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Dietary Inflammatory Index and Renal Cell Carcinoma Risk in an Italian Case-Control Study

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Abstract

Background: The relation between diet related inflammation and renal cell carcinoma (RCC) has not been investigated.

Methods: In this study, we explored the association between the dietary inflammatory index (DII) and RCC in an Italian case-control study conducted between 1992 and 2004. Cases were 767 patients with incident, histologically confirmed RCC. Controls were 1534 subjects admitted to the same hospitals as cases for various acute, non-neoplastic conditions. The DII was computed based on dietary intake assessed using a reproducible and validated 78-item food frequency questionnaire. Odds ratios were estimated through logistic regression models conditioned on age, sex and center, and adjusted for recognised confounding factors, including total energy intake.

Results: Subjects in the highest quartile of DII scores (i.e., with a more pro-inflammatory diet) had a higher risk of RCC compared to subjects in the lowest quartile (OR 1.41, 95% CI 1.02, 1.97;

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Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

p-trend=0.04). Apparently stronger associations were observed among females (OR 1.68, 95% CI 0.93, 3.03), subjects aged <60years (OR 1.77, 95% CI 1.05, 2.98), BMI ≥25 kg/m^2 (OR 1.64, 95% CI 1.07, 2.51), and ever smokers (OR 1.66, 95% CI 1.08, 2.57), in the absence of significant heterogeneity.

Conclusion: A pro-inflammatory diet is associated with increased RCC risk.

Keywords

DII; diet; inflammation; renal cell carcinoma; case-control; Italy

Introduction

Renal cell carcinoma (RCC) is the most common type of renal tumour and represents 2%–3% of all new malignancies and is more as frequent in men as in women (1, 2). Major recognized risk factors for RCC are tobacco smoking, overweight and obesity, and family history of the disease (2, 3).

Considerable evidence has been gathered over the past few years linking increased cancer risk with chronic inflammation, and several clinical and experimental studies have linked tumour progression with the upregulation of pro-inflammatory molecules (4). Aspirin has been inversely related to kidney cancer(5). Evidence is accumulating on the role of chronic inflammation in RCC (6, 7).

Diet represents a varied set of exposures that often interact, and whose effect modifies both inflammatory responses and health outcomes. Various dietary components have different effect on inflammation (8, 9). The Western-type diet − characterized by a high consumption of red meat, high-fat dairy products, and refined grains − has been associated with higher levels of C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen (10, 11). On the other hand, the Mediterranean diet − characterized by a high consumption of whole-grains, fruit and green vegetables, fish, and olive oil, a low consumption of meat and butter, and a moderate alcohol and dairy products consumption − has been associated with lower levels of inflammation (12). Despite the circumstantial evidence, the possible relation between inflammation deriving from dietary exposure and RCC risk has not yet been investigated.

A literature-derived dietary inflammatory index (DII) was developed to assess the inflammatory potential of an individual’s diet (13). A typical pro-inflammatory diet is characterized by high consumption of foods rich in saturated fats, carbohydrates, and protein and low consumption of foods rich in poly-unsaturated fatty acids, flavonoids, and other selected components and micronutrients. The DII has been validated with various inflammatory markers, including CRP (14), IL-6(15, 16), and homocysteine (15).

High scores of this DII have been positively associated with a variety of cancers, including colorectal cancer (17, 18), and esophageal cancer (19–21) and, among urological cancers, prostate (22, 23), bladder cancers (24) renal cancer (25) and urothelial cancer (26). Using this case-control study conducted in Italy (27), this is the first attempt to examine the association between the DII and RCC risk.

Methods

Design and Participants.

The data were derived from a case–control study on RCC conducted between 1992 and 2004 in 4 Italian areas, including the greater Milan area and the provinces of Udine and Pordenone in northern Italy, the province of Latina in central Italy, and the urban area of Naples in southern Italy (27). Cases were 767 patients (494 men and 273 women) under the age of 80 years (median age 62 years, range 24–79 years) with incident, histologically confirmed RCC (ICD-9: 189.0), admitted to the major teaching and general hospitals of the study areas. Cancers of the renal pelvis and ureter (ICD-9: 189.1–189.2) were not included. Controls were 1,534 subjects (988 men and 546 women) under age 80 years (median age 62 years, range 22–79 years) admitted to the same hospitals as cases for a wide spectrum of acute nonneoplastic conditions, unrelated to known or potential risk factors for RCC, and to long-term dietary modifications. Controls were matched with cases by study center, sex, and quinquennia of age, with a case: control ratio of 1:2. Twenty-six percent of controls were admitted for traumas (mostly fractures and sprains), 32% for other orthopaedic disorders (such as low back pain and disc disorders), 14% for surgical conditions, and 27% for miscellaneous other illnesses including eye, nose, ear, skin or dental disorders. Less than 5% of both cases and controls contacted refused to participate.

Centrally trained and supervised interviewers collected information on socio-demographic characteristics, anthropometric measures, life-style habits, including tobacco smoking and alcohol drinking, and history of selected diseases during their hospital stay using a structured questionnaire. Subjects' usual diet prior to cancer diagnosis (for cases) or hospital admission (for controls) was assessed using an interviewer-administered food frequency questionnaire (FFQ), consisting of 78 items on foods and beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. Nutrient and total energy intake was determined using an Italian food composition database (28, 29). The FFQ showed a satisfactory validity (30) and reproducibility (31) with satisfactory results. The study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and informed consent were obtained from all participants.

Dietary Inflammatory Index

In order to compute the DII score, dietary information for each study participant were first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered (13). These parameters then were used to derive the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. To minimize the effect of "right skewing," this value was converted to a centred percentile score, which was then multiplied by the respective food parameter effect score (derived from a literature review on the basis of 1943 articles, (13). All of these food parameter-specific DII scores were then summed to create the overall

DII score for every subject in the study, with highest scores meaning a pro-inflammatory and with lowest scores meaning an anti-inflammatory diet. The DII computed on this study's FFQ includes data on 31 of the 45 possible food parameters comprising the DII: carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea.

Statistical analysis

The DII was analysed both by quartiles of exposure computed among controls and as a continuous variable, with each point corresponding to ≈10% of its range (5.00 to −5.20). Differences in food groups and nutrients across quartiles of DII were carried out using ANOVA. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models conditioned on study centre, sex and quinquennia of age, and adjusted for year of interview, education (<7, 7–11, ≥12 years, categorically), body mass index (BMI) (<25, 25–30, ≥30 kg/m^2, categorically), tobacco smoking (never smoker, ex-smoker from at least 4 years, current smoker of <20 and ≥20 cigarettes/day, categorically), family history of kidney cancer in first-degree relatives (yes, no), and total energy intake (<1786.8, 1786.8–2134.2, 2134.3–2460.0, 2460.1–2945.3, ≥2945.4 kcal/day, quintiles among controls, categorically). Tests for linear trend were performed using the median value within each quartile as an ordinal variable. Stratified analyses were carried out according to sex, age (<60, ≥60 years), BMI (<25, ≥25 kg/m^2) and tobacco smoking (never smokers, and ever smokers). Statistical analysis was performed using SAS® 9.3 (SAS Institute Inc., Cary, NC).

Results

The mean DII value was +0.13 (standard deviation, SD = 1.39) among cases and −0.06 (SD = 1.38) among controls, indicating a more pro-inflammatory diet among cases.

Characteristics of control subjects across quartiles of DII are provided in Table 1. There were significant differences in sex, age, and BMI across quartiles of DII. Compared to subjects in the lowest quartile (most anti-inflammatory group), subjects in the highest quartile (most pro-inflammatory group) of DII were more likely to be females (44.6% vs 25.9), older (24.0% vs 18.5% for ≥70 years' age group), have family history of kidney cancer (0.3% vs 0%) and less likely to be obese (14.2% vs 15.7%).

Table 2 shows the distribution of 10 food groups across DII quartiles among controls. Servings of fruit, vegetables and fish decreased significantly across quartiles, whereas servings of processed meat, sugar and desserts increased significantly.

Table 3 shows the distribution of 13 selected nutrients across DII quartiles among controls, these nutrients were selected to incorporate macro nutrients, vitamins, minerals and flavanoids. Intake of protein, niacin, riboflavin, vitamin B6, A and C, iron and zinc decreased significantly across quartiles.

Table 4 shows the OR of RCC according to the DII. Subjects in the highest quartiles of DII had an increased OR for RCC cancer compared to subjects in the lowest quartile ($OR_{Quartile4vs1}$= 1.41, 95% C.I=1.02, 1.97; P_{trend}=0.04). When analyses were carried out using DII as a continuous variable, the OR was 1.08 (95% CI 1.01, 1.15) for a one-unit ~10% of its range (5.00 to −5.20)) increase in DII.

Table 5 shows the OR of RCC in strata of selected covariates. Apparently stronger associations were observed among females ($OR_{Quartile4vs1}$= 1.68, 95% CI 0.93, 3.03), subjects aged <60years ($OR_{Quartile4vs1}$= 1.77, 95% CI 1.05, 2.98), BMI ≥25 kg/m^2 ($OR_{Quartile4vs1}$= 1.64, 95% CI 1.07, 2.51), and ever smokers ($OR_{Quartile4vs1}$= 1.66, 95% CI 1.08, 2.57), in the absence, however, of significant heterogeneity (all *p* values >0.10).

Discussion

We observed positive associations between RCC and inflammatory potential of diet as expressed by increasing DII scores in an Italian population. This result supports the hypothesis that individuals with a pro-inflammatory diet have a higher risk of developing RCC.

Adiposity, which is a strong correlate of higher BMIs, is known to contribute to inflammation (32, 33) . Our results showing that the subjects with higher DII having lower BMI may reflect the fact that the effect of adiposity overwhelms the effect of diet-associated inflammation in overweight and obese subjects. We also observed a greater percentage of older subjects in the most pro-inflammatory group, and the reason could be through the process of cellular senescence from damaged macromolecules and cells that accumulate with age; this results in the further release of inflammatory cytokines all of which are exacerbated with a pro-inflammatory diet (34). Compared to men, women were more frequently represented in the pro-inflammatory DII quartiles. This is reflected in the appreciably higher OR among women and is likely a consequence of a smaller influence of tobacco in a population level in men than in women in this (35)and other populations (36).

Previous results from this study showed a positive association between RCC and foods such as bread, pasta and rice, and milk and yoghurt whereas inverse association was observed for poultry, and vegetables intake, and no relation was found for coffee and tea, soups, eggs, red meat, fish, cheese, pulses, potatoes, fruits, desserts and sugars (27). With reference to macronutrients, a positive association was observed with increase starch intake and a protective effect was observed with polyunsaturated acid, including linoleic and linolenic acids (37). Concerning micronutrients, vitamin E and C were found to be protective (38). In relation to DII, vitamin E and C, and polyunsaturated fatty acid have high anti-inflammatory scores whereas carbohydrates from starch intake have high pro-inflammatory values (13).

Previous research on diet and RCC has been mixed. In a cohort study conducted among Swedish women, high intake of fresh fruits and vegetables and moderate intake of alcohol were associated with reduced risk (39, 40) whereas in the European prospective investigation into cancer and nutrition (EPIC) no appreciable association with fruit and vegetables was observed (41). An earlier review of the literature showed increased risk of RCC with

consumption of fried/sautéed meat and low intakes of magnesium or vitamin E (42). A recent meta-analyses suggested that high intake of cruciferous vegetables (43) and dietary fiber intake (44)were associated with reduced RCC risk.

One of the possible mechanisms of the positive association between DII and RCC risk is through the effect of diet-related chronic inflammation in the upregulation of various cytokines like tumor growth factor-b and IL-6 which play a role in promoting cell transformation, survival, proliferation of tumor cells, and metastasis (45). These cytokines including c-reactive protein also play a major role in the prognosis of RCC (6).

This hospital-based case-control study shares some of the limitations of such design. Potential recall and selection biases are possible, but the comparability of recall between cases and controls was improved by interviewing all subjects in a hospital setting. In addition, awareness about any particular dietary hypothesis in RCC etiology was limited in the Italian population. The strengths of this study include its large dataset, and the almost complete participation of both cases and controls, which reduces the role of selection bias. In addition, the catchment areas were comparable for cases and controls. Great attention was paid to exclude all diagnoses that might have been associated with or have determined long-term modifications of diet in controls. Other strengths are the use of a reproducible (31) and validated (30) FFQ, and the similar setting of interviews for cases and controls, which limit information bias. Also, the DII score, which takes into account both pro- and anti-inflammatory food parameters that characterize virtually all human diets, more accurately reflects the relationship of the inflammatory potential of diet to affect cancer risk than would single nutrients considered individually. DII has previously shown to be associated with prostate, pancreatic, colorectal, esophageal, endometrial and hepatocellular cancers in a similar Italian population (46–49). With reference to confounding, we were able to adjust for energy intake and major recognized confounding factors for RCC.

In conclusion, this study indicates a detrimental role of a pro-inflammatory diet (e.g., high consumption of sugar, processed meat) on RCC risk through a process of inflammation.

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Table 1.

Participants' characteristics across quartiles of dietary inflammatory index (DII) among 1534 controls. Italy, 1992–2004.

Characteristics	DII quartiles				
	< −1.88	−1.88,−0.66	−0.65,0.78	>0.78	*p* value[b]
	N (%)	N (%)	N (%)	N (%)	
Sex					<0.0001
Male	284 (74.1)	256 (66.7)	236 (61.5)	212 (55.4)	
Female	99 (25.9)	128 (33.3)	148 (38.5)	171 (44.6)	
Age (years)					0.004
<50	79 (20.6)	65 (16.9)	53 (13.8)	49 (12.8)	
50–59	108 (28.2)	111 (28.9)	108 (28.1)	80 (20.9)	
60–69	125 (32.6)	130 (33.8)	138 (35.9)	162 (42.3)	
≥70	71 (18.5)	78 (20.3)	85 (22.1)	92 (24.0)	
Education (years)					0.35
<7	207 (54.1)	198 (51.6)	216 (56.3)	228 (59.5)	
7–11	120 (31.3)	118 (30.7)	115 (30.0)	104 (27.2)	
≥12	56 (14.6)	68 (17.7)	53 (13.8)	51 (13.3)	
Body mass index(kg/m^2)[a]					0.01
<25	120 (31.3)	125 (32.6)	158 (41.4)	158 (41.6)	
25 to <30	203 (53.0)	201 (52.3)	178 (46.6)	168 (44.2)	
≥30	60 (15.7)	58 (15.1)	46 (12.0)	54 (14.2)	
Tobacco smoking					0.13
Never smokers	150 (39.2)	156 (40.6)	161 (41.9)	173 (45.2)	
Ex-smokers[c]	130 (33.9)	105 (27.3)	97 (25.3)	96 (25.1)	
Current smokers					
<20 cigarettes/day	60 (15.7)	79 (20.6)	70 (18.2)	68 (17.8)	
≥20 cigarettes/day	43 (11.2)	44 (11.5)	56 (14.6)	46 (12.0)	
Family history of kidney cancer[d]					0.01
No	383	383 (99.7)	378 (98.4)	382 (99.7)	
Yes	0 (0.0)	1 (0.3)	6 (1.6)	1 (0.3)	

[a]The sum does not add up to the total because of some missing values

[b]*p* value from Chi-square test

[c]Ex-smokers were subjects who had stopped smoking for at least 4 years

[d]In first-degree relatives

Table 2.

Distribution of servings of selected food groups across quartiles of DII among 1534 controls. Italy, 1992–2004.

Servings/week. mean± SD	−5.20, −1.88	−1.88,−0.66	−0.65,0.78	0.78, 5.00	P-value[a]
Fruit	25.1±11.9	19.6±9.1	16.4±9.4	11.5±10.6	<0.001
Vegetables	16.5±6.2	13.6±5.8	10.8±5.4	7.6±5.0	<0.001
Fish	2.1±1.3	1.9±1.2	1.8±1.2	1.5±1.0	<0.001
Egg	1.6±1.3	1.7±1.5	1.5±1.2	1.4±1.4	0.007
Coffee	19.0±12.8	19.0±11.4	18.8±11.8	17.8±12.3	0.17
Processed meat	2.4±2.1	2.7±1.9	2.9±2.3	3.0±2.3	<0.001
Red meat	4.1±2.4	4.5±2.4	4.5±2.5	3.9±2.5	0.15
Sugar	27.0±21.9	31.5±24.0	33.4±26.5	34.1±29.7	<0.0001
Cheese	3.9±2.0	4.6±2.4	4.3±2.5	4.3±3.4	0.07
Desserts	3.9±3.9	4.5±4.3	5.2±6.1	5.8±8.8	<0.0001

Abbreviation: SD= standard deviation

[a] p values were obtained from ANOVA

Table 3.

Distribution of selected nutrients across quartiles of DII among 1534 controls. Italy, 1992–2004.

Nutrients mean± SD	−5.20, −1.88	−1.88,−0.66	−0.65,0.78	0.78, 5.00	P-value[a]
Energy	2357.7±499.5	2502.8±674.3	2473.3±834.3	2285.2±1001.8	0.16
Carbohydrates	285.4±66.7	298.8±86.0	298.6±108.2	277.0±133.6	0.27
Protein	91.1±19.4	95.7±24.2	92.1±25.8	85.1±31.1	<0.001
Cholesterol	285.7±95.7	306.8±110.1	294.6±111.7	278.8±133.1	0.20
Niacin	19.9±4.3	19.6±5.0	18.7±5.2	16.6±6.2	<0.001
Riboflavin	1.7±0.4	1.6±0.5	1.5±0.5	1.4±0.6	<0.001
Vitamin B6	2.1±0.4	2.0±0.5	1.9±0.6	1.7±0.7	<0.001
Vitamin A	1999.7±1345.7	1768.4±1166.4	1375.7±1120.6	913.5±766.3	<0.001
Vitamin C	193.2±75.1	154.3±60.0	128.1±73.8	92.3±65.9	<0.001
Iron	15.2±3.3	14.7±4.0	13.9±4.5	12.1±5.4	<0.001
Zinc	13.1±2.8	13.6±3.4	12.9±3.6	11.8±4.2	<0.001
Anthocyanidins	21.2±14.4	19.9±15.8	20.3±18.1	19.1±22.0	0.14
Isoflavanoids	59.1±23.7	112.8±1208.5	45.5±21.6	36.2±24.0	0.32

Abbreviation: SD= standard deviation

[a] p values were obtained from ANOVA

Table 4.

Odds ratios (OR) of renal cell carcinoma and corresponding 95% confidence intervals (CI) according to dietary inflammatory index (DII) among 767 cases and 1534 controls. Italy, 1992–2004.

	DII quartiles, OR (95% CI)				*p* value for trend	DII continuous[a], OR (95% CI)
	−5.20, −1.88	**−1.88,−0.66**	**−0.65,0.78**	**0.78, 5.00**		
Cases/Controls	163/383	187/384	206/384	211/383		767/1534
Model 1[b]	1 [c]	1.25 (0.96, 1.64)	1.44 (1.09, 1.91)	1.57 (1.15, 2.15)	0.005	1.11 (1.04, 1.18)
Model 2[d]	1 [c]	1.20 (0.90, 1.58)	1.31 (0.97, 1.76)	1.41 (1.02, 1.97)	0.04	1.08 (1.01, 1.15)

[a] One-unit increase equals to approximately 10% of its range (5.00 to −5.20).

[b] Conditioned on study centre and quinquennia of age and adjusted for energy intake.

[c] Reference category.

[d] Model 1 additionally adjusted for year of interview, education, body mass index, tobacco smoking, and family history of renal cell carcinoma.

Table 5.

Odds ratios (OR) of renal cell carcinoma and corresponding 95% confidence intervals (CI) according to quartiles of dietary inflammatory index (DII), among 767 cases and 1534 controls, in strata of selected covariates. Italy, 1992–2004.

	Cases/Controls	DII quartiles, OR (95% CI)[a]				*p* value for trend	*p* value for interaction
		−5.20, −1.88	**−1.88,−0.66**	**−0.65,0.78**	**0.78, 5.00**		
Sex							0.20
Male	494/988	1 [a]	1.22 (0.87, 1.69)	1.28 (0.90, 1.83)	1.28 (0.85, 1.92)	0.27	
Female	273/546	1 [a]	1.10 (0.64, 1.88)	1.44 (0.83, 2.50)	1.68 (0.93, 3.03)	0.05	
Age (years)							0.15
<60	323/653	1 [a]	1.44 (0.94, 2.20)	1.61 (1.02, 2.53)	1.77 (1.05, 2.98)	0.04	
≥60	444/881	1 [a]	1.05 (0.72, 1.53)	1.17 (0.79, 1.74)	1.27 (0.82, 1.97)	0.24	
BMI (kg/m^2)							0.76
<25	281/561	1 [a]	1.08 (0.67, 1.75)	1.04 (0.63, 1.73)	1.12 (0.64, 1.93)	0.75	
≥25	483/968	1 [a]	1.25 (0.88, 1.79)	1.60 (1.11, 2.33)	1.64 (1.07, 2.51)	0.02	
Tobacco smoking							0.30
Never smokers	314/640	1 [a]	1.18 (0.75, 1.86)	1.15 (0.71, 1.86)	1.14 (0.67, 1.93)	0.75	
Ever smokers	450/894	1 [a]	1.13 (0.78, 1.64)	1.41 (0.96, 2.07)	1.66 (1.08, 2.57)	0.01	

[a] Estimated from multiple logistic regression models, conditioned on sex, quinquennia of age and centre and adjusted for year of interview, education, body mass index, tobacco smoking, family history of renal cell carcinoma, and energy intake.

[b] Reference category.