlation structure, and then adjusted by age, gender, ethnicity, smoking, BMI and hypertension status, and proband age, smoking and hypertension status. The GEEs were used to account for dependence within family members through the specification of the covariance structure (or within-group correlation structure) for measurements from members in the same family. All statistical tests were two sided with a Type I error rate of 5%. All statistical analyses were performed with the Stata 8.2 statistical software package (Stata Corporation, College Station, Texas).

For the meta-analysis, we included studies reporting different measures of RR: case-control studies (odds ratios), cohort studies (rate ratios), and cohort studies using external population comparisons (standardized incidence ratios). Such an approach is warranted since these three measures of effect yield similar estimates of RR due to the absolute risk of RCC being low. Summary RRs were estimated with the statistical program STATA, version 8.2, by inverse-variance weighting, using fixed- and random-effects models that included a term for heterogeneity. All reported summary estimates in this study were based on the random-effects model. The χ^2 test of heterogeneity (Q –test), which is based on a weighted sum of the squares of the log odds ratios, was estimated in the individual studies. Publication bias was assessed using the funnel plot method of Begg and Mazumdar (21) and the Egger regression asymmetry test (22).

RESULTS

Family Aggregation Analyses

A total of 325 RCC cases and 329 controls were available for this analysis. Approximately 64% of the cases and controls were male (Table 1). There was no significant difference between the cases and the controls in terms of age ($P = 0.780$), ethnicity ($P = 0.138$), or smoking status ($P = 0.160$).Among ever smokers, cigarette consumption defined through median pack-years revealed no significant differences between cases and controls ($P = 0.283$). However, significant differences were observed between cases and controls for body mass index with cases having significantly higher BMI than the controls (29.6 vs. 28.4, $P = 0.013$). 56.3% of the cases had a history of hypertension/high blood pressure as compared to only 40.6% in controls ($P < 0.001$).

In the case-control analysis, there was a non-significant increased risk of RCC associated with a positive family history of any cancer (adjusted OR, 1.15; 95% CI, 0.81–1.62). When the analysis was stratified by relative type, we observed a 1.67-fold increase in RCC if the family member with cancer was a sibling (95% CI, 1.13–2.47) (Table 2). We did not observe an elevated risk for parents or offspring. When the analysis was limited to a family history of

kidney cancer, a 4.32-fold increased risk of RCC was observed among those with at least one family member with kidney cancer (95% CI, 1.57–11.88) (Table 2).

A second analytical approach was applied to control for risk factors of kidney cancer among the first-degree relatives. In this approach, each first-degree relative was treated as a study subject and cancer status of first-degree relatives was treated as the outcome variable. The 325 case probands reported a total of 2,536 first-degree relatives and the 329 control probands reported 2,333 first-degree relatives (Table 3). The case probands reported 362 (14.6%) first-degree relatives with any type cancer and the control probands reported 327 (14.2%) (P = 0.712). First-degree relatives of cases with kidney cancer (0.8%) differed significantly from first-degree relatives of the controls (0.2%) (P = 0.003). A family history of kidney cancer was associated with a borderline significant increased risk of kidney cancer (OR 2.76; 95% CI, 0.98 to 7.78), after adjusting for age, sex, smoking status of relatives, proband age, proband sex, proband smoking status, proband history of hypertension, and proband BMI (results not shown).

Meta-analysis

Studies included in meta-analysis are summarized in Table 4. An overall combined estimate was generated for a family history of kidney cancer for both genders and all first-degree relatives combined (Figure 1). One study was excluded because it reported RRs stratified by type of relative and did not report enough information to compute a combined RR (9). As shown in Figure 1, the overall combined RR for the development of RCC associated with a positive family history of kidney cancer was 2.21 (95% CI, 1.55 – 2.87). When the current case-control and family-based studies were included separately, the RRs increased to 2.43 (95% CI, 1.73 – 3.12) and 2.27 (1.62 – 2.89), respectively. There was evidence of between-study heterogeneity (Q= 74.14, P = 0.000). The heterogeneity increased to 97.64 (P = 0.000) when the current case-control analysis was included and 77.80 (P = 0.000) when the current family-based analysis was included.

Stratification by study design showed that a family history of kidney cancer was associated with a 2.32-fold increase in RCC (95% CI, 1.27 – 3.36) among case-control studies and a 1.93-fold increase in RCC (95% CI, 1.07 – 2.79) among cohort studies. When the current analyses were included, a 2.59-fold increase in RCC (95% CI, 1.55 – 3.64) was observed among case-controls studies and a 2.17-fold increase (95% CI, 1.35 – 2.99) among cohort studies. Further stratification showed a 2.87-fold increase (95% CI, 0.39 – 5.36) among hospital-based studies and a 2.37-fold increase in RCC (95% CI, 1.28 – 3.45) among population-based studies, including the current study. Evidence of heterogeneity fluctuated when stratified by type of study (cohort: Q= 5.03, P = 0.025; case-control: Q= 84.74, P = 0.000; hospital-based case-control: Q= 47.97, P = 0.000; population-based case-control: Q= 28.72, P = 0.000).

When the analysis was stratified by type of relative, the summary estimate among siblings with kidney cancer was 4.02 (95% CI, 2.48 – 5.56) including the current case-control study and 3.91 (95% CI, 2.30 – 5.51) including the current family-based study. The summary estimates were similar for studies conducted in North America were slightly lower than those conducted in Europe (RR = 2.22, 95% CI, 1.53 – 2.90 and RR = 2.57, 95% CI, 1.31 – 3.84, respectively). Likewise, studies published in or before 2000 observed slightly lower estimates than those published after 2000 (RR = 1.75, 95% CI, 1.18 – 2.32 and RR = 2.56, 95% CI, 1.49 – 3.63, respectively). Although decreased, there still existed statistically significant heterogeneity within most subgroups.

The funnel plot showed slight asymmetry, reflecting the relative absence of studies with small sample sizes and negative effects. However, both the Begg's and Egger's tests showed no indication of significant publication bias (P-values = 0.174 and 0.188, respectively).

Discussion

To our knowledge, this is the first study to use three analytic strategies (case-control analysis, family-based analysis and meta-analysis) to investigate the association between a family history of kidney cancer and risk of RCC, and the first systematic evaluation of the relative risk for developing RCC associated with family history. Through a case-control analysis and a family-based population analysis, we observed significant associations between a family history of kidney cancer and RCC. The results of the meta-analysis further confirmed that a family history of kidney cancer is associated with a significant increase in RCC risk. Of utmost interest is the finding that the observed risks were higher when the affected relative was a sibling rather than a parent or child suggesting the presence of low penetrance genes (23).

Our findings are in agreement with previous research examining the association between a family history of kidney cancer and RCC risk. Consistent with our case-control estimate, which suggests a significant positive association, a population-base case-control study in Denmark with a similar sample size observed a statistically significant OR of 4.1 (95% Confidence Interval, 1.1–14.9) in men and 4.8 in women (95% Confidence Interval, 1.0–23) and combined risk of 3.6 (95% CI, 1.6 – 8.2) (12). However, an inherent limitation in studying family history through a case-control analysis is that the family clustering may be explained by shared exposures among relatives and probands, including smoking habits. We therefore applied a family-based population analysis which makes it possible to control for such confounding effects. In our family-based population analysis, we observed a borderline significantly increased risk associated with family history of kidney cancer (OR 2.76; 95% CI, 0.98 to 7.78), Consistent with our result, in a Utah study, a familial relative risk of 2.5 (95% CI: 1.1 – 4.5) among first-degree relatives was observed(8).

Although the vast majority of RCC occurs sporadically, several hereditary conditions, including VHL syndrome (24), hereditary papillary renal cancer related to germline mutations, activation of the MET and the FH gene (25), and BHD (26), have been linked to RCC development. However, these syndromes are rare and probably most of the familial risk is not due to these highly penetrant genes (27). Other lower penetrance genes may exist with higher frequency in the population and may account for more cases of RCC (28).

The genetic interpretation of the familial risks is that dominant effect is reflected in offspring risk, whereas recessive effect is signaled by elevated sibling risk (23). Previous studies examining the familial risk of RCC observed higher risks among siblings than among parents and offspring (9,10,12,13,16). The present study also observed a higher risk of RCC among siblings with any type of cancer than among parents and offspring. The same difference in risk was not observed when our analyses were focused on kidney cancer. A limitation of our familial aggregation analyses is small sample size and thus inability to study stratified analyses comprehensively. However, our meta-analysis did render a combined RR of 3.52 (95% CI, 2.23 – 4.82) for siblings that was higher than the overall combined estimate of 2.37 (95% CI, 1.70 – 3.04). This observation among siblings supports the importance of recessive effects in familial RCC, in contrast with von Hippel-Lindau and other identified dominant familial RCC syndromes, and supports the existence of lower penetrance susceptibility genes in RCC etiology.

A limitation of the current study is that information on family history of first-degree relatives was self-reported, which could have resulted in recall bias. However, research evaluating the accuracy and completeness of reporting family history has proven to be accurate for first-degree relatives (29,30). By limiting family history to include only first-degree relatives, this study hoped to increase the validity of our exposure measurement. There exists the possibility of information bias due to proband cases reporting relatives with kidney cancer more than proband

controls. However, several studies have reported that case or control status was not important for accurate reporting of first degree-relative family history (31–33). Specifically, Soegaard et. al. observed no significant differences between cases and controls in the sensitivity (0.81 and 0.83, respectively), specificity (0.95 and 0.95, respectively) or kappa (0.72 and 0.75, respectively) of reporting of familial cancer.

In literature, the relatively low response rates of the RDD screening have been extensively discussed (34,35). A study comparing ovarian cancer controls selected through RDD and through a commercial database observed similar overall response rates to our study (36). Although the relatively low response rates of RDD screening in potential controls could have resulted in selection bias, researches have shown that controls selected by RDD usually represent characteristics of target population. For example, a study evaluating RDD suggest that control groups selected by RDD are representative of the general population (37). Brogon et al. (2001) reported that controls selected by RDD had characteristics similar to US Census demographic characteristics of the target population (34). Nevertheless, there still exists the possibility of selection bias among the current case-control analysis and the results should be interpreted with caution. Meta-analyses of observational studies are prone to biases and confounding factors that are inherent in the original studies. Nonetheless, as the first systematic assessment of its kind, the current meta-analysis suggests a significant association between family history of kidney cancer and RCC and an increased risk among siblings indicating a need for the further examination of recessive effects. Lastly, the results of the current meta-analysis should be interpreted with caution. Although substantially decreased, significant heterogeneity remained after the current meta-analysis was stratified by type of study, region, year of publication and relative type, indicating that other factors, such as differences in RCC histology, may be contributing to the heterogeneity.

Overall, our data suggests a significant positive association between a family history of kidney cancer and risk of RCC, and confirms this association through a significant combined estimate from our meta-analysis. With higher risks among siblings, our data also predict the existence of genes with low penetrance germline mutations and warrant further examination of the genetic factors associated with RCC risk.

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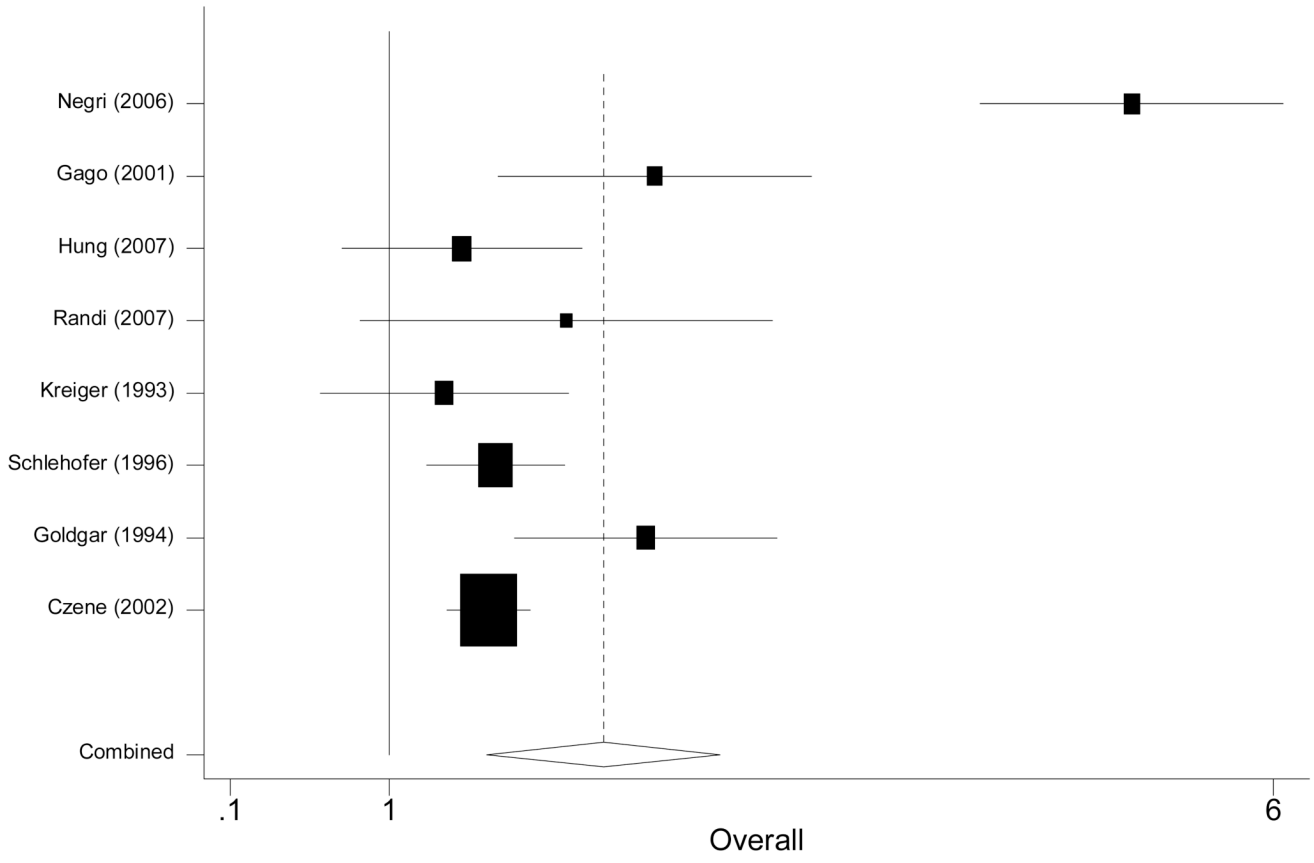

Figure 1.
A forest plot for estimated relative risk is shown for all studies reporting adjusted relative risk. If adjusted was not reported, crude relative risk were calculated and included.

Table 1

Distribution of demographic characteristics by case-control status

Variable	Case patients (n = 325)[1]	Control subjects (n = 329)[1]	p-value[2]
Sex, n (%)			
Male	209 (64.3)	210 (63.8)	
Female	116 (35.7)	119 (36.2)	0.899
Age, mean ± S.D.	58.3 ± 10.6	58.1 ± 10.0	0.780
Ethnicity, n (%)			
Caucasian	231 (71.1)	263 (79.9)	
Hispanic	59 (18.2)	41 (12.5)	
African American	28 (8.6)	20 (6.1)	
Other	4 (1.2)	3 (0.9)	
Unknown	3 (0.9)	2 (0.6)	0.138
Smoking status, n (%)			
Never smoker	168 (51.7)	152 (46.2)	
Ever smoker	157 (48.3)	177 (53.8)	0.160
Pack-years, median (range)	19.0 (0.3, 150.0)	22.0 (0.2, 133.0)	0.283
Body mass index (kg/m^2), mean ± S.D.	29.6 ± 6.4	28.4 ± 5.7	0.013
History of Hypertension, n(%)			
Yes	183 (56.3)	133 (40.6)	
No	142 (43.7)	195 (59.5)	<0.001

[1] Values might not sum to 100% because of missing data

[2] *P*-value for student's t-test (continuous variables) or $\chi 2$ test (categorical variables).

Table 2

Renal cell carcinoma adjusted risk estimates for having a first-degree relative with cancer among case and controls study participants.

Variable	Case patients (n = 325)[2]	Control subjects (n = 329)[2]	Adjusted OR[1] (95% CI[1])[3]
Family History of Any Cancer			
At Least One First Degree Relative			
No	120 (37.04)	128 (39.14)	Ref[1]
Yes	204 (62.96)	199 (60.86)	1.15 (0.81–1.62)
At Least One Parent			
No	163 (50.31)	160 (48.93)	Ref[1]
Yes	161 (49.69)	167 (51.07)	0.96 (0.69–1.33)
At Least One Sibling			
No	231 (71.30)	259 (79.20)	Ref[1]
Yes	93 (28.70)	68 (20.80)	1.67 (1.13–2.47)
At Least One Offspring			
No	297 (91.67)	309 (94.50)	Ref[1]
Yes	27 (8.33)	18 (5.50)	1.74 (0.88–3.47)
Family History of Kidney Cancer			
At Least One First Degree Relative			
No	303 (93.52)	322 (98.47)	Ref[1]
Yes	21 (6.48)	5 (1.53)	4.32 (1.57–11.88)
At Least One Parent			
No	312 (96.30)	326 (99.69)	Ref[1]
Yes	12 (3.70)	1 (0.31)	11.82 (1.48–94.36)
At Least One Sibling			
No	316 (97.53)	323 (98.78)	Ref[1]
Yes	8 (2.47)	4 (1.22)	1.98 (0.58–6.76)
At Least One Offspring			
No	323 (99.38)	327 (99.39)	Ref[1]
Yes	2 (0.62)	2 (0.61)	2.48 (0.21–28.89)

[1] OR denotes Odds Ratio; CI denotes Confidence Interval; Ref denotes Reference

[2] Values might not sum to 100% because of missing data.

[3] Unconditional multivariate logistic regression adjusted for age, sex, ethnicity, smoking status, BMI, and history of high blood pressure.

Table 3

Characteristics of First-Degree Relatives of the Case and Control Probands

	Case Relatives			Control Relatives		
Relative type	**Total no.**	**No. with any cancer (%)**	**No. with kidney cancer (%)**	**Total no.**	**No. with any cancer (%)**	**No. with kidney cancer (%)**
All	2,536	362 (14.6)	21 (0.8)	2,333	327 (14.2)	5 (0.2)
Males	1,289	179 (14.3)	12 (0.9)	1,198	166 (14.0)	4 (0.3)
Females	1,245	183 (14.9)	9 (0.7)	1,133	161 (14.4)	1 (0.1)
Parents	644	193 (30.7)	12 (1.9)	648	213 (33.5)	1 (0.2)
Fathers	322	101 (32.7)	6 (1.9)	324	111 (35.5)	0
Mothers	322	92 (28.8)	6 (1.9)	324	102 (31.7)	1 (1.3)
Siblings	1,094	140 (13.2)	8 (0.7)	997	92 (9.3)	4 (0.4)
Brothers	569	67 (12.3)	6 (1.1)	524	44 (8.5)	4 (0.8)
Sisters	524	73 (14.2)	2 (0.4)	475	48 (10.2)	0
Offspring	797	29 (3.7)	1 (0.1)	686	22 (3.2)	0
Sons	398	11 (2.8)	0	352	11 (3.1)	0
Daughters	399	18 (4.6)	1 (0.3)	334	11 (3.3)	0

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Table 4

Case-Control studies used in meta-analysis estimates

Reference*	Study type	Study Participants	Control type	Region
1) Kreiger *et al.*, 199311	Case-control	518 cases 1,381 controls	Population	Canada
2) Schlehofer *et al* , 199615	Case-control	1,732 cases 2,309 controls	Population	Australia, Europe, North America
3) Gago-Dominguez *et al.*, 20027	Case-control	550 cases 550 controls	Population	Los Angeles
4) Negri *et al.*, 200613	Case-control	767 cases 1,534 controls	Hospital	Italy
5) Hung *et al.*, 200710	Case-control	1,097 cases 1,555 controls	Hospital	Central Europe
6) Randi *et al.*, 200714	Case-control	348 cases 1,076 controls	Hospital	Northern Italy
7) Current Study	Case-control	325 cases 329 controls	Population	Houston
8) Goldgar *et al.*, 19948	Systematic population-based assessment	687 first degree-relatives	—	Utah
9) Gudbjartsson *et al.*, 20029	Population-based familial aggregation	1,078 cases	—	Iceland
10) Czene *et al.*, 200218	Cohort	23,137 cases	—	Sweden
11) Current Study	Family-based population analysis	4,869 first-degree relatives	—	Houston

*Superscripts in this column are references

**Adjusted for: 1) age, active cigarette smoking status, Quetelet index, 2) center, age, gender, BMI, pack-years of tobacco smoke, 3) number of cigarettes smoked per day, current smoking status, BMI, history of hypertension, regular use of analgesics and amphetamines, cruciferous vegetable intake, 4) age, sex, study center, year of interview, education, smoking, BMI, number of brothers and sisters, 5) age, sex, country, smoking pack-years, BMI, medical history of hypertension, 6) age, sex, study centre, education, BMI, smoking habit, alcohol consumption, number of brothers and sisters, 7) age, sex, ethnicity, smoking status, BMI, history of hypertension, 11) proband age, proband sex, proband ethnicity, proband smoking status, proband BMI, proband history of hypertension, relative age, relative sex, relative smoking status