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Dietary inflammatory index and risk of renal cancer in the Iowa Women's Health Study

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Abstract

Background—The association between inflammatory potential of diet and renal cancer risk has not been investigated.

Methods—In this study, we explored the association between the dietary inflammatory index (DII) and risk of renal cancer in the Iowa Women's Health Study. From 1986 to 2011, 33,817 women initially recruited at 55–69 years of age were followed for incident renal cancers ($n = 263$). The DII was computed based on dietary intake assessed using a reproducible and valid 121-item food frequency questionnaire. Cox proportional hazards regression was used to estimate hazard ratios (HR) adjusting for age, body mass index, energy intake, smoking status, education, pack years of smoking, hypertension, and hormone replacement therapy.

Results—Multivariable analyses revealed positive association between higher DII scores and renal cancer risk (HR for $DII_{continuous}$: 1.07 per unit increase in DII (corresponding to 10% change in the DII range in the current study); 95% CI 1.00, 1.15; HR for $DII_{tertile3vs1} = 1.52$; 95% CI 1.09, 2.13). Stratified analyses produced slightly stronger associations between DII and renal cancer risk among women with BMI <30 kg/m^2 ($HR_{Tertile3vs1} = 1.57$; 95% CI = 1.04, 2.36) and ever smokers ($HR_{tertile3vs1} = 2.35$; 95% CI = 1.22, 4.55), although the corresponding interaction p values were not significant.

Conclusion—Pro-inflammatory diet, as indicated by higher DII scores, was associated with increased renal cancer risk.

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Keywords

Dietary inflammatory index (DII); Diet; Inflammation; Renal cancer risk; Cohort

Introduction

Renal cancer encompasses malignant tumors of renal parenchyma and renal pelvis, with renal cell carcinoma being the most common type of renal tumor. Renal cancer is the seventh most common cancer for men, and it is the tenth most common cause of cancer for women in the United Stated, with an estimated 62,700 adults (39,650 men and 23,050 women) that will be diagnosed with renal cancer in the year 2016 [1]. Major recognized risk factors for renal cancer are tobacco smoking, overweight, and obesity [2, 3].

Over the past several years, considerable evidence has been accumulating linking increased cancer risk with chronic inflammation, and several clinical and experimental studies have linked tumor progression with the upregulation of pro-inflammatory molecules, especially during late stages of the disease [4]. In addition to chronic inflammation, known properties of premalignant cells and other determinants promote tumor development and progression [5]. Evidence is accumulating on the role of chronic inflammation in renal cancer [6, 7].

Diet represents a varied set of exposures that often interact, leading to the modification of both inflammatory responses and health outcomes. Various dietary components have different effects 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]. Conversely, the Mediterranean diet—characterized by a high consumption of whole grains, fruit and green vegetables, fish, and olive oil, a low consumption of red meat and butter, and a moderate alcohol and dairy products consumption— has been associated with lower levels of inflammation [12]. Various dietary factors such as dietary fiber [13] and nutrients such as vitamin E [14] also have been associated with renal cancer. Despite the circumstantial evidence, the possible relation between inflammation deriving from dietary exposures and renal cancer 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 [15]. A typical pro-inflammatory diet is characterized by high consumption of foods rich in saturated fats and simple carbohydrates and low consumption of foods rich in polyunsaturated (especially *n*-3) fatty acids, flavonoids, spices, and micronutrients. The DII score has been validated and is correlated with various inflammatory markers, including CRP [15, 16], IL-6 [17], and homocysteine [18].

The DII also has been associated with a variety of cancers, including: colorectal and esophageal cancers [19–24] and, among urological cancers, with increased risk of prostate and bladder cancers [25–28]. In the Iowa Women's Health Study (IWHS), the DII has been shown to be associated with colorectal and breast cancer incidence [29, 30] and mortality [31]. In this paper, we examine the association between DII and renal cancer in the IWHS

prospective cohort. Our working hypothesis is that women with higher DII scores, representing a greater inflammatory potential of diet, are at higher risk of developing renal cancers.

Methods

Design and participants

Full details regarding the IWHS design have been published elsewhere [32]. In brief, 41,836 women aged 55–69 years, selected at random from Iowa Driver's License holders with 42% response rate, were enrolled in 1986. Incident cancer cases and deaths were identified through annual linkage with the State Health Registry of Iowa (a Surveillance, Epidemiology and End Results program member) and the National Death Index. Emigration from Iowa was less than 1% annually, resulting in nearly complete follow-up of cancer incidence [33]. Women with self-reported history of cancer prior to baseline, except non-melanoma skin cancer (n = 3830); or extreme energy intake (<600 or ≥5000 kcal per day) or incomplete dietary data (≥30 items blank) on the food frequency questionnaire (FFQ) (n = 3096) were excluded from the present study, yielding an analytic sample consisting of 35,216 study participants (exclusions were not mutually exclusive). After further exclusion for missing covariates, data from 33,817 women were included in the analysis.

Dietary intake data were collected using the FFQ at baseline. This 121-item FFQ was adapted from the 126-item instrument developed by Willett and colleagues [34]. Questions related to supplements were part of this FFQ and were incorporated in to the DII calculation. FFQ-derived dietary data were used to calculate DII scores for all participants. The University of Minnesota Institutional Review Board approved this study, and all participants gave consent.

To compute the DII score, dietary information for each study participant was first linked to the global database derived from 11 countries across the world 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 [18]. These parameters then were used to calculate the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the global 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 centered percentile score by doubling and subtracting one. The derived value was then multiplied by the respective food parameter effect score, which was derived from a literature review on the basis of 1943 articles scored [18]. All of these food parameter-specific DII scores were then summed to create the overall DII score for each subject in the study. Higher scores indicate a more pro-inflammatory, while lower scores indicate a more anti-inflammatory diet. The DII computed based on this study's FFQ includes data on 29 of the 45 possible food parameters comprising the DII: energy, carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, trans fat, niacin, thiamin, riboflavin, vitamin B_6, vitamin B_{12}, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene and garlic.

Outcome variables—cancer of renal parenchyma and renal pelvis—were coded using ICD-O-3 codes-(C64.0–C65.9). In total, there were 263 renal cancer cases. Person-years of exposure time were accumulated from baseline until first renal cancer diagnosis, move from Iowa, death, or administrative censoring on 12/31/2011. Hazard ratios and 95% confidence intervals (HR; 95% CI) were estimated using Cox proportional hazards regression models, adjusting only for age in the crude model and additionally adjusting for body mass index [BMI = weight (kg)/weight $(m)^2$], smoking status, pack-years of smoking, education, hormone replacement therapy (HRT) use, total energy intake and history of hypertension in another. The covariates were chosen a priori, as they previously were shown to be risk factors for renal cancer in this cohort. A test for linear trend was conducted by including the median value for each DII tertile as a continuous term into the regression model. The assumption of proportional hazards was tested by adding to the model an interaction term between follow-up time and DII; there was no evidence that these assumptions were violated. The DII was analyzed both as a continuous variable, with each point corresponding to ≈10% of its range (−5.75 to +4.66), and by tertiles. Test for interaction was carried out by including the interaction term in the model and via stratification by hypertension (yes/no), BMI (<30, ≥30 kg/m^2), and cigarette smoking (never vs. ever smokers). Statistical tests were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The mean DII and the corresponding standard deviation (SD) in this study is −0.87 ± 2.02. Baseline characteristics of women across tertiles of DII are provided in Table 1. Women in the third tertile (representing the most proinflammatory diet) were significantly younger, more likely to be obese, to consume fewer calories, to have lower educational attainment, be current smokers, to have more pack years of smoking and be less likely to have ever used hormone therapy.

Table 2 shows age-adjusted and multivariable-adjusted HRs of renal cancers according to the DII presented as tertiles and continuous DII. A one-unit increase in DII, corresponding to ≈10% of the range of DII in this cohort, was associated with a 7% increase in risk of renal cancer (HR = 1.07; 95% CI 1.00, 1.15). Women in the highest tertile of DII had a 52% higher risk of developing renal cancer compared to women in the lowest tertile (P_{trend} = 0.01) (Table 2). Table 3 shows multivariable HRs of renal cancer in strata of selected covariates. Apparently stronger associations were observed between DII and renal cancer risk among women with BMI <30 kg/m^2 ($HR_{Tertile3vs1}$ = 1.57; 95% CI = 1.04, 2.36) and smokers ($HR_{Tertile3vs1}$ = 2.35; 95% CI = 1.22, 4.55) in the absence, however, of significant interaction ($p > 0.20$).

Discussion

We observed positive association between renal cancer and the inflammatory potential of diet, as expressed by increasing DII scores, among older women in Iowa. This result supports the hypothesis that individuals with a pro-inflammatory diet have a higher risk of developing renal cancer.

Previous research on diet and renal cancer risk produced mixed findings. In a cohort study conducted among Swedish women, high intake of fresh fruits and vegetables and moderate intake of alcohol was associated with reduced risk [35, 36]; whereas in the European Prospective Investigation into Cancer and Nutrition (EPIC) no association with fruit and vegetables was observed [37]. The results from a population-based case-control study of renal cancer conducted in the US support the protective role of vegetables and increased risk with meat consumption [38]. An earlier review of the literature showed increased risk of renal cancer associated with consumption of fried/sautéed meat and low intakes of magnesium or vitamin E [39]. A recent meta-analysis conducted using results from 13 observational studies, suggested an inverse relationship between vitamin E intake and renal cancer risk [14]. Another meta-analysis suggested that high intake of cruciferous vegetables [40] and dietary fiber intake [13] may be associated with reduced renal cancer risk. Previous results on diet and renal cancer analyses in the IWHS showed low intake of alcohol and vitamin E, higher intake of vitamin C to increase risk of renal cancer [41]. Despite mixed results with diet and renal cancer, the evidence suggests a potential role of diet in the development of renal cancer. Distribution of food groups across categories of DII in the IWHS has been described previously. The food groups that showed the greatest reduction are vegetables other than green leafy vegetables or potatoes, low-fat dairy, green leafy vegetables, fish/seafood, nuts, fruits and whole grains; and the food groups that showed greatest increase were butter, beer, coffee, fried food and liquor [29].

One of the possible mechanisms through which the observed positive association between DII and renal cancer risk could occur is through the effect of diet-related chronic inflammation in the upregulation of various cytokines such as tumor growth factor-beta and IL-6, which play a role in promoting cell transformation, survival, proliferation of tumor cells, and metastasis [42]. These cytokines, as well as CRP, were also associated with the risk and prognosis of renal cancer [6, 43].

We observed stronger associations between DII and renal cancer among hypertensives, smokers and those with a normal or low BMI (<25 kg/m^2). Smoking [44] and long-term hypertension [45] are among established risk factor for renal cancer and are also known to increase level of inflammation [46, 47]. Thus, it may be possible that diet-associated inflammation amplifies these effects resulting in increased risk of renal cancer. Adiposity, which is a strong correlate of higher BMIs, is known to contribute to inflammation [48, 49]. Our results showing that the DII is more strongly associated with renal cancer in women with lower BMIs may reflect the fact that the effect of adiposity overwhelms the effect of diet-associated inflammation in overweight and obese women. Because the test for heterogeneity was not significant all of these results should be viewed with caution.

Strengths of the present study include: its large sample size, prospective data collection with extended follow-up, near-complete case ascertainment, and ability to adjust for multiple potential confounding factors. One recognized limitation is that dietary data were collected by a single FFQ at baseline. However, adult dietary patterns appear to remain relatively stable over time [50–55] and there was no specific dietary intervention applied to participants during the course of the study. 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. Another limitation would be the non-availability of data on the remaining 16 food parameters for DII calculation; however, we feel that this would not have played a major role because some of the food parameters that were missing (e.g., turmeric, ginger, saffron) are generally consumed in small quantities in US populations [16, 17]. Previously, we showed that in the IWHS, DII scores derived from the same number of food parameters to have been associated with the risk of colorectal cancer (HR for $DII_{quintiles:Q5vsQ1}$ = 1.20; 95% CI 1.01, 1.43) [29] and mortality (HR for $DII_{Quartiles:Q4vsQ1}$ 1.07; 95% CI 1.01,1.13; p_{trend} = 0.006) [31]. Another limitation would be low power for subgroup analyses, because of the relatively small number of renal cancer cases.

In conclusion, this study is consistent with a detrimental role of a pro-inflammatory diet on renal cancer risk. More studies need to be conducted to confirm this hypothesis in general population.

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Table 1

Prevalence of characteristics at baseline across tertiles of dietary inflammatory index (DII) in the Iowa Women's Health Study, 1986–2011

Characteristics[a] (mean (SD) or %)	**DII tertiles[c]**		
	<−2.08	**−2.09 to −0.05**	**>−0.05**
Age (years)[b]	61.9 (4.2)	61.5 (4.2)	61.3 (4.1)
Energy intake (kcal)	2091.5 (656.5)	1826.1 (537.4)	1478.4 (437.6)
BMI categories (%) (kg/m^2)[b]			
≤24.9	41.6	39.2	38.9
25–30	37.1	37.4	36.2
≥30	21.3	23.4	24.9
Education (%)[b]			
Less than high school	15.3	17.7	20.2
High school	38.4	41.6	46.6
More than high school	46.3	40.7	33.2
Smoking (%)[b]			
Never	70.0	66.8	61.3
Former	19.5	18.7	19.2
Current	10.5	14.5	19.5
Number of pack years of smoking	7.5 (16.1)	9.2 (17.6)	11.6 (19.4)
Hormone therapy use (yes) (%)[b]	42.6	38.5	35.2
Hypertension (yes, %)	56.3	57.0	56.1

[a] All variables are at baseline (1986) unless otherwise noted

[b] Characteristics showing significant trend across tertiles

[c] First tertile represents a more anti-inflammatory diet; third tertile represents a more pro-inflammatory diet

Table 2

Hazard ratios (HR) of renal cancer and corresponding 95% confidence intervals (CI) according to dietary inflammatory index (DII) in the Iowa Women's Health Study, 1986–2011

	DII tertiles, HR (95% CI)			p_{trend}	DII continuous
	<−2.08	**−2.09 to −0.05**	**>−0.05**		
Cases/person years	73/230,473	85/229,779	105/229,144		263/689,397
Model 1[b]	1[a]	1.20 (0.88, 1.64)	1.51 (1.12, 2.03)	0.007	1.07 (1.01, 1.14)
Model 2[c]	1[a]	1.19 (0.86, 1.63)	1.52 (1.09, 2.13)	0.01	1.07 (1.00, 1.15)

[a]Reference category

[b]Age-adjusted

[c]Model 1 additionally adjusted for BMI, smoking status, pack-years of smoking, education, HRT use, hypertension, total energy intake

Table 3

Hazards ratios (HR) of renal cancer and corresponding 95% confidence intervals (CI) according to tertiles of dietary inflammatory index (DII), in the Iowa Women's Health Study, 1986–2011

	Cases	DII Tertiles, HR (95% CI)[b]			p_{trend}	$p_{interaction}$
		<−2.08	−2.09 to −0.05	>−0.05		
Hypertension						0.79
Yes	159	1[a]	1.12 (0.75, 1.69)	1.54 (1.01, 2.37)	0.04	
No	104	1[a]	1.31 (0.78, 2.19)	1.52 (0.89, 2.61)	0.14	
BMI (kg/m^2)						0.28
<30	172	1[a]	1.16 (0.78, 1.71)	1.57 (1.04, 2.36)	0.04	
≥30	91	1[a]	1.28 (0.73, 2.24)	1.51 (0.83, 2.73)	0.44	
Tobacco smoking						0.23
Never smokers	185	1[a]	1.10 (0.76, 1.60)	1.31 (0.88, 1.95)	0.18	
Ever smokers	78	1[a]	1.54 (0.80, 2.98)	2.35 (1.22, 4.55)	0.009	

[a] Reference category

[b] Adjusted for age, BMI, smoking status, pack-years of smoking, education, HRT use, hypertension, total energy intake