

# Family History of Cancer and the Risk of Renal Cell Cancer

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## Abstract

Only scant information is available on the association between family history of kidney cancer and risk of renal cell cancer (RCC), particularly as concerns the variation of the risk according to sex, age, and type of relative or the association of family history of other cancers with RCC. We thus investigated the issue using data from a large multicentric case-control study conducted in Italy between 1992 and 2004 on 767 patients (494 men and 273 women) under age 80 years, with incident, histologically confirmed RCC, and 1,534 controls under age 80 years, admitted to hospital for a wide spectrum of acute, nonneoplastic conditions and frequency matched 2:1 to cases by center, sex, and age. Conditional logistic regression models, conditioned on center, sex, and age and adjusted for year of interview, smoking, body mass index,

and number of brothers and sisters were used to estimate odds ratios (OR). Eighteen RCC and 8 controls reported a family history of kidney cancer in one first-degree relative [OR, 5.2; 95% confidence interval (95% CI), 2.2-12.2]. No significant heterogeneity emerged according to sex or age of the proband or of the affected relative, or smoking habits, body mass index, and history of hypertension of the proband. Although not significant, the OR was higher when the affected relative was a sibling (OR, 7.0; 95% CI, 1.8-27.7) rather than a parent or child (OR, 4.3; 95% CI, 1.5-12.9), as suggested from previous studies. The OR of RCC was also significantly elevated for a family history of prostate cancer (OR, 1.9), leukemias (OR, 2.2), or any cancer (OR, 1.5). (Cancer Epidemiol Biomarkers Prev 2006;15(12):2441-4)

## Introduction

For most cancer sites, first-degree relatives of affected individuals have a 2- to 5-fold increased risk of developing a cancer at the same site (1, 2). Only a few studies, however, have investigated the risk of renal cell cancer (RCC)/kidney cancer in those who have a family history of the disease. A population-based case-control study from Canada (3), based on 518 RCCs and using a mailed questionnaire, did not find an association between family history and risk of RCC [odds ratio (OR); 1.1 in both sexes]. Conversely, three other population-based case-control studies (4-6) reported significantly increased risks: a study from Denmark on 368 RCCs found an OR of 4.1 in men and 4.8 in women (4); an international study conducted in Denmark, Sweden, Germany, Australia, and the United States and including 1,732 RCCs found an OR of 1.6 for one first-degree relative affected, whereas 7 cases and no controls reported two affected relatives (5); and a study from Los Angeles, United States, based on 550 RCCs, found an OR of 2.5 for an affected first-degree relative (6).

Three linkage studies analyzed the familial risk of kidney cancer. In a systematic population-based assessment using the Utah Population database (1), based on 687 kidney cancers, the familial relative risk was 2.5. In the nationwide Swedish Family Cancer database (7), including 23,137 kidney cancers, the standardized incidence ratio of kidney cancer was 1.6 in offspring and 4.7 in siblings of kidney cancer cases. Finally, a population-based familial aggregation analysis based on 1,078

RCC cases in Iceland (8) found relative risks of 2.5 for siblings and 2.2 for parents.

Only scant information is available on the issue, particularly as concerns the variation of the risk according to sex, age, and type of relative or the association of family history of other cancers with RCC. Moreover, virtually all epidemiologic evidence relies on studies from North America or Northern Europe. We thus investigated the relation between family history of kidney and other cancers and risk of RCC using data from a large multicentric case-control study conducted in Italy.

## Materials and Methods

A case-control study of RCC was conducted between 1992 and 2004 in four areas of Italy, including greater Milan and the provinces of Pordenone and Gorizia in northern Italy, the province of Latina in central Italy, and the urban area of Naples in southern Italy.

Cases consisted of 767 patients (494 men and 273 women) under age 80 years, admitted to major teaching and general hospitals in the areas under study with incident, histologically confirmed RCC (*International Classification of Diseases-9* 189.0; median age, 62 years; range, 24-79) diagnosed no earlier than 1 year before the interview. Cancers of the renal pelvis and ureter were excluded (*International Classification of Diseases-9* 189.1-189.2). The histology was clear cell carcinoma for 416 (54%), other types for 150 (20%), and unknown for 201 (26%). Controls were 1,534 subjects under age 80 years (median age, 62 years; range, 22-79), selected among patients admitted to the same hospitals as cases for a wide spectrum of acute, nonneoplastic conditions, unrelated to known or potential risk factors for RCC. Controls were frequency matched 2:1 to cases by center, sex, and age. Twenty-six percent of the controls were admitted for traumas, 32% for other orthopedic disorders, 14% for acute surgical conditions, and 28% for miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders.

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**Table 1. Distribution of 767 cases of RCC and 1,534 controls according to age, sex, and other selected covariates: Italy, 1992-2004**

	RCC, n (%)	Controls, n (%)
Sex		
Male	494 (64.4)	988 (64.4)
Female	273 (35.6)	546 (35.6)
Age (y)		
<50	123 (16.0)	246 (16.0)
50-59	200 (26.1)	407 (26.5)
60-69	281 (36.6)	555 (36.2)
70-79	163 (21.3)	326 (21.3)
Education (y)		
<7	372 (48.5)	849 (55.3)
7-11	212 (27.6)	457 (29.8)
≥12	183 (23.9)	228 (14.9)
Smoking habit*		
Never smoker	314 (41.1)	640 (41.7)
Current smoker		
<20 cigarettes/d	109 (14.3)	277 (11.1)
≥20 cigarettes/d	126 (16.5)	189 (12.3)
Ex-smoker	215 (28.1)	428 (27.9)
BMI* (kg/m <sup>2</sup> )		
<25	281 (36.8)	561 (36.7)
25 to <30	347 (45.4)	750 (49.1)
≥30	136 (17.8)	218 (14.2)
History of hypertension		
No	486 (63.4)	1,152 (75.1)
Yes	281 (36.6)	382 (24.9)
No. brothers*		
0	182 (23.8)	296 (19.3)
1	253 (33.0)	445 (29.0)
2	134 (17.5)	359 (23.4)
≥3	197 (25.7)	434 (28.3)
No. sisters*		
0	191 (24.9)	334 (21.8)
1	248 (32.4)	422 (27.5)
2	145 (18.9)	335 (21.8)
≥3	182 (23.8)	443 (28.9)

\*The sum does not add up to the total because of a few missing values.

Less than 5% of both cases and controls contacted refused to participate.

Cases and controls were interviewed during their hospital stay, using a structured questionnaire that included information on sociodemographic characteristics, anthropometric measures, life style habits (including tobacco smoking and alcohol drinking), usual diet, personal medical history, and, for women, obstetric and gynecologic history and use of exogenous female hormones. The subjects were specifically asked how many sisters and brothers they had and whether their parents, siblings, children, grandparents, or spouse had ever had cancer (excluding nonmelanoma skin cancer). For each relative with a history of cancer, we recorded the vital status at the time of interview, the current age or the age at death, the site of the tumor, and the age at diagnosis. In the present analysis, we considered the history of cancer in first-degree relatives only (i.e., parents, siblings, and children). On account of recall and classification difficulties, some sites were combined (i.e., the whole intestinal tract, Hodgkin's and non-Hodgkin lymphomas, cervix, and corpus uteri).

**Statistical Analysis.** We estimated the OR of RCC according to history of cancer at selected sites in first-degree relatives using conditional multiple logistic regression models (9). The models were conditioned on sex, age, and study center and included terms for year of interview, education, smoking, body mass index [BMI; weight (kg) / height (m)<sup>2</sup>] and number of brothers and sisters. Interaction tests between different strata of the characteristics of proband were done by comparing the -2log likelihood of

the models with and without the interaction term to the  $\chi^2$  distribution with 1 degree of freedom. To test heterogeneity of ORs according to characteristics of the affected relative, the model with a common OR was compared, again by means of the -2log likelihood test, to a model with an additional term estimating the difference in the OR according to the relative's characteristic.

## Results

Table 1 gives the distribution of cases of RCC and of controls according to sex, age, education, smoking habits, BMI, and number of brothers and sisters. Cases were more educated than controls, were more frequently heavy smokers or in the highest category of BMI, and reported more frequently a history of hypertension. Controls tended to have a larger family size than cases.

Table 2 shows the OR of RCC according to family history of kidney cancer in the whole data set and according to selected characteristics of the affected relative. Eighteen cases and 8 controls reported a first-degree relative affected with kidney cancer, and the corresponding OR was 5.2 [95% confidence interval (95% CI), 2.2-12.2]. The OR ranged between 4.1 and 10.0 across categories of relative's sex, age at diagnosis, or type of relative, and no significant heterogeneity was found. In particular, the OR was 4.3 (95% CI, 1.5-12.9) when the affected relative was a parent or a child of the proband and 7.0 (95% CI, 1.8-27.7) when the affected relative was a sibling.

In Table 3, the OR of family history is presented in different strata of sex, age, smoking habits, BMI, and history of hypertension in the proband. In all strata, the OR was above unity, the point estimates ranging between 3.8 and 7.7, and all heterogeneity tests were not significant.

Table 4 presents the OR of RCC according to family history of cancers at other sites. The OR was significantly elevated in subjects reporting a family history of prostate cancer (OR, 1.9; 95% CI, 1.0-3.6), leukemias (OR, 2.2; 95% CI, 1.1-4.2), and all sites (OR, 1.5; 95% CI, 1.2-1.8), also after exclusion of kidney cancer (OR, 1.4; 95% CI, 1.1-1.7). The OR was >2, although not significant, for melanoma (OR, 2.3; 95% CI, 0.8-6.9) and ovary (OR, 3.9; 95% CI, 0.9-16.6).

**Table 2. OR of RCC and 95% CI for a family history of kidney cancer in first-degree relatives, also according to some characteristics of the affected relative: Italy, 1992-2004**

	RCC (n = 767)	Controls (n = 1,534)	OR (95% CI)
Family history of kidney cancer			
No	749 (97.6)	1,526 (99.5)	1*
Yes	18 (2.3)	8 (0.5)	5.2 (2.2-12.2)
Sex of affected relative			
Male	8 (1.0)	5 (0.3)	4.1 (1.3-13.0)
Female	10 (1.3)	3 (0.2)	6.8 (1.8-25.6)
Youngest age at diagnosis in relatives (y) <sup>†</sup>			
<60	9 (1.2)	4 (0.3)	5.1 (1.5-17.1)
≥60	8 (1.0)	2 (0.1)	10.0 (2.1-48.1)
Relative affected			
Parent/son	10 (1.3)	5 (0.3)	4.3 (1.5-12.9)
Brother	8 (1.0)	3 (0.2)	7.0 (1.8-27.7)

NOTE: ORs from conditional logistic regression, conditioned on age, sex, and study center and adjusted for year of interview, education, smoking, BMI, and number of brothers and sisters.

\*Reference category.

<sup>†</sup>For some relatives, age at diagnosis was unknown.

**Table 3. OR of RCC according to family history of kidney cancer in strata of selected characteristics of the proband: Italy, 1992-2004**

Stratum	No. (%) with family history		OR (95% CI)
	RCC (n = 767)	Controls (n = 1,534)	
Sex			
Men	11 (2.2)	5 (0.5)	4.3 (1.5-12.5)
Women	7 (2.6)	3 (0.6)	7.2 (1.8-28.9)
Age (y)			
<60	10 (3.1)	4 (0.6)	5.5 (1.7-18.4)
≥60	8 (1.8)	4 (0.5)	4.6 (1.4-15.8)
Smoking habits			
Never smoker	11 (2.4)	5 (0.6)	4.1 (1.4-12.8)
Ever smoker	7 (2.2)	3 (0.5)	5.5 (1.3-22.8)
BMI (kg/m <sup>2</sup> )			
<26.12	6 (1.7)	4 (0.5)	3.8 (1.0-14.1)
≥26.12	12 (3.0)	4 (0.5)	6.0 (1.8-20.1)
History of hypertension			
No	12 (2.5)	7 (0.6)	4.7 (1.7-12.5)
Yes	6 (2.1)	1 (0.3)	7.7 (0.8-73.2)

NOTE: ORs from conditional logistic regression, conditioned on age, sex, and study center and adjusted for year of interview, education, smoking, BMI, and number of brothers and sisters. Reference category: no family history of kidney cancer.

## Discussion

This study confirms that a family history of kidney cancer in first-degree relatives increases the risk of RCC, and provides support to the hypothesis that the risk is higher when the affected relative is a sibling rather than a parent or child. Moreover, the risk was independent from smoking or BMI. A family history of prostate cancer, leukemias, and any cancer was also directly associated with RCC risk.

Possible sources of bias should be considered in evaluating these results. Although the use of hospital controls has long been debated (9), we included in the comparison group only subjects admitted for a wide spectrum of acute, nonneoplastic conditions, unrelated to the major risk factors for kidney cancer. Moreover, hospital admission for controls is unlikely to be related to the same genetic aspects as familial kidney cancer. The practically complete participation and the comparable catchment area of cases and controls contribute to the strength of our study.

Information on family history was self-reported and may thus be inaccurate. Apparently, RCC cases tend to recall cancers in the family better than controls. A review of studies evaluating the accuracy and completeness of reporting of family history in first-degree relatives of cancer patients and controls found satisfactory results for family history of breast, colon, and prostate cancer and less so for endometrial and ovarian cancer (10). The positive predictive value of self-reported family history (i.e., the proportion of subjects who actually had a positive family history among those who report it) was generally higher for cancer cases than controls: 81% versus 71% for colon, 85% versus 68% for prostate, 93% versus 74% for breast, 37% versus 17% for endometrial, and 69% versus 25% for ovarian cancer. Thus, given the difficulties in evaluating its role, differential reporting must be considered when interpreting the results of this study. In a study conducted on the same Italian population, the reproducibility of self-reported family history of digestive and respiratory tract cancers in first-degree relatives was tested for hospital controls, interviewed first in hospital and subsequently at home (11). The reproducibility of data on family history was satisfactory, although controls tended to report family history of cancer more frequently in hospital than at home (11). Thus, in the present study, the common hospital setting for cases and

controls, hence the similar attention to medical history, may have improved the comparability of information.

Our findings of an elevated risk of RCC in subjects with a family history of kidney cancer are in broad agreement with other reports, although our point estimate is somewhat higher than in other studies (1, 3-8). Given the broad confidence interval due to the small number of subjects reporting a family history of kidney cancer, our results are nonetheless in line with other reports. Possible explanations for the higher OR in our study include, besides chance, a difference in the population studied or a more marked differential recall in this study compared with other case-control studies.

Besides family history, the major recognized risk factors for kidney cancer are smoking, high BMI, and history of hypertension/drug treatment for hypertension (12). Although we did not find strong associations with these factors, the risk was significantly elevated in heavy smokers, obese subjects, in particular obese women, and in those reporting a history of hypertension. This is consistent with the epidemiologic evidence, given that smoking has a moderate effect on RCC risk and that in several studies the relation with obesity is stronger in, or confined to, women.

In this study, the familial risk was independent from these factors, as it was observed in both smokers and nonsmokers, in those with BMI below and above the median, and in those with or without a history of hypertension.

In the Los Angeles case-control study (6), the risk was higher in younger patients (<55 years; OR, 4.5; 95% CI, 0.97-20.8) than in older patients (≥55 years; OR, 1.7; 95% CI, 0.7-4.4). Similar results emerged in the most recent analysis of the Swedish Cancer database (13): the risks of children of RCC probands were 3.5 (95% CI, 2.3-5.3) when the age of proband at diagnosis was <50 years and 2.1 (95% CI, 1.5-2.9) otherwise. Corresponding values for siblings of RCC cases were 18.9 (95% CI, 10.1-35.4) and 7.7 (95% CI, 4.7-12.6). In our study, no consistent pattern of risk emerged when either the proband or the relative was <60 years at the onset of RCC. In recent

**Table 4. OR of RCC according to family history of selected cancers in first-degree relatives: Italy, 1992-2004**

Cancer site in the relative	Subjects with family history (%)		OR (95% CI)
	RCC (n = 767)	Controls (n = 1,534)	
Oral cavity	21 (2.7)	33 (2.2)	1.3 (0.7-2.2)
Esophagus	6 (0.8)	15 (1.0)	0.9 (0.4-2.4)
Stomach	49 (6.4)	74 (4.8)	1.4 (0.9-2.0)
Intestine (chiefly colorectum)	39 (5.0)	63 (4.0)	1.4 (0.9-2.1)
Liver	32 (4.2)	60 (3.9)	1.1 (0.7-1.7)
Gallbladder	2 (0.3)	3 (0.2)	1.1 (0.1-8.3)
Pancreas	11 (1.4)	30 (2.0)	0.8 (0.4-1.7)
Larynx	9 (1.2)	14 (0.9)	1.5 (0.6-3.7)
Lung	58 (7.6)	88 (6.1)	1.3 (0.9-1.9)
Bone	0 (0.0)	6 (0.4)	—
Skin, including melanoma	7 (0.3)	6 (0.4)	2.3 (0.8-6.9)
Breast	41 (5.3)	65 (2.8)	1.3 (0.9-2.0)
Uterus	26 (3.4)	32 (2.1)	1.6 (0.9-2.7)
Ovary	5 (0.7)	3 (0.2)	3.9 (0.9-16.6)
Prostate	19 (2.5)	21 (0.9)	1.9 (1.0-3.6)
Bladder	6 (0.8)	15 (1.0)	0.8 (0.3-2.2)
Brain	17 (2.2)	21 (0.9)	1.6 (0.8-3.0)
Lymphomas	7 (0.9)	12 (0.8)	1.2 (0.5-3.0)
Leukemias	19 (2.5)	17 (1.1)	2.2 (1.1-4.2)
All sites	321 (41.9)	520 (33.9)	1.5 (1.2-1.8)
Excluding kidney	307 (40.0)	514 (33.9)	1.4 (1.1-1.7)

NOTE: ORs from conditional logistic regression, conditioned on age, sex, and study center and adjusted for year of interview, education, smoking, BMI, and number of brothers. Reference category: no family history of the investigated cancer.

periods, incidental detection of RCC has increased following the increased use of ultrasonography and other imaging procedures (14). Diagnostic anticipation of RCC over recent periods may have confounded the relation between age at diagnosis of RCC and family history of kidney cancer in this study.

In the Swedish Family Cancer database (13), the risk of RCC was considerably higher for siblings (OR, 10.2; 95% CI, 7.0-15.1) of RCC probands than for their children (OR, 2.5; 95% CI, 1.9-3.2). The authors concluded that recessive effects may be important for familial aggregation of RCC. In our study too, the OR was higher when the affected relative was a sibling (OR, 7.0) rather than a parent or child (OR, 4.3), although these ORs were not significantly heterogeneous. However, this may be due to lack of power, given the small number of subject reporting a family history of kidney cancer in our study.

Several autosomal dominant inherited syndromes predisposing to RCC have been described (15, 16), the most common being the von Hippel-Lindau syndrome, characterized by excesses of RCC and other neoplasms and caused by germ-line mutations in the *von Hippel-Lindau* tumor suppressor gene, a gene that is also involved in sporadic RCC (15, 16).

However, these syndromes are rare and probably, as for many other cancers, most of the familial risk in older patients is not due to these highly penetrant genes (2). Other susceptibility genes may exist, with lower penetrance but much higher frequency in the population, which might account for more cases of RCC. Identification of these genes is extremely difficult because their low penetrance does not cause striking familial aggregations (2). The observation that recessive effects may be important in familial RCC, in contrast with von Hippel-Lindau and other identified dominant familial RCC syndromes, supports the existence of such lower penetrance susceptibility genes (13).

We cannot determine whether any of the individuals with a family history was related to any of the other individuals with a family history of renal cancer. However, by comparing the age, sex, areas of birth and residence of the interviewees, and more important, the data on the cancer in the relative, it seems unlikely that the same kidney cancer case was reported by more than one study subject. On the other hand, we collected data on history of cancer in first-degree relatives and in grandparents only. Not having data on kidney cancers in the enlarged family, we have no way to determine whether multiplex renal cancer families account for some of the increase in risk we found.

We had no data on the histology of the kidney cancer in the relative, and because only 18 cases reported a family history of kidney cancer, our study did not have the power to investigate whether the distribution of histologic types of RCC cases with a family history of kidney cancer differed from that of cases without kidney cancers in first-degree relatives.

A major strength and originality of this study is that the information was systematically collected on history of cancer at various sites in relatives, meaning that quantitative estimates of RCC risk could be made with reference to family aggregation of other cancers. Such a systematic assessment has been done previously by two linkage studies. In the Utah Population database (1), no significant associations were found between family history of other cancers and risk of kidney cancer, whereas in the Swedish Family Cancer database (7), discordant sites that were associated with kidney cancer in siblings were ovaries, endocrine glands, and pancreas. In our study too, cases reported a family history of ovarian cancer more frequently than controls, although the association was not significant, probably given the small numbers, whereas no association with family history of pancreatic cancer emerged.

In contrast with our finding of an increased risk of prostate cancer in relatives of kidney cancer cases, family history of prostate (7) or urinary tract cancers (6) did not increase the risk

of RCC in other studies. However, in a companion study on prostate cancer with a similar design and setting, the risk of prostate cancer was elevated in men with a family history of kidney cancer (17). In addition, the association with family history of leukemia is not confirmed in the two linkage studies from Utah (1) and Sweden (7).

Finally, we found a nonsignificant excess of cancer of the anus reported in relatives of RCC cases compared with relatives of controls (four cases and two controls). In particular, a woman diagnosed with RCC at age 71 years reported an anal cancer at 62 years in the father, an anal cancer at 49 years in a brother, and a uterine cancer at 52 years in a sister. The best identified risk factor for anal cancer is human papillomavirus infection (18). A higher susceptibility to human papillomavirus-induced carcinogenesis would also explain the nonsignificantly increased risk for family history of uterine cancers observed in this study. However, there is no clear evidence that human papillomavirus plays a role in RCC (19). Given the multiple tests done, this and other associations may as well be false-positive results and should be considered with great caution, in the absence of confirmatory results from other studies. Moreover, a more precise reporting of intestinal sites by cases cannot be ruled out.

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