Short Communication

Family History and the Risk of Kidney Cancer: a Multicenter Case-control Study in Central Europe

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Abstract

An elevated familial relative risk may indicate either an important genetic component in etiology or shared environmental exposures within the family. Incidence rates of kidney cancer are particularly high in Central Europe, although no data were available on the familial aggregation or genetic background of kidney cancer in this region. We have, therefore, investigated the role of family history in first-degree relatives in a large multicenter case-control study in Central Europe. A total number of 1,097 cases of kidney cancer and 1,555 controls were recruited from 2000 to 2003 from seven centers in Czech Republic, Poland, Romania, and Russia. The risk of kidney cancer increased with the increasing number of relatives with history of any cancer [odds ratio (OR), 1.15; 95% confidence interval (95% CI), 1.00-1.31 per affected relative], and this association seemed to be more prominent among subjects with young onset (OR, 1.55; 95% CI, 1.09-2.20 per affected relative). Overall, the OR was 1.40 (95% CI, 0.71-2.76) for the subjects who had at least one first-degree relative with kidney cancer after adjusting for tobacco smoking, body mass index, and medical history of hypertension, and this association was most apparent among subjects with affected siblings (OR, 4.09; 95% CI, 1.09-15.4). Based on the relative risk to siblings in our study population, we estimated that 80% of the kidney cancer cases are likely to occur in 20% of the population with the highest genetic risk, which indicate the importance of further investigation of genetic factors in cancer prevention for kidney cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(6):1287–90)

Introduction

Several registry-based studies, including the Swedish Family Cancer Database, deCODE Genetics, and Utah database, have reported an increased risk of kidney cancer for subjects with affected first-degree relatives, with a familial relative risk around 2-fold (1-3). Few case-control studies presented quantitative risk estimates for the association between family history of cancer and risk of kidney cancer (4-6), with results ranging from no association to a 2-fold increase of risk. An elevated familial relative risk may indicate a genetic component in etiology or shared environmental exposures within the family. The contribution of these two factors may be dissected by twin studies; however, the largest twin study has not been informative for the familiality of kidney cancer due to the lack of concordant twins (7).

Several genetic syndromes have been identified that are associated with histologic subtypes of kidney cancer, including germ-line mutations in Von Hippel-Lindau (*VHL*) and met proto-oncogene (*MET*; ref. 8). VHL syndrome is a rare autosomal-dominant condition caused by the germ-line mutations of the *VHL* tumor suppressor gene at chromosome 3p25-26 (9), and it is associated with the familial clear cell renal cell carcinoma (10). Individuals with *VHL* alterations also have an increased risk of developing benign or malignant tumors of central nervous system, eye, inner ear, and endocrine glands, in addition to kidney (10). On the other hand, hereditary papillary renal cell carcinoma has also been described, which is mainly associated with activating germ-line changes of *MET* oncogene in chromosome 7q31 (11).

Most previous studies on family history were conducted in North America or Scandinavia. However, the familial predisposition to kidney cancer is likely to vary among populations, which might have different genetic background and entail different environmental exposures. Incidence rates of kidney cancer vary widely, with particularly high rates being observed in some regions of Central Europe, in particular in the Czech Republic whose age-specific incidence rates are among the highest in the world (21.1 and 10.2 per 100,000 person-years compared with an average incidence of 10.4 and 5.1 per 100,000 person-years for men and women in the Europe, respectively; refs. 12, 13). Therefore, we investigated the role of family history in first-degree relatives and risk of kidney cancer in a large multicenter case-control study in Central Europe.

Materials and Methods

The study was conducted in seven centers in four countries of Central and Eastern Europe, including Czech Republic (Prague, Olomouc, Brno, and Ceske Budejovice), Poland

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(Lodz), Romania (Bucharest), and Russia (Moscow). Each center followed an identical protocol and was responsible for recruiting a consecutive group of newly diagnosed cases of kidney cancer as well as a comparable group of hospital controls. All subjects were residents of the study area recruited between 2000 and 2003. A total number of 1,097 cases of kidney cancer and 1,555 controls were recruited. All tumors originated in the parenchyma and contain a mixture of histology subtypes, with clear cell predominating. Controls in all centers were chosen among subjects admitted as in-patients or out-patients in the same hospital as the cases, with non–tobacco-related conditions, including minor surgical conditions, benign disorders, common infections, eye conditions (except cataract or diabetic retinopathy), and common orthopedic diseases (except osteoporosis), etc. Although controls had to be free from cancer at time of enrollment, previous history of cancer was not an exclusion criterium in either cases or controls. Controls are frequency matched with the case group by sex, age (±3 years), center, and referral (or residence) area. Both cases and controls underwent an identical interview with the same questionnaire. Written consent for participation was obtained from all study subjects, and ethical approval was obtained for all study centers as well as at IARC and National Cancer Institute.

Information of family history of cancer was collected for all first-degree relatives (parents, siblings, and offspring) on cancer sites and age at diagnosis. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for subjects who had relatives with any cancer and subjects who had relatives with kidney cancer using subjects who did not have any family history of cancer as reference group, after adjusting for potential confounders, including country of residence, age, sex, cumulative tobacco smoking, body mass index, and medical history of hypertension, using multivariate logistic regression. The effect of family history of cancer was evaluated separately by type of affected relatives (parents, siblings, and offspring). We also assessed the effect of number of relatives with history of cancer on the risk of kidney cancer. Stratified analyses were conducted to evaluate the effect of family history for subjects by age of onset. All the analyses were conducted with STATA software version 8.

Results

The frequency distribution of demographic variable and putative risk factors of kidney cancer is shown in Table 1. Each country contributed 9% to 53% of the cases. As expected, cases seemed to have higher body mass index than controls, and more cases reported to have medical history of hypertension than controls. However, we did not observe a higher smoking prevalence among cases versus controls in our study population.

The association between family history of cancer and the risk of kidney cancer is presented in Table 2. In general, the adjustment of demographic variables, tobacco consumption, body mass index, and history of hypertension had a very minor effect in bringing the effect estimates toward to the null; however, the association was retained after adjusting for these potential confounders. Overall, when the subjects had at least one first-degree relative with any cancer or with kidney cancer, the OR was 1.17 (95% CI, 0.99-1.39) and 1.40 (95% CI, 0.71-2.76), respectively. The risk of kidney cancer increased with the increasing number of relatives with history of cancer (OR, 1.15; 95% CI, 1.00-1.31 per affected relative). In general, the association between family history of cancer and risk of kidney cancer seemed to be more prominent among subjects diagnosed at age 50 or younger as opposed to older onset (OR per affected relative, 1.55; 95% CI, 1.09-2.20). In the analysis stratified by type of affected relatives, the effect was most apparent for subjects with affected siblings (OR, 4.09; 95% CI, 1.09-15.4).

Table 1. Frequency distribution of demographic variables and putative risk factors for kidney cancer

	Cases, *n* (%)	Controls, *n* (%)
Total	1,097	1,555
Country		
Romania	95 (9)	178 (11)
Poland	99 (9)	200 (13)
Russia	317 (29)	468 (30)
Czech Republic	586 (53)	709 (46)
Sex		
Female	449 (41)	543 (34)
Male	648 (59)	1,012 (65)
Age at interview		
≤40	49 (4)	60 (4)
41-50	163 (15)	232 (15)
51-60	350 (32)	501 (32)
61-70	351 (32)	492 (32)
>70	184 (17)	270 (17)
Smoking		
Never	510 (47)	628 (40)
Former	251 (23)	378 (25)
Current	333 (30)	543 (35)
Education		
Low	344 (31)	380 (25)
Medium	630 (58)	1040 (67)
High	118 (11)	131 (8)
Body mass index (kg/m^2)		
<20	23 (2)	47 (3)
20-25	307 (28)	514 (33)
26 to <30	473 (43)	648 (42)
>30	293 (27)	339 (22)
Hypertension		
No	600 (55)	951 (61)
Yes	496 (45)	603 (39)

We also looked into the effect of family history by country, as the incidence of renal cell varies substantially among our recruiting countries. We found that the effect of family history seemed to be most apparent in Czech Republic among subjects with young onset with OR of 2.33 (95% CI, 1.22-4.44) for family history of any cancer as opposed to 0.66 (95% CI, 0.12-3.71), 0.68 (95% CI, 0.16-2.83), and 1.48 (95% CI, 0.75-2.93) in Romania, Poland, and Russia respectively ($P_{\text{heterogeneity}}$ = 0.29). When the analysis for Czech Republic was limited to those with family history of kidney cancer, the OR was 14.6 (95% CI, 1.26-169), although the sample size was small (five cases and one control).

Discussion

As one of the largest studies on kidney cancer to date, our results provided evidence of familiality in kidney cancer in Central Europe, with risk estimates similar to the previous reports. Interestingly, we observed the stronger risk of kidney cancer associated with affected siblings, which is consistent with the results of the Swedish family cancer database as well as the recent case-control study in an Italian population (14, 15).

In general, an elevated risk in the offspring reflects a dominant genetic effect, whereas an elevated risk in the siblings signals a recessive effect (2). The moderate increased risk for parental family history might be partially explained by the germ-line mutations, such as *VHL* and *MET*, that are inherited in the dominant fashion (8). The elevated risk from affected siblings might be resulted from shared environment exposures in the childhood or indicate there are recessive genes involved. Cases did not have more siblings than controls: 85.5% of the controls and 85.8% of cases had siblings,

Table 2. OR and 95% CI of kidney cancer for family history of cancer

	Overall			Young onset (≤50)			Old onset (>50)		
	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)	Case	Control	OR (95%CI)
Type of cancer									
No FH of any cancer	725	1,094	1.00 (reference)	146	238	1.00 (reference)	579	856	1.00 (reference)
With FH of any cancer	370	454	1.17 (0.99-1.39)	66	67	1.55 (1.03-2.33)	304	387	1.10 (0.92-1.33)
With FH of kidney cancer	18	17	1.40 (0.71-2.76)	5	1	9.03 (1.00-81.5)	13	16	1.04 (0.49-2.20)
No. first-degree relatives with family history of any cancer									
0	725	1,094	1.00 (reference)	146	238	1.00 (reference)	579	856	1.00 (reference)
1	301	379	1.14 (0.95-1.37)	56	62	1.40 (0.91-2.16)	245	317	1.08 (0.89-1.33)
≥2	69	75	1.32 (0.93-1.87)	10	5	3.34 (1.10-10.2)	59	70	1.19 (0.83-1.73)
Trend			1.15 (1.00-1.31)			1.55 (1.09-2.20)			1.09 (0.94-1.26)
No. of first degree relatives with family history of kidney cancer									
0	736	1,125	1.00 (reference)	148	245	1.00 (reference)	588	880	1.00 (reference)
1	16	16	1.33 (0.65-2.70)	4	1	6.82 (0.72-64.57)	12	15	1.05 (0.48-2.27)
2	2	1	2.80 (0.25-31.6)	1	0	—	1	1	1.20 (0.07-19.5)
Trend			1.41 (0.77-2.59)			7.53 (0.91-62.40)			1.06 (0.54-2.09)
Parental family history									
No FH of any cancer	725	1,094	1.00 (reference)	146	238	1.00 (reference)	579	856	1.00 (reference)
With FH of any cancer	291	361	1.16 (0.96-1.39)	60	56	1.70 (1.10-2.62)	231	305	1.06 (0.87-1.31)
With FH of kidney cancer	10	15	0.86 (0.38-1.95)	5	1	9.03 (1.00-81.5)	5	14	0.45 (0.16-1.26)
Sibling family history*									
No FH of any cancer	611	930	1.00 (reference)	126	205	1.00 (reference)	485	725	1.00 (reference)
With FH of any cancer	98	120	1.17 (0.87-1.57)	9	10	1.31 (0.51-3.41)	89	110	1.16 (0.85-1.59)
With FH of kidney cancer	9	3	4.09 (1.09-15.4)	1	0	—	8	3	3.48 (0.90-13.4)
Offspring family history†									
No FH of any cancer	647	983	1.00 (reference)	123	208	1.00 (reference)	524	775	1.00 (reference)
With FH of any cancer	14	8	2.24 (0.92-5.43)	2	2	2.18 (0.28-16.7)	12	6	2.47 (0.91-6.74)
With FH of kidney cancer	0	0		0	0	—	0	0	—

NOTE: OR is adjusted for age, sex, country, smoking pack-years, body mass index, and medical history of hypertension.
Abbreviation: FH, family history of first-degree relatives.
*Restricted to those who had siblings.
†Restricted to those who had offspring.

and the average number of siblings among cases and controls were 1.99 and 2.22, respectively. Nevertheless, another factor that needs to be considered when interpreting the strong sibling risk is the age distribution, as affected siblings often have younger age of onset compared with the affected parents of the cancer probands (2). In our study, the mean age of diagnosis for affected siblings and affected parents of the index cases was 51 and 64 years, respectively. Therefore, the stronger familial relative risks observed in siblings might be partially associated with an earlier age of onset.

A stronger association observed in Czech Republic, which has the highest incidence of kidney cancer in the world, may simply have resulted from adequate study power as more than half the subjects were recruited in Czech Republic, or it may imply a founder effect of an unknown genetic mutation or familial aggregation of exposures. Random variation is could also be an explanation of inter-country differences in results.

Our study has several limitations. In addition to the limitations inherited in the hospital-based design, our information of family history was self-reported without verification. Cases might recall differently than controls; however, the use of diseased controls in theory should reduce such bias. In addition, we only collected information of family history of cancer for the first-degree relatives, for whom self-reported information on cancer is likely to be more valid than for more distant relatives. Moreover, a registry-based study shows that the familial relative risk kidney cancer is less elevated when considering second- or higher-degree relatives (1), which implicates that the loss of information when only considering first-degree relatives is marginal.

In summary, our results supported the notion that family history of cancer increases the risk of kidney cancer. This association is most important among subjects with early onset and those with affected siblings, adjusted for the major environmental risk factors of kidney cancer, including tobacco smoking, obesity, and hypertension.

Although germ-line mutations identified thus far might explain part of the familiality, they are rare syndromes and can only account for a very small proportion of familial cases. Based on the relative risk to siblings we observed in our study population (λ = 4.09), we estimated that 80% of the kidney cancer cases are likely to occur in 20% of the population with highest genetic risk (16), based on the model proposed by Pharoah et al. (17). Assuming only half of the susceptibility genes identified, one can capture 88% of the cases among the 50% of the population that have the highest genetic risk, which indicate the importance of further investigation of genetic factors in cancer prevention for kidney cancer.

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