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A case-control study of risk factor for renal cell cancer in northern Italy

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A hospital-based case-control study of renal cell cancer was conducted in northern Italy between 1986 and 1989, with 240 cases of renal cell cancer (150 males and 90 females), and 665 controls (445 males and 220 females) chosen on the basis of age, sex, and area of residence. No associations were found between renal cell cancer and: body mass index (BMI); number of cigarettes smoked; age at starting to smoke; years of smoking; consumption of wine, beer, spirits, coffee, decaffeinated coffee; tea; intake of animal protein, fruits, and vegetables; various reproductive factors; hormonal use; sexual habits; sexually transmitted diseases; or selected occupational exposures. The odds ratio (OR) was above unity in smokers (OR = 1.34 for ≥ 15 cigarettes/day), but the trends in risk with dose or duration were not statistically significant. Significant positive associations were found between renal cell cancer and sources of fat intake, especially margarine (OR for highest *vs* lowest intake = 1.71), and oils (OR = 1.89) whereas carrot intake showed a negative association (OR = 0.62). Also, a history of nephrolithiasis and multiple episodes of cystitis showed weak positive associations (OR = 2.00, 95 percent confidence interval (CI) 1.07 – 3.73; and OR = 1.60, 95 percent CI 0.95 – 2.70, respectively).

Key words: Diet, obesity, occupation, renal cell cancer, smoking.

Introduction

Cancer of the kidney is a relatively common cancer in many western countries, with age-specific incidence and mortality rates in some areas showing generally increasing trends, about one to two percent per year over the last decade.[1-3] In Italy, where only mortality rates are available, rates (3.3/100,000 for males and 1.3/100,000 for females in 1978 – 82, World standard) were comparable to those of Britain, but lower than in most northern and central European countries.[4,5] Furthermore, mortality was substantially higher in both sexes in northern (and mostly northeastern) Italian areas, with more than a two-fold difference in comparison with overall rates in the southern region.[5,6]

Renal cell cancer constitutes about 85 percent of all kidney cancers;[7] there is, however, very little known about the causes of this tumor.[1,2] A number of epidemiologic investigations[8-14] give support to the role of cigarette smoking, although others[15-20] do not. In particular, the role of smoking appears to be more consistent with the development of renal pelvic cancer[21-23] and less consistent with the development of renal cell cancer. The association of kidney cancer with obesity;[8,9,20,24,25] with coffee, tea, and alcohol consumption;[8,9,14,17-20,24,26] with meat consumption;[9,17-19] and with certain occupational exposures[8,9,14,17,18,27-31] has been explored; but the results are not consistent.

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To further clarify the role of these known factors and other potential factors, a case-control study was undertaken in the northern part of Italy.

Materials and Methods

From March 1986 to June 1989, a hospital-based case-control study on renal cell cancer (International Classification of Disease 9th Revision [ICD-9], 189.0) was conducted. Cases were drawn from two areas of northern Italy: (i) the western part of the Friuli-Venezia Giulia region (province of Pordenone) and the eastern part of the Veneto region (provinces of Treviso and Venice, northeastern Italy); and (ii) the greater Milan area in the Lombardy region.

The two areas under study were not covered by cancer registries and it was not possible to estimate the proportion of kidney cancer cases interviewed with respect to the total incidence rate. The study hospitals, however, included the majority of diagnostic and therapeutic facilities available in the areas under surveillance and, therefore, the largest proportion of renal cell cancer cases will have been referred there. All cases had histologically confirmed renal cell cancer. According to the ICD-9 nosology, the selected code excludes all but renal parenchymal cancers. Great care was taken to exclude cancers of the renal pelvis. The cases and controls were restricted to patients aged 20 – 74 years, whose diagnosis was made within 12 months of the date of interview. A total of 240 cases, 150 males and 90 females, were interviewed.

Controls were individuals of both sexes admitted only for acute conditions to the same hospital-based framework as the cases. About three controls were chosen per case on the basis of area of residence, sex, and age within quinquennia. Acceptable controls were individuals admitted to hospital for non-tobacco, non-alcohol, and non-hormone related diseases. A total of 665 controls, 445 males and 220 females, were interviewed. Of these, 26 percent were admitted for nontraumatic orthopedic conditions (mostly low back pain and disc disorders), 25 percent for traumatic conditions (mostly fractures and sprains), 19 percent for surgical conditions (mostly abdominal hernia), 17 percent for eye diseases, and 13 percent had other illnesses (*e.g.*, ear, nose, throat, and skin disorders).

All study subjects were interviewed during the course of their hospitalization. In each study area, a pre-coded questionnaire was used and interviewers were pilot-trained to reduce variability between interviewers. Relevant medical staff granted permission for the interview. The proportions of refusals were three percent for cases and four percent for controls. Information was obtained on sociodemographic factors; on lifestyle; on occupation; and on past medical history, including history of selected urologic, infectious, and hormone-related diseases. Self-reported height and weight one year before diagnosis were used to calculate body mass index (BMI).

Smokers were defined as individuals who had smoked at least one cigarette, pipe, or cigar every day for a continuous period of one year or more. Ex-smokers were defined as those who gave up smoking at least one year before diagnosis. The dietary part of the questionnaire included the frequency of consumption per week of 14 selected food items which constitute the major sources of retinoids, β-carotene, and fats in the Italian diet. The subjects were asked to describe their weekly intake of every food item during the year preceding the first symptoms of the disease. Simple subjective scores (low, intermediate, or high) were used as measures of intake of condiments, such as butter, margarine, and oils. It was not possible to obtain detailed information on the type of oil used throughout the patient's life, but non-olive oils are chiefly used in the study areas. Cases and controls were also asked to recall any major change in the frequency of intake of the same food during the 10 years preceding diagnosis. No significant or appreciable difference emerged between the cases and controls regarding changes in diet. Therefore, we considered only information on recent diet in all analyses.

Personal habits about intake of beverages containing methylxanthine (*e.g.* coffee, tea, and cola) and alcohol were also elicited. An alcohol score was computed as the product of the alcohol equivalent (g × ml) and amount of wine, beer, and spirits consumed each day, using tables of values issued by the Italian Department of Agriculture.[32,33]

Multiple logistic regression was used to estimate the odds ratios (OR), together with their 95 percent approximate confidence intervals (CI),[34] for the levels of all variables after accounting simultaneously for potential confounding effects.[34,35,36] In addition to risk factors of interest, the regression equations included terms for age, sex, education as an indicator of social class, area of residence, and BMI. Dose-response effects for some variables were assessed using the linear trend test of Mantel.[37]

Results

Background variables

No large differences between cases and controls were found for any of the demographic variables examined in Table 1. The mean age was approximately the same for male cases and controls (58.0 years *vs* 57.5 years), and for female cases and controls (58.6 years *vs* 58.7 years).

Many years of education were 7.2 and 7.0 for male cases and controls, and 5.5 and 5.4 for female cases and controls, respectively.

Body mass

Table 2 shows that, using BMI of less than 24 as a referent, the adjusted ORs for the development of renal cell cancer were 0.84 (95 percent CI 0.59 – 1.21) for individuals with BMI of 24 – 27, and 0.74 (95 percent CI 0.51 – 1.07) for subjects with indices of 28 or more.

Tobacco use

In Table 3, no significantly increased risk was noted for any of the three tobacco-related variables (*i.e.*, number of cigarettes smoked, age at starting to smoke, and years of cigarette smoking). Daily smokers of 25 or more cigarettes showed an OR = 1.16 (95 percent CI 0.58 – 2.35) and smokers who had smoked for 35 years or more had an OR = 1.18 (95 percent CI 0.74 – 1.87).

Alcohol, coffee, tea, and cola-containing beverages

The effects of alcohol and other beverage intake are shown in Table 4. No trend was found in the OR for disease by amount consumed per day of wine, beer, spirits, regular (caffeinated) coffee, decaffeinated coffee, tea, or cola-containing beverages.

Food items

Table 5 shows the estimated effects of weekly frequency of consumption of various indicator foods. There were no significant trends with increasing amounts of items such as meat, fish, liver, salami and sausages, and cheese. ORs greater than one were found, however, for increasing amounts of items that comprise some of the major sources of fat in the Italian diet, *i.e.*, milk, butter, margarine, and oils. Specifically, significant trends were found for margarine and for oil consumption. Conversely, frequent consumption of carrots showed a protective effect for renal cell cancer. Margarine, oils, and carrots, were included together in a logistic model (not shown), and each of the three variables remained significantly associated with renal cell cancer, even after adjusting for the effects of the other two risk factors.

Past history of selected diseases and sexual habits

Among the diseases displayed in Table 6, positive associations were found with a history of nephrolithiasis (OR = 2.00, 95 percent CI 1.07 – 3.73), and of multiple episodes of cystitis (OR = 1.60, 95 percent CI 0.95 – 2.70). There was no evidence of an association between renal cell cancer and number of marriages, age at first intercourse, or number of sexual partners.

Table 1. Distribution of cases and control according to sex and demographic features[a]

	Males				Females			
	Cases (N = 150)		Controls (N = 445)		Cases (N = 90)		Controls (N = 220)	
	Number	%	Number	%	Number	%	Number	%
Age (yrs)								
<50	28	18.7	93	20.9	20	22.2	50	22.7
50 – 59	51	34.0	149	33.5	26	28.9	62	28.2
60 – 69	49	32.7	149	33.5	27	30.0	70	31.8
>69	22	14.7	54	12.1	17	18.9	38	17.3
Education (yrs)								
<6	77	51.3	242	54.6	69	76.7	163	74.1
6 – 8	35	23.3	97	21.9	13	14.4	33	15.0
>8	38	25.3	104	23.5	8	8.9	24	10.9
Marital status								
Never	9	6.0	38	8.5	7	7.8	14	6.4
Ever	141	94.0	407	91.5	83	92.2	206	93.6
Occupation								
Clerical-professional	62	41.6	162	37.0	13	14.4	36	16.4
Manual worker	54	36.2	212	48.4	19	21.1	59	26.9
Farmer	27	18.1	56	12.8	10	11.1	34	15.5
Other, including housewife	6	4.0	8	1.8	48	53.3	90	41.1
Area of residence								
Northeastern Italy	83	55.3	234	52.6	51	56.7	146	66.4
Greater Milan area	67	44.7	211	47.4	39	43.3	74	33.6

[a]Some figures do not add up to the total because of missing values.

Table 2. Number of subjects, odds ratios, and confidence intervals for body mass index[a]

	Males		Females		Odds Ratio[b]	95% CI
	Cases ($N = 150$) N	Controls ($N = 445$) N	Cases ($N = 90$) N	Controls ($N = 220$) N		
Body mass index (Kg/m^2)						
<24	57	129	33	82	1	
24 - 27	52	165	28	63	0.84	(0.59 - 1.21)
>27	41	150	29	75	0.74	(0.51 - 1.07)
[c]						

[a]Some figures do not add up to the total because of missing values.
[b]Estimates from multiple logistic regression adjusted for age, sex, education, area of residence.
[c]Chi-square for trend (χ^2 trend = 2.60).

Table 3. Number of subjects, odds ratios, and confidence intervals (CI) for smoking habits[a]

	Males		Females		Odds Ratio[b]	95% CI
	Cases ($N = 150$) N	Controls ($N = 445$) N	Cases ($N = 90$) N	Controls ($N = 220$) N		
Smoking habit						
Never-smokers	26	106	71	170	1	
Ex-smokers	49	151	6	10	1.35	(0.83 - 2.21)
Current smokers:[c]						
<15 cigarette/day	24	61	5	20	1.07	(0.63 - 1.81)
15 - 24	38	86	6	17	1.31	(0.82 - 2.11)
>24	12	36	2	3	1.16	(0.58 - 2.35)

[a]Some figures do not add up to the total because of missing values.
[b]Estimates from multiple logistic regression adjusted for age, sex, education, area of residence, and BMI.
[c]Chi-square for trend was calculated excluding ex-smokers (χ^2 trend = 0.90).

Occupation

Twenty occupationally related exposures were investigated. No significant effect on renal cell cancer was found for any of them. Categories with 10 or more exposed cases are presented in Table 7.

Discussion

While several potential risk factors for renal cell cancer have been studied here, the results indicate that only a few of them may play a role in the etiology of this tumor. In contrast to previous studies that have reported an association with increased relative weight or BMI, at least in women,[8,9,20,24,25] this case-control study of renal cell cancer found no increased risk with respect to BMI. Recently, Asal *et al.*[24] and Goodman *et al.*[20] reported an increased risk of renal cell cancer by BMI in both males and females, a finding which has also been confirmed in a preliminary report.[38]

Since our findings are not consistent the other studies that show a positive association with BMI or with relative weight, we considered the possibility of a selection bias in the control group, which included many individuals whose admission to hospital was possibly related to increased relative weight. The present results, however, held true when analysis was restricted, in turn, to each major disease category in the control group. Furthermore, the weight distribution of subjects in the present investigation is comparable to that found in the 1983 Italian National Health Survey, which was based on 89,755 individuals representative of the Italian population, randomly selected within strata of geographical area, size of municipality, and size of household.[39]

While an increased risk of renal cell cancer resulting from exposure to tobacco smoke has been found in some studies,[8-14] our study, as well as others,[15-20] found only a moderate association. To this extent, it must be remembered that carcinogenic constituents of tobacco smoke remain in contact with renal cell tissue for shorter amounts of time compared to other sites of the urological

Table 4. Number of subjects, odds ratios, and confidence intervals (CI) for highest category examined for consumption of alcohol, coffee, tea, and cola-containing beverages

Variable	Category (drinks per day)[a]	Number of Subjects				Odds Ratio[b]	95% CI	χ^2 Trend
		Males		Females				
		Cases	Controls	Cases	Controls			
Wine	≥4	84	288	14	17	0.85	0.55 – 1.32	0.51
Beer	≥1	47	132	6	25	1.02	0.69 – 1.52	
Spirits	≥1	64	183	13	24	1.20	0.84 – 1.73	
Alcohol	≥100	17	70	1	1	0.71	0.39 – 1.30	0.98
Coffee	≥3	47	140	33	73	1.14	0.78 – 1.64	0.46
Decaffeinated coffee	≥1	12	12	6	19	1.56	0.85 – 2.88	
Tea	≥1	19	57	22	36	1.21	0.81 – 1.82	
Colas	≥1	4	14	1	6	0.72	0.27 – 1.97	

[a]Except for alcohol, which is g/day.
[b]Estimates from multiple logistic regression adjusted for age, sex, education, area of residence, and BMI.

Table 5. Number of subjects, odds ratios, and confidence intervals (CI) for highest *vs* lowest tertile of consumption of various food items

Variable	Highest tertile	Number of Subjects				Odds Ratio[a]	95% CI	χ^2 Trend
		Males		Females				
		Cases	Controls	Cases	Controls			
Meat	≥7[b]	62	170	40	84	1.05	0.73 – 1.50	0.14
Fish	≥2[b]	33	107	19	50	0.99	0.66 – 1.48	0.02
Liver	≥1[b]	29	83	14	56	1.01	0.63 – 1.61	0.11
Salami	≥3[b]	66	151	24	59	1.25	0.85 – 1.85	1.63
Eggs	≥3[c]	56	147	30	63	1.24	0.86 – 1.78	1.19
Milk	≥14[d]	56	124	31	92	1.44	0.96 – 2.14	3.48
Cheese	≥8[b]	43	126	22	57	1.00	0.66 – 1.51	0.03
Bread	≥4[b]	13	25	3	22	0.93	0.51 – 1.70	0.00
Carrots	≥2[b]	35	110	18	86	0.62	0.43 – 0.90	7.13
Green vegetables	≥14[b]	59	158	45	118	1.18	0.73 – 1.91	0.44
Fruits	≥14[b]	53	141	39	104	0.92	0.63 – 1.35	0.09
Butter	[e]	18	47	12	29	1.34	0.82 – 2.19	3.65
Margarine	[e]	32	62	17	30	1.71	1.07 – 2.74	5.14
Oils	[e]	20	76	18	26	1.89	1.11 – 3.24	6.27

[a]Estimates from multiple logistic regression adjusted for age, sex, education, area of residence, and BMI.
[b]Servings/week.
[c]Number per week.
[d]Glasses per week.
[e]"High."

tract, such as bladder and renal pelvis.[21-23] Alternatively, discrepancies between studies conducted in different geographical areas may derive from other risk correlates (*e.g.*, fluid intake).[20]

There is no conclusive evidence regarding the role of alcohol or of methylxanthine-containing beverages in renal cell cancer. This study, consistent with other case-control studies,[8,9,14,17] showed no positive relationship between renal cell cancer and beer, wine, or spirit consumption. Coffee, decaffeinated coffee, and tea have been considered in a few studies[8,9,17-20] showing predominantly no association, as in our study, or at most a weak positive association.

Dietary factors appear to correlate most with renal cell cancer in ecological studies. In Wynder *et al.*[8] and Armstrong and Doll,[40] positive associations between renal cell cancer and intake of fat and animal protein were reported. In a previous case-control study, Maclure and MacMahon[38] and McLaughlin *et al.*[9] observed a positive association with animal protein and meat intake. McCredie *et al.*[19] obtained a positive association with high milk intake, but no associations with intake of other animal protein or fat. Whereas no significant trends emerged in our study for the major sources of protein and fat in the Italian diet (*i.e.*, meat, liver, cheese, and butter), although increased ORs were found, positive

Table 6. Number of subjects, odds ratios, and confidence intervals (CI) for history of selected diseases and indicators of sexual habits

History[b]	Number of Subjects				Odds Ratio[a]	95% CI	χ^2 Trend
	Males		Females				
	Cases	Controls	Cases	Controls			
Cholelithiasis	10	23	16	24	1.60	0.97 - 2.65	-
Nephrolithiasis	15	22	3	10	2.00	1.07 - 3.73	-
Cystitis[c]	5	17	22	28	1.60	0.95 - 2.70	1.80
Gonorrhea	5	8	-	-	1.70	0.54 - 5.34	-
Syphilis	1	2	-	2	0.65	0.07 - 5.87	-
Condylomatosis	2	3	-	1	1.42	0.26 - 7.82	-
Skin warts	5	9	3	4	1.66	0.68 - 4.01	-
No. of marriages	7	13	1	8	1.23	0.47 - 3.21	0.30
AFI[d]	52	144	54	107	1.21	0.81 - 1.81	1.10
NSP[e]	41	157	1	2	0.69	0.46 - 1.03	3.50

[a]Estimates from multiple logistic regression adjusted for age, sex, education, area of residence.
[b]Positive history, unless otherwise stated.
[c]Three episodes or more *vs* none.
[d]Age at first intercourse.
[e]Number of sexual partners.

Table 7. Number of subjects, odds ratios, and confidence intervals (CI) for renal cell cancer (RCC) by occupation,[a] northern Italy, 1986 - 1989

Occupation	RCC Cases N. of exposed	Controls N. of exposed	Odds Ratio[b]	(95% CI)
Farmers	46	147	0.82	(0.55 - 1.24)
Wood and furniture workers	11	45	0.70	(0.35 - 1.39)
Food factory workers	10	23	1.24	(0.58 - 2.66)
Animal caretakers	42	112	1.10	(0.71 - 1.70)
Sheet metal workers	25	114	0.59	(0.37 - 0.95)

[a]Occupations with 10 or more exposed cases.
[b]Estimates from multiple logistic regression adjusted for age, sex, education, and area of residence.

significant trends were found for margarine and oils.

Little data on renal cell cancer exist with respect to vegetable and fruit intake,[9] but many observational studies have shown that among subjects with low intake of vegetables and fruit, cancer incidence rates were higher than expected.[41-45] Peto *et al.*,[46] have hypothesized that β-carotene or other (micro) nutrients contained in green and yellow vegetables may be responsible for a reduction in the incidence of human cancer, as observed in the negative association with carrot intake in this study.

The roles of sexual habits, sexually transmitted diseases, and other diseases have not been considered in most previous investigations of renal cell cancer correlates and none were found to be risk factors in this study. Significantly elevated ORs have been reported for some urinary infections[9,19] and for a history of kidney stones.[9,38] The present investigation provides further support for the possibility that nephrolithiasis and multiple episodes of cystitis may enhance the risk of renal cell cancer. However, in light of the weakness of such associations, it is difficult to completely disregard the influence of recall bias.

Some occupational exposures have been shown to produce an elevated risk for renal cell cancer. Specifically, asbestos workers,[30] petroleum workers,[27,31] and truck drivers[14] appear to be at increased risk. In the present study, some of the most common occupations (*i.e.*, farmers, ranchers and animal caretakers, sheet metal workers, wood and furniture workers, and food factory workers) were considered as sources of exposure to potential carcinogens, but no significantly increased ORs were found.

In conclusion, the absence of strong findings in the present investigation should be stressed. In fact, despite the large number of potential risk factors investigated, only two plausible and significant positive associations (with high fat and low carrot intakes) emerged, thus confirming the difficulties in studying epidemiologically the etiology of specific histological types of neoplasias such as renal cell cancer.

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