Family History and Risk of Renal Cell Carcinoma

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Abstract

Few analytical epidemiological studies have investigated family history (FH) of urinary tract cancers as a potential risk factor for renal cell carcinoma (RCC). A population-based case-control study involving 550 non-Asian RCC patients 25 to 74 years of age and an equal number of sex-, age-, and race-matched neighborhood controls was conducted in Los Angeles, California. Detailed information on FH of cancer, medical and medication histories, and other life-style factors was obtained through in-person interviews. Having a first-degree relative with kidney cancer was associated with a significantly increased risk of RCC [odds ratio (OR), 2.5; 95% confidence interval (CI), 1.04–5.9] after adjustment for potential confounding factors. Having a first and/or second-degree relative with kidney cancer was similarly associated with an increased risk of RCC (OR, 2.9; 95% CI, 1.4–6.3). Risk factors for RCC identified in the Los Angeles study include cigarette smoking, chronic obesity, history of hypertension, regular use of analgesics and amphetamines, intake of cruciferous vegetables (protective), and history of hysterectomy. None of the above risk factor-RCC associations differed significantly between RCC cases with and without a FH of kidney cancer. A FH of urinary tract cancers other than kidney cancer was not associated with RCC risk (OR, 0.7; 95% CI, 0.3–1.7). A FH of nonurinary tract cancers also was unrelated to RCC risk (OR, 1.1; 95% CI, 0.9–1.5).

Introduction

Kidney cancer is an uncommon malignancy. In the United States, there are ~30,000 new cases each year, accounting for ~2% of all of the incident cancer cases diagnosed annually (1). Nonetheless, the incidence of kidney cancer has been increasing during the last three decades, such that the rates for both men and women in the mid-1990s are 50% higher than the comparable rates in the early 1970s (2, 3). RCC accounts for 80–85% of all of the kidney cancers in the United States. The remaining 15–20% of kidney cancers are mostly cancers of the renal pelvis, which are anatomically and histologically distinct from RCC (4).

A series of case reports first linked FH of kidney cancer to the development of RCC (5, 6). These uncontrolled observations were later followed by four case-control studies, three of which reported increased risks of RCC in subjects having a first-degree relative with kidney cancer (7–10). Schlehofer et al. (10) noted an OR of 1.6 (95% CI, 1.1–2.4), whereas the comparable figures in Mellemgaard et al. (9) and McLaughlin et al. (8) were 4.3 (95% CI, 1.53–14.86; derived from data presented in report) and 2.1 (95% CI, 0.80–6.08; derived from data presented in report), respectively. Kreiger et al. (7), on the other hand, observed no association between FH of kidney cancer and RCC risk (OR, 1.1).

The aim of the present study was to evaluate FH of cancer (kidney, bladder, or other parts of the urinary tract, other sites) in relation to RCC, using data from a population-based case-control study conducted in Los Angeles, California. We also investigated if a positive FH of kidney cancer modifies any of the risk factor-RCC associations identified in this Los Angeles-based study.

Materials and Methods

The study design and data collection have been described previously (11–15). In brief, the population-based cancer registry of Los Angeles County identified 1724 non-Asian patients, ages 25–74 years, with histologically confirmed RCC between April 1986 and December 1994. Among these, 832 patients (diagnosed between 1988 and 1994) were eligible for the present study after the study questionnaire was revised in January 1992 to include information on FH of cancer. Of the 832 patients, 147 died before we could contact them or were too ill to be interviewed. Permission to contact 28 patients was denied by their physicians. Sixty-four patients refused to be interviewed. Thus, we interviewed 71% (593 of 832) of all of those excluded because of lack of matched control subjects. Thus, 550 cases were included in this study. The mean time interval between cancer diagnosis and interview was 13 months. A comparison by gender, race, and age of recruited patients with the Los Angeles study include cigarette smoking, chronic obesity, history of hypertension, regular use of analgesics and amphetamines, intake of cruciferous vegetables (protective), and history of hysterectomy. None of the above risk factor-RCC associations differed significantly between RCC cases with and without a FH of kidney cancer. A FH of urinary tract cancers other than kidney cancer was not associated with RCC risk (OR, 0.7; 95% CI, 0.3–1.7). A FH of nonurinary tract cancers also was unrelated to RCC risk (OR, 1.1; 95% CI, 0.9–1.5).

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3 The abbreviations used are: RCC, renal cell carcinoma; OR, odds ratio; CI, confidence interval; FH, family history; VHL, von Hippel-Lindau.
control subject who was matched to the index case patient by sex, date of birth (within 5 years), race, and neighborhood of residence at the time of cancer diagnosis. To search for these “neighborhood” control subjects, we followed an invariant procedure that defines a sequence of houses on specified neighborhood blocks. We attempted to identify the sex, age, and race of all of the inhabitants of each housing unit; “not at home” units were systematically revisited to complete the census. The first resident along this defined route who satisfies all of the eligibility criteria for controls is asked to participate in this study (i.e., first eligible control). If the individual refuses, the next eligible control (i.e., second eligible control) in the sequence is asked and so on until we locate an eligible control who agrees to be interviewed. When we failed to find any resident who met our matching criteria after canvassing 150 housing units, we excluded race from the matching criteria. If a matched control subject based on this relaxed criterion could not be found within a maximum of 300 housing units, the case patient was dropped from the study. As stated above, 43 cases were excluded from the study because of lack of a matched control. We completed in-person interviews on 550 control subjects. There were 54 controls who were not matched on race to the index case. Of the control subjects, 365 (66%) were first eligible controls, whereas 119 (22%) and 66 (12%) were second and third eligible controls, respectively.

In-person, structured interviews were conducted in the homes of the subjects. The questionnaire requested information up to 2 years before the diagnosis of cancer for cases and 2 years before diagnosis of cancer of the index case for matched controls. In addition to FH of cancer, the questionnaire requested information on demographic characteristics, height and weight, lifetime use of tobacco and alcohol, usual adult dietary habits, lifetime occupational history, prior medical conditions, and previous use of medications. Study subjects were explicitly asked if any of their first-degree relatives (parents, siblings, or children) had ever been diagnosed with kidney cancer. Similar questions were asked regarding “other urinary tract cancers,” and “nonurinary tract cancers.” The same three sets of questions were then repeated for second-degree relatives (uncles/cousins, grandparents, or nieces/nephews).

Data were analyzed by standard matched-pair methods (16). The associations of RCC with various FH variables were measured by ORs and their corresponding 95% CIs. Conditional logistic regression models were used to examine the FH-RCC relationships with and without adjustment for other risk factors identified in the Los Angeles study, which included cigarette smoking, chronic obesity, history of hypertension, regular use of analgesics and amphetamines, and cruciferous vegetable intake (in quintiles).

### Results

The mean age of the patients at diagnosis of RCC was 58.6 years. Most patients were non-Hispanic whites (n = 407) with the remaining being Hispanic whites (n = 85) and African-Americans (n = 58). On average, RCC patients had lower level of education than controls. The OR for RCC was 0.6 (95% CI, 0.5–0.7) in subjects who had attended college (13 years or more of schooling) compared with those who had a high school education or lower. Addition of an “education” covariate to all logistic regression models used to examine FH and RCC risk did not appreciably change any of the study results and, thus, was not retained.

Twenty-one (3.8%) cases and 9 (1.6%) controls reported having a first-degree relative with kidney cancer, yielding an

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**Table 1** Family history of cancer and risk of RCC

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
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<tr>
<td><strong>Kidney cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>First-degree relatives only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>1.0</td>
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<tr>
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<td>21</td>
<td>9</td>
<td>2.3 (1.1–5.1)</td>
<td>2.5 (1.04–5.9)</td>
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<td>First- and/or second-degree relatives</td>
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<td></td>
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<td>482</td>
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<td>1.0</td>
</tr>
<tr>
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<td>11</td>
<td>2.9 (1.5–5.8)</td>
<td>2.9 (1.4–6.3)</td>
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<tr>
<td><strong>Other urinary tract cancers</strong></td>
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<td></td>
<td></td>
<td></td>
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<td>370</td>
<td>386</td>
<td>1.0 (0.8–1.3)</td>
<td>1.0 (0.8–1.4)</td>
</tr>
</tbody>
</table>

*a* The sum of cases or controls in each exposure category might be less than the total number of subjects because of exclusion of subjects with missing values.

*b* ORs were adjusted for number of cigarettes smoked/day, current smoking status, body mass index, history of hypertension, regular use of analgesics and amphetamines, and cruciferous vegetable intake (in quintiles).
OR for RCC of 2.3 (95% CI, 1.1–5.1; Table 1). Because of the lack of information on sibship size (thus, inability to control for this potential confounder) in study subjects, we also examined the risk of kidney cancer associated with affected parent(s). The latter OR was 3.5 (95% CI, 1.3–9.6; 17 cases and 5 controls). Similarly, sibship size may vary by level of education. Therefore, we repeated the analyses of FH of cancer (kidney cancer, other urinary tract cancer, and nonurinary tract cancer) stratified by level of education. Results were similar to those presented in Table 1 (data not shown). Only two cases reported more than one first-degree relative with kidney cancer; one female case reported that her father and two siblings had kidney cancer (the family was diagnosed with the VHL syndrome), and the other case (male) reported the mother, two siblings, and a grandmother being affected with kidney cancer. There were no controls with multiple affected first-degree relatives. Having a first and/or second-degree relative with kidney cancer was similarly associated with an increase in risk of RCC (OR, 2.9; 95% CI, 1.5–5.8). On the other hand, no increase in RCC risk was observed in subjects with a FH of urinary tract cancers other than kidney cancer or in subjects with a FH of nonurinary tract cancers (Table 1). Adjustment for other risk factors for RCC did not appreciably change any of the FH-RCC associations (Table 1).

The mean age at RCC diagnosis among patients with affected first-degree relatives (55.1 years) was lower than that in patients without such a history (58.7 years), although the difference was not statistically significant. In addition, the risk of RCC associated with having one or more affected first-degree relatives was higher in younger (<55 years; OR, 4.5; 95% CI, 0.97–20.8) than older (55+ years) patients (OR, 1.7; 95% CI, 0.7–4.4).

We compared the RCC risk factor profiles between cases with [FH (+)] and without [FH (−)] a FH of kidney cancer. Regardless of whether FH was defined by first-degree relatives only or first- or second-degree relatives, risk factor profiles were not significantly different between FH (+) and FH (−) cases of RCC (data not shown).

There were 54 case-control pairs that were not matched on race. We repeated all of the analyses after excluding these 54 pairs. The results were consistent with those based on the full data set. We also repeated all of the analyses on the subset of 365 case-control pairs in which the control subjects were first eligible controls. Again, results were similar to those based on the full data set.

Discussion

Four analytical epidemiological studies of RCC have reported on a FH of cancer in relation to disease risk [Ref. 7 (limited to subjects’ parents) and Refs. 8–10], and three of them (8–10) provided supporting evidence of an association between FH of kidney cancer and risk of RCC. The present study adds to the evidence that there is a familial component in RCC etiology. In this study, we found that having a first-degree relative affected with kidney cancer is associated with a 2.3-fold risk of RCC (21 exposed cases and 9 exposed controls).

Only two epidemiological studies of RCC have examined a FH of other urinary tract cancers or nonurinary tract cancers in relation to disease risk (9, 10). In the first study, Mellemgaard et al. (9) found that having a sibling who had been diagnosed with a cancer other than kidney cancer was associated with a modest but statistically significant increased risk in men but not in women. In the same study, having a parent who had been diagnosed with a cancer other than kidney cancer did not increase risk significantly in either men or women. The second study examined the relationship of FH of thyroid cancer to RCC risk and found that the likelihood of RCC was not increased significantly by having a parent or sibling with thyroid cancer (10). In the present study, having a FH of urinary tract cancers other than kidney cancer or a FH of nonurinary tract cancers was unrelated to RCC risk.

Recently, there have been reports of heightened susceptibility to environmental risk factors for particular forms of cancer among individuals with genetic susceptibility to the disease (17, 18). In the present study, we investigated if positive FH of kidney cancer is associated with a heightened susceptibility to RCC risk factors in the environment. Study results provide no evidence of such heightened susceptibility among familial cases. However, the study has relatively low statistical power to detect interaction effects between FH of RCC and environmental risk factors (such as smoking) for RCC. As an example, the minimum interaction relative risk between FH, including first- and second-degree relatives, and smoking that this study is capable of detecting with an expected study power of ≥80% and a two-sided significance level of 5% is 4.3. The comparable figures for a history of hypertension and regular use of analgesics are 3.1 and 3.4, respectively.

Although the vast majority of RCC occurs in sporadic form, several hereditary conditions, including VHL disease and hereditary papillary RCC, have been linked to RCC development. The most common cause of inherited RCC is VHL disease, a dominantly inherited multisystem disorder in which affected individuals are at risk to develop tumors in a number of organs. In the kidneys, patients with VHL often develop multiple, bilateral tumors and cysts; the cumulative risk of RCC among VHL disease patients is >70% by 60 years of age (19). The VHL tumor suppressor gene, located in chromosome 3p, is involved in both spontaneous and hereditary RCC (20). Mutation in this gene is associated almost exclusively with the most common histological type of RCC, the clear cell carcinomas (21). Hereditary papillary RCC is histologically and genetically distinct from RCC. The syndrome is characterized by, among other manifestations, multifocal, bilateral papillary RCC, a histological type that is found in only 10% of sporadic cases of RCC (22).

Our study has several limitations. This study is based on information reported by the subjects, and, therefore, it is conceivable that cases may recall FH of cancer more completely than controls. Recall of cancer history is generally more accurate for first-degree than second-degree relatives (23). For this reason, we present our analysis separately for first-degree relatives only and first- and second-degree relatives combined. Comparable ORs were noted whether FH was defined by first-degree relatives only or first- and second-degree relatives combined. Furthermore, if recall bias is present among cases, one would either expect excess risk across multiple sites (i.e., cases had better recall of cancer occurrence in relatives than controls) or deficit in risks for other (i.e., nonkidney) cancers (i.e., cases were more likely than controls to mis-report kidney cancers in relatives when the primary cancer sites were actually not kidney). Our data exhibit none of the above. Therefore, it is not likely that recall bias is responsible for our observed FH-kidney cancer association.

There is also the possibility of bias introduced by a control group that is more educated than the case group. Higher education may lead to more accurate recall by the control group, resulting in a higher degree of recall bias among cases. On the other hand, higher education may be associated with lower sibship size, a potential confounder that this study is incapable...
of controlling (we did not ask about sibship size). However, we found no difference in rates of positive FH by level of education among control subjects. In addition, stratified analysis showed comparable relative risks associated with FH of kidney cancer in subjects with low (high school or less) versus high levels of education. Therefore, it is unlikely that our observed FH-RCC association is a spurious finding as a result of higher level of education among controls relative to cases.

As stated above, another limitation of the current study is that we did not collect information on sibship size such that risks of FH could be calculated with adjustment for this potential confounder. We recognized the potential seriousness of this missing piece of information. Thus, we repeated all of the analyses of FH-cancer association restricting to affected parents only. We noted a stronger association with kidney cancer, whereas similarly null results were seen with all of the other cancers. Thus, it is unlikely that our observed association between FH and kidney cancer risk results from confounding by sibship size.

Only 71% of all eligible patients were included in the present study. It is possible that cases with and without a FH of kidney cancer differ in their disease prognosis (i.e., differential survival times). However, our data show comparable proportions of affected cases between RCC patients with shorter (<6 years after diagnosis) versus longer survival time (4.4% and 3.6%, respectively). Furthermore, we found no difference in the age and sex distributions of eligible patients who were excluded from the study because of death compared with study patients. Therefore, it is unlikely that our inability to recruit all of the eligible kidney cancer patients has resulted in a spurious association between FH of kidney cancer and disease risk.

In this study, we showed that familial occurrence of RCC is associated with a 2.3-fold increase in RCC risk in the proband but only a small fraction (3.8%) of patients in this population-based series are affected. We found no evidence that any of the risk factor-RCC associations differ between cases with and without a positive FH. However, our study only has sufficient statistical power to detect substantial interactions between FH and environmental risk factors, interaction relative risks of ≥3.0 given expected power of ≥80% and two-sided significance level of 5%.

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References
