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Fruit, vegetables, fibre and micronutrients and risk of US renal cell carcinoma

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Abstract

The association between renal cell cancer (RCC) and intake of fruit, vegetables and nutrients was examined in a population-based case–control study of 323 cases and 1827 controls; dietary intake was obtained using a mailed questionnaire. Cancer risks were estimated by OR and 95% CI, adjusting for age, sex, smoking, obesity, hypertension, proxy status, alcohol consumption and dietary fat intake and energy. Intake of vegetables was associated with a decreased risk of RCC (OR 0·5; 95% CI 0·3, 0·7; $P_{trend} = 0·002$), (top compared to the bottom quartile of intake). When intake of individual nutrients was investigated, vegetable fibre intake was associated with decreased risks (OR 0·4; 95% CI 0·2, 0·6; $P<0·001$), but this was not the case with fruit fibre (OR 0·7; 95% CI 0·4, 1·1) or grain fibre (OR 1·0; 95% CI 0·6, 1·5). β-Cryptoxanthin and lycopene were also associated with decreased risks, but when both were included in a mutually adjusted backwards stepwise regression model, only β-cryptoxanthin remained significant (OR 0·5; 95% CI 0·3, 0·8). When other micronutrients and types of fibre were investigated together, only vegetable fibre and β-cryptoxanthin had significant trends ($P<0·01$) (OR 0·6; 95% CI 0·3, 0·9) (OR 0·5; 95% CI 0·3, 0·9), respectively. These findings were stronger in those aged over 65 years ($P_{interaction} = 0·001$). Among non-smokers, low intake of cruciferous vegetables and fruit fibre was also associated with increased risk of RCC ($P_{interaction} = 0·03$); similar inverse associations were found for β-cryptoxanthin, lycopene and vitamin C. When nutrients were mutually adjusted by backwards regression in these subgroups, only β-cryptoxanthin remained associated with lower RCC risk. These findings deserve further investigation in ongoing prospective studies when sample size becomes sufficient.

Key words: Renal cell carcinoma: Vegetable fibre intake: β-Cryptoxanthin: Cruciferous vegetables: Fruit: Non-smokers: Elderly

Renal cell carcinoma (RCC) accounts for 3% of adult malignancies in the USA, and the incidence has been increasing in the USA for the last 30 years, with annual increments of 1·6 and 1·7% in white men and white women[1]. In 1990, rates of RCC were 12 and 5 per 100 000 among white men and women[2]. Recent rates (2005) are reported as 18 and 9 per 100 000, respectively[3]. The increase cannot be fully explained by early detection of pre-symptomatic tumours[1]. The reported ongoing epidemic of obesity in the USA[4] and/or the increase in hypertension[5] and diabetes[6] may explain part of this increase, which occurred despite a drop in smoking rates[7,8]. Although smoking[7,8], obesity[9–12], hypertension[10,11,13] and diabetes[14] have consistently been associated with RCC risk, few studies have tried to assess the association of decreased dietary intake of fruit and vegetable intake, taking into account constituent forms of fibre and other micronutrients, as well as assessing for interaction with sex, age and smoking[15–17]. An increase in lipid peroxidation may partially explain some of the reason for increasing RCC risk[18–20]. To evaluate the association of dietary intake of fruits, vegetables and different types of fibre and other micronutrients with risk of RCC, we analysed RCC dietary data, along with other established and potential risk factors collected as part of a large population-based case–control study.

Abbreviations: NHANES II, National Health and Nutrition Examination Survey II; RCC, renal cell carcinoma.

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Material and methods

Study sample

A population-based case–control study of RCC and cancers of five other anatomic sites was conducted in Iowa between 1986 and 1989. Detailed methods are reported elsewhere[8,21,22]. Briefly, eligible cases were residents of the state of Iowa, aged 40–85 years, newly diagnosed with histologically confirmed RCC (ICD-O code 189.0) during July 1985–December 1987, and without a previous diagnosis of a malignant neoplasm. Cases were identified by the State Health Registry of Iowa[23]. An introductory letter was followed by a telephone call in which potential participants were invited to complete a mailed questionnaire, designed either for direct respondents or their proxies, sent per request during the telephone contact. Of the 463 eligible RCC cases, questionnaires were completed for 406 (87·7% response rate). Among these, 287 subjects completed the questionnaire designed for direct respondents and 119 completed a proxy questionnaire. An early version of the direct-respondent questionnaire, which did not include a question about possible proxy status, was completed by eighty-one of the 287 'direct questionnaire' respondents. In the present analysis, these respondents were assumed to be the study subject since almost all of the 206 respondents who completed the later version of the direct respondent's questionnaire that asked about possible proxy status, were study subjects. Both versions asked the same questions on food consumption.

Controls were frequency-matched to all cases in the overall study by sex and 5-year age group. Controls, like cases, had to be without previous diagnosis of a malignant neoplasm. Controls under 65 years of age were selected randomly from computerised State of Iowa driver's license records, whereas controls aged 65 years and older (65+) were selected randomly from lists of Iowa residents provided by the USA Health Care Financing Administration (now the Centers for Medicare and Medicaid Services). Both sampling frames have been shown to achieve greater than 95% coverage of the intended population[24]. Of the 999 eligible controls under age 65 years, 817 (82%) participated by returning a completed questionnaire; of 2036 eligible controls aged 65+ years, a total of 1617 participated (79%). Among the 2432 control subjects sent direct-respondent questionnaires, 2064 were completed by the subject, 241 by a proxy and 127 by an undetermined respondent (assumed to be a direct respondent, as described).

The study was approved by the Institutional Review Boards of the USA National Cancer Institute and the University of Iowa.

Data collection

Data were collected by means of a self-administered mailed questionnaire, supplemented by a telephone interview where necessary. The questionnaire included information on demographics, anthropometric measures (weight history and adult height), usual non-occupational physical activity, smoking history, occupational history, past medical history (including self-report of physician-diagnosed hypertension and history of bladder/kidney infection), history of cancer among first-degree relatives and other factors. Of the 2434 controls, 607 did not have sufficient dietary data for analysis. A total of sixty-six controls were missing information on BMI and/or a history of hypertension. Of the 406 RCC cases, eighty-three did not have sufficient dietary information and ten did not have BMI and/or hypertension information. These subjects were excluded, leaving 323 cases and 1827 controls for the dietary analysis. Most of the 607 controls and eighty-three cases who were excluded due to insufficient dietary information had responded to a truncated telephone questionnaire that did not include diet.

Dietary analysis

Usual adult dietary intake was gathered with a FFQ that asked about the number of times per d, week, month or year (or rarely/never) of consumption for each of fifty-five food items, excluding dietary changes in the previous couple of years. Intake per d for each item was calculated and these data were summed to derive frequency of intake within each food group. Estimates of usual intake were derived for individual food items by multiplying the frequency of consumption of each item by an average serving size for males and females, separately, obtained from the National Health and Nutrition Examination Survey II (NHANES II)[25,26]. Nutrients were then estimated by multiplying the intake of these foods by nutrient values derived from the United States Department of Agriculture food composition tables[26] and a USDA-National Cancer Institute food composition database[25]. Adjustment for total food intake was carried out by the nutrient density method[27]. Each nutrient was individually divided by the subject's total energy intake before quartiles of intake were calculated. When nutrients were analysed, total energy consumption in kJ (continuous variable) was entered into a logistic regression model along with the other potential confounders. Two statistical packages were used: Statistical Package for the Social Sciences (version 11; SPSS, Inc.) and EPICURE (EPICURE, Inc.)[28].

Multiple logistic regression analysis was used to adjust for confounding by age (continuous), sex, smoking (eight categories of smoking duration and amount, respectively (based on distribution in controls), and smoking status), BMI at age 40 years, history of high blood pressure (yes, no), proxy status of respondents (direct or proxy respondent), alcohol intake[29,30] and fatty spreads consumption[21]. The maximum likelihood estimate of the OR, with 95% CI, was used as the measure of association between either high food group intake or macro- or micronutrient intake and RCC[31]. Tests for the trend across quartiles were performed by assigning the mean value of each respective quartile to the score variable and then testing the linear trend using a likelihood ratio test[31]. Interactions between each variable (age, sex, smoking, hypertension and obesity) and the fruit- and vegetable-intake variables for RCC risk were tested by the likelihood ratio test[31] by comparing the log-likelihoods of logistic regression models with and without additional multiplicative terms for the interactions.

Results

Compared with controls, cases were somewhat younger and were more likely to be current smokers (OR 1·5; 95 % CI 1·1, 2·2), overweight or obese at age 40 years (OR 1·4, 95 % CI 1·1, 1·8), to report a history of hypertension (OR 1·8, 95 % CI 1·2, 2·4), to drink less alcohol (OR for more than two drinks/d 0·4, 95 % CI 0·3, 0·6), to consume more fatty spreads (OR 2·0, 95 % CI 1·3, 3·0) and to differ by respondent status (proxy; Table 1)[10,21]. Therefore, these variables were included as confounders in subsequent analyses. Neither physical activity, coffee/tea consumption, education, family history of kidney cancer, nor history of kidney infection were risk factor and thus these factors were not included as covariates in any of the models. Among direct and proxy respondents, OR for smoking, obesity and hypertension, alcohol use and high fat consumption followed similar patterns ($P_{interaction} > 0·5$; data not shown)[14].

We compared energy and percentage contribution of fat, protein and carbohydrate, by sex and case–control status, in our data with that in the NHANES II, which includes a nutritional survey conducted approximately contemporaneously[24]. This was done as no validation studies were available from 1986 and we wanted an indication of the generalisability of our data to the general US population at the time. The dietary composition of total energy and distribution of macronutrients among both male and female controls from this study in Iowa was remarkably similar to the NHANES II study sample. In both populations, men consumed approximately 8000 kJ/d, of which fat comprised almost 40 % and women consumed approximately 5550 kJ/d, of which fat comprised about 35 %[21].

Table 2 presents associations between RCC risk and vegetables and fruits, either by food group, fibre nutrient or micronutrients in the total population; OR for vegetables and fruits either by food group, fibre nutrient or micronutrients in direct respondents followed similar patterns (data not shown as $P_{interaction} = 0·84$). Intake of vegetables was the only food group associated with a decreased risk of RCC (OR 0·5; 95 % CI 0·3, 0·7; $P_{trend} = 0·002$) (for the top quartile compared to the bottom quartile of intake).

When intake of individual fibre constituents was investigated, only vegetable fibre intake was independently associated with decreased risks (OR 0·4; 95 % CI 0·2, 0·6; $P_{trend} < 0·001$), but not fruit fibre OR 0·7; 95 % CI 0·4, 1·1) or grain fibre (OR 1·0; 95 % CI 0·6, 1·5).

β-Cryptoxanthin and lycopene were also associated with decreased risks, but when both were included in a mutually adjusted backwards model, only β-cryptoxanthin remained significant (OR 0·5; 95 % CI 0·3, 0·8; $P_{trend} = 0·01$; data not shown in Table 2).

When fibre groups and nutrients were mutually adjusted for each other (in models that included other confounders), only consumption of vegetable fibre and β-cryptoxanthin remained

Table 1. Demographic and life-style risk factors: Iowa case–control study of renal cell cancer
(Number of cases, number of controls, percentages, odds ratios and 95 % confidence intervals)

	No. of cases (*n* 323)	%	No. of controls (*n* 1827)	%	OR*	95 % CI
Age (years)						
40–54	58	18	205	11		
55–64	110	34	479	26		
65–74	113	35	713	39		
75–85	42	13	430	24		
Proxy status						
Proxy respondent	245	76	1681	92		
Sex						
Male	202	63	1219	67		
Smoking						
Never	122	38	797	44	1·0	
Former	110	34	672	36	1·3	0·9, 1·8
Current	91	28	358	20	1·5	1·1, 2·2
BMI at age 40 years (kg/m^2)						
< 25	156	48	1109	61	1·0	
≥ 25	167	52	718	39	1·4	1·1, 1·8
Hypertension history						
Never	166	51	1181	65	1·0	
Ever	157	49	646	35	1·8	1·4, 2·4
Alcohol consumption/d						
Never	280	87	1516	83	1·0	
Once	21	7	146	8	0·8	0·5, 1·0
Twice	14	4	73	4	0·8	0·5, 1·0
≥ Twice	8	2	92	5	0·4	0·3, 0·6
Fatty spreads servings/d						
< 1·0	58	18	492	27	1·0	
1·0–1·4	82	25	452	25	1·5	1·0, 2·2
1·5–2·0	83	26	452	25	1·6	1·1, 2·3
≥ 2·0	100	31	431	23	2·0	1·3, 3·0

* Adjusted for age, sex, proxy status, years of smoking, number of cigarettes smoked per d, never/ever smoke, BMI age 40 years, blood pressure, alcohol consumption, fat consumption and energy where relevant.

Table 2. Associations between fruit and vegetables and renal cell cancer risk (food groups and nutrients) in the total population and stratified by age and smoking
(Odds ratios and 95 % confidence intervals)

					Age				Smoking			
			Total (*n* 2150)		< 65 years (*n* 852)		≥ 65 years (*n* 1298)		Non-smoker (*n* 918)		Smoker (*n* 1232)	
Food groups	Case (*n* 323)	Control (*n* 1827)	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI
Vegetables (servings/d)												
0–1·0	101	391	1·0		1·0		1·0		1·0		1·0	
> 1·0–1·4	82	457	0·8	0·6, 1·3	0·8	0·4, 1·6	1·2	0·7, 2·1	0·5	0·3, 0·8	1·2	0·7, 2·1
> 1·4–2·1	83	471	0·8	0·5, 1·2	1·1	0·6, 1·9	0·7	0·4, 1·4	0·4	0·2, 0·7	1·0	0·5, 1·9
> 2·1	57	508	0·5	0·3, 0·7	0·5	0·3, 1·1	0·4	0·2, 0·8	0·4	0·2, 0·7	0·6	0·3, 1·1
P_{trend}				0·002		0·228		0·003		0·001		0·057
$P_{interaction}$							0·423				0·234	
Fruits (servings/d)												
0–1·0	109	417	1·0		1·0		1·0		1·0		1·0	
> 1·0–1·7	82	460	1·1	0·7, 1·6	0·6	0·3, 1·1	1·2	0·7, 2·3	0·5	0·3, 0·8	1·0	0·5, 1·7
> 1·7–2·4	79	491	0·8	0·6, 1·3	0·9	0·5, 1·7	0·8	0·4, 1·5	0·5	0·3, 0·9	0·7	0·4, 1·4
> 2·4	53	459	0·7	0·4, 1·1	0·7	0·3, 1·4	0·6	0·3, 1·2	0·3	0·2, 0·6	0·7	0·4, 1·4
P_{trend}				0·082		0·468		0·071		0·001		0·253
$P_{interaction}$							0·512				0·096	
Cruciferous vegetables (servings/d)	Missing (*n* 7)	Missing (*n* 35)										
0–0·02	89	428	1·0		1·0		1·0		1·0		1·0	
>0·02–0·1	82	456	1·1	0·7, 1·6	0·7	0·3, 1·4	1·1	0·6, 2·0	1·0	0·5, 1·7	0·7	0·3, 1·3
>0·1–0·3	87	462	1·2	0·8, 1·8	1·4	0·8, 2·7	0·9	0·5, 1·7	0·7	0·4, 1·2	1·4	0·8, 2·5
>0·3	58	446	0·8	0·5, 1·2	0·6	0·3, 1·2	0·7	0·4, 1·4	0·5	0·3, 1·0	1·0	0·6, 1·9
P_{trend}				0·391		0·500		0·270		0·024		0·421
$P_{interaction}$							0·870				0·028	
Macronutrients												
Vegetable fibre (g/d)												
0–1·9	107	401	1·0		1·0		1·0		1·0		1·0	
> 1·9–2·7	85	447	0·6	0·4, 0·9	0·5	0·3, 1·0	0·8	0·5, 1·5	0·7	0·4, 1·2	0·8	0·4, 1·3
> 2·7–3·6	68	454	0·5	0·3, 0·8	0·6	0·3, 1·1	0·5	0·3, 1·1	0·7	0·4, 1·2	0·5	0·3, 0·9
> 3·6	63	525	0·4	0·2, 0·6	0·5	0·2, 0·9	0·4	0·2, 0·8	0·7	0·4, 1·2	0·4	0·2, 0·8
P_{trend}				0·000		0·024		0·004		0·198		0·202
$P_{interaction}$							0·334				0·098	
Fruit fibre (g/d)												
0–1·2	109	448	1·0		1·0		1·0		1·0		1·0	
> 1·2–2·1	87	408	0·9	0·6, 1·3	0·9	0·5, 1·7	0·7	0·4, 1·4	0·9	0·5, 1·6	1·0	0·6, 1·9
> 2·1–3·4	69	458	0·8	0·5, 1·2	0·8	0·4, 1·6	0·5	0·3, 1·0	0·5	0·3, 1·0	0·9	0·5, 1·7
> 3·4	58	513	0·7	0·4, 1·1	0·7	0·4, 1·5	0·6	0·3, 1·3	0·4	0·2, 0·8	0·9	0·4, 1·6
P_{trend}				0·105		0·384		0·122		0·002		0·556
$P_{interaction}$							0·180				0·234	
Grain fibre (g/d)												
0–2·2	88	399	1·0		1·0		1·0		1·0		1·0	
> 2·2–3·0	87	473	0·9	0·6, 1·4	1·2	0·7, 2·1	0·8	0·4, 1·5	0·8	0·4, 1·4	1·0	0·6, 1·9
> 3·0–4·0	78	458	0·9	0·6, 1·5	0·9	0·5, 1·7	1·1	0·6, 2·0	0·7	0·4, 1·3	1·2	0·7, 2·2
> 4·0	70	497	1·0	0·6, 1·5	1·1	0·5, 2·2	0·8	0·4, 1·5	0·6	0·3, 1·1	1·0	0·5, 1·8
P_{trend}				0·956		0·995		0·703		0·122		0·917
$P_{interaction}$							0·534				0·563	
Micronutrients												
Vitamin C (mg/d)												
0–53	96	416	1·0		1·0		1·0		1·0		1·0	
> 53–78	101	435	1·3	0·9, 1·9	1·1	0·6, 2·0	1·0	0·6, 1·9	1·4	0·8, 2·5	1·0	0·6, 1·9
> 78–112	68	457	0·9	0·6, 1·4	1·2	0·6, 2·2	0·7	0·4, 1·3	0·6	0·3, 1·1	0·8	0·4, 1·5

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Table 2. *Continued*

Food groups	Case (*n* 323)	Control (*n* 1827)	Total (*n* 2150)		Age				Smoking			
					<65 years (*n* 852)		≥65 years (*n* 1298)		Non-smoker (*n* 918)		Smoker (*n* 1232)	
			OR*	95 % CI	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI
> 112	58	519	0·7	0·5, 1·1	0·9	0·5, 1·8	0·6	0·3, 1·1	0·5	0·3, 1·0	0·9	0·5, 1·7
P_{trend}			0·097		0·978		0·053		0·003		0·558	
$P_{interaction}$						0·025				0·218		
Folate (μg/d)												
0–143	105	408	1·0		1·0		1·0		1·0		1·0	
> 143–175	85	414	1·3	0·9, 1·9	1·0	0·5, 1·8	1·1	0·6, 2·0	0·7	0·4, 1·3	1·3	0·7, 2·4
> 175–216	62	482	0·8	0·5, 1·3	1·2	0·7, 2·2	0·6	0·3, 1·2	0·5	0·3, 0·9	1·0	0·5, 1·9
> 216	71	523	0·8	0·5, 1·2	0·9	0·4, 1·7	0·5	0·3, 1·0	0·7	0·4, 1·3	0·7	0·4, 1·4
P_{trend}			0·125		0·919		0·022		0·159		0·233	
$P_{interaction}$						0·022				0·722		
Xanthin (μg/d)												
0–281	90	446	1·0		1·0		1·0		1·0		1·0	
> 281–1384·1	88	449	1·3	0·9, 1·9	1·3	0·7, 2·3	1·1	0·6, 2·0	1·0	0·6, 1·7	1·1	0·6, 2·1
> 1384–2072	82	480	1·1	0·7, 1·7	1·5	0·8, 2·7	0·7	0·4, 1·5	0·8	0·5, 1·4	1·0	0·5, 1·9
> 2072	63	452	1·0	0·6, 1·5	1·0	0·5, 2·1	0·9	0·5, 1·6	0·5	0·2, 1·0	1·0	0·5, 1·9
P_{trend}			0·735		0·659		0·507		0·046		0·962	
$P_{interaction}$						0·746				0·107		
β-Cryptoxanthin (μg/d)												
0–71	103	390	1·0		1·0		1·0		1·0		1·0	
> 71–113	78	454	0·7	0·5, 1·0	0·9	0·5, 1·7	0·6	0·3, 1·1	0·4	0·2, 0·8	0·7	0·4, 1·3
> 113–171	73	480	0·6	0·4, 1·0	1·0	0·5, 1·9	0·3	0·2, 0·6	0·7	0·4, 1·2	0·4	0·2, 0·8
> 171	69	503	0·7	0·5, 1·1	1·1	0·6, 2·1	0·6	0·3, 1·1	0·3	0·2, 0·6	0·8	0·4, 1·4
P_{trend}			0·070		0·784		0·021		0·002		0·314	
$P_{interaction}$						0·007				0·323		
Lycopene (μg/d)												
0–150	97	437	1·0		1·0		1·0		1·0		1·0	
> 150–231	82	465	0·8	0·5, 1·2	0·8	0·4, 1·5	0·8	0·4, 1·4	0·8	0·4, 1·4	1·0	0·5, 1·8
> 231–357	78	448	0·7	0·5, 1·1	0·6	0·3, 1·1	1·0	0·5, 1·9	0·8	0·5, 1·5	1·0	0·5, 1·8
> 357	66	477	0·6	0·4, 1·0	0·5	0·3, 1·0	0·7	0·4, 1·3	0·5	0·3, 0·9	0·7	0·4, 1·3
P_{trend}			0·037		0·034		0·434		0·045		0·259	
$P_{interaction}$						0·507				0·728		
β-Carotene (μg/d)												
0–878	89	413	1·0		1·0		1·0		1·0		1·0	
> 878–1401	85	470	0·9	0·6, 1·3	0·8	0·5, 1·5	0·8	0·4, 1·5	1·0	0·6, 1·8	1·0	0·6, 1·8
> 1401–2242	83	462	1·0	0·6, 1·5	0·8	0·4, 1·4	1·0	0·6, 1·8	1·0	0·6, 1·8	1·0	0·5, 1·8
> 2242	66	482	0·7	0·4, 1·1	0·6	0·3, 1·2	0·7	0·4, 1·3	1·1	0·6, 1·9	0·7	0·3, 1·3
P_{trend}			0·157		0·147		0·402		0·844		0·288	
$P_{interaction}$						0·941				0·239		
α-Carotene (μg/d)												
0–129	93	425	1·0		1·0		1·0		1·0		1·0	
> 129–210	83	463	0·9	0·6, 1·3	0·9	0·5, 1·7	0·7	0·4, 1·3	1·1	0·6, 2·0	0·9	0·5, 1·7
> 210–330	75	454	0·8	0·5, 1·2	1·0	0·5, 1·9	0·6	0·3, 1·1	1·4	0·8, 2·5	0·7	0·4, 1·2
> 330	72	485	0·7	0·4, 1·1	0·6	0·3, 1·2	0·7	0·4, 1·3	1·3	0·7, 2·4	0·8	0·4, 1·5
P_{trend}			0·123		0·237		0·194		0·286		0·032	
$P_{interaction}$						0·662				0·223		

* Adjusted for age, sex, proxy status, years of smoking, number of cigarettes smoked per d, never/ever smoke, BMI age 40 years, blood pressure, alcohol consumption, fat consumption and energy.

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significantly associated with lower RCC rates (OR 0·6, 95 % CI 0·3, 0·9, $P_{trend} = 0·03$; OR 0·5, 95 % CI 0·3, 0·9, $P_{trend} = 0·02$), respectively (for the top quartile compared to the bottom quartile of intake; data not shown in Table 2).

There was interaction between risk of RCC and vegetables and fruits either by food group or by micronutrients with two subgroups: smoking ($P_{interaction\ cruciferous \times smoking} = 0·03$) and age ($P_{interaction\ \beta\text{-cryptoxanthin} \times age} = 0·007$); there were no significant interactions with BMI, hypertension or sex (Table 2).

Thus in Table 2, the associations between RCC risk and these food groups and macro- and micronutrients are presented not only in the total population but also stratified by age and smoking. In those 65+ years of age, there was a significant negative association between RCC risk and intake of vegetable fibre, folate, vitamin C and β-cryptoxanthin. In non-smokers, we also found associations between RCC risk and higher intake of the fruit food group, cruciferous vegetables and fruit fibre (OR 0·3, 95 % CI 0·2, 0·6, $P_{trend} = 0·001$; OR 0·5, 95 % CI 0·3, 1·0, $P_{trend} = 0·02$; OR 0·4, 95 % CI 0·2, 0·8, $P_{trend} = 0·002$), respectively (top compared to the bottom quartile of intake (Table 2)). When micronutrients were investigated, intake of both vitamin C and β-cryptoxanthin was associated with RCC among non-smokers but not smokers.

When nutrients were mutually adjusted in a stepwise regression model by subgroups, β-cryptoxanthin was the only one that remained associated with lower RCC risk among those aged 65+ years (OR 0·4; 95 % CI 0·2, 0·6; $P_{trend} < 0·001$), and among non-smokers (OR 0·4; 95 % CI 0·2, 0·8, $P_{trend} = 0·002$) (top compared to the bottom quartile of intake; data not shown in Table 2). Similar risks were seen when analyses were limited to direct respondents ($P_{interaction} > 0·5$).

Discussion

Results from this population-based, case–control study provide evidence for a link between high dietary intake of vegetables and a decreased risk of RCC. As decreased risks were also associated with increased vegetable intake, the individual fibre constituents and micronutrients were also investigated. Once the effect of dietary energy and fat consumption was taken into account, vegetable fibre, but not fruit and grain fibre, was significantly associated with decreased RCC risk. Vegetable fibre and β-cryptoxanthin showed the strongest association with RCC risk after mutual adjustment of all variables. These associations of low RCC risk with high intake of vegetable fibre and the micronutrient β-cryptoxanthin were also seen in those aged 65+ years and in non-smokers.

Our findings of a significant effect of vegetable intake are consistent with both past and recent large case–control, cohort and pooled studies. Our data showing an association for food groups are similar to those of Canadian[32], Italian[33] and US[34] case–control studies. An Italian case–control study (with hospital controls) reported a significant two-fold association, similar to ours[35]. Out of thirteen case–control[32–44] and six cohort studies[45–50], all case–control studies, three[48,49,51] of the five large cohorts, and a large pooled analysis of thirteen cohort studies[52] reported an association of vegetable intake with a decrease in RCC risk.

Our data also showed an association with cruciferous vegetables among non-smokers. In a pooled case–control study from four countries[43] and in a Californian study[44], cruciferous vegetables were also found to be protective. Our finding of selected types of dietary fibre as the major nutrient associated with RCC risk is in accordance with the two studies which investigated the role of macronutrients, where fibre[16,17] was investigated.

When all food groups and types of fibre were entered in the same logistic model, vegetable fibre and β-cryptoxanthin remained as the micronutrients associated with inverse associations with RCC risk in our study. This result is consistent but more marked than that reported by Galeone *et al.*[15] who investigated fibre constituents and found vegetable fibre to be significant (OR 0·73; 95 % CI 0·54, 0·97), but not fruit fibre (OR 1·01; 95 % CI 0·76, 1·34).

It is interesting that the only nutrient that was significantly associated with RCC risk in the pooled study of cohorts[52] was α-carotene; however, other carotenoids were close to significance (β-carotene, β-cryptoxanthin and lycopene); the same carotenoids were also found to be associated with RCC risk in a large Canadian study and a US case–control study[39,44] but not in an Italian case–control study[53]. No association was observed for lycopene in these three studies[39,44,53]. Unlike the findings of Hu *et al.*[16], the effect of vegetable fibre on RCC risk in our study remained reduced but significant after mutual adjustment with β-cryptoxanthin. We did not find any interaction with obesity or hypertension and nutrients with respect to RCC risk. Some other studies[44] have also found β-cryptoxanthin to be inversely associated with RCC risk, with effects stronger among non-smokers, as we observed. However, the association is not consistent among studies, and other investigations have not observed an association[17,53,54]. β-Cryptoxanthin and lycopene are found in a variety of fruit and vegetables such as oranges and tomatoes. In our population, these micronutrients were derived primarily from orange juice and tomato paste consumption and thus are significantly correlated with α-carotene, β-carotene and lutein (r^2 0·3 in all three, $P<0·05$).

Results for micronutrients from individual cohort studies have been mainly null (with the exception of a finding in men in the USA)[30], with most showing no effects of individual carotenoids except when stratified by genotype. A study in the Netherlands found no effects of micronutrients[54] except for an association of α-carotene and β-cryptoxanthin and folate with RCC risk in carriers of the wild-type gene for Von-Hippel Landau (VHL) tumours[54].

In a large multicentre case–control study from Central and Eastern Europe, vegetable intake was found to be modified by three key folate metabolism genes[55]. Blood levels of folate were found to be inversely associated with RCC risk in a cohort of Finnish male smokers[56], but interestingly, no dietary nutrient effects of any carotenoids or folate or fibre were observed in this cohort[45].

It is interesting that on subgroup analysis of non-smokers, fruit and vitamin C were also related to RCC risk, which has

also been noted by others[17,44]. Whether this is due to consumption patterns of non-smokers (i.e. a healthier diet) or a real biological effect, needs to be elucidated; and this requires more work in a larger cohort of non-smokers.

A recently proposed putative mechanism that may shed light on these findings is the 'lipid peroxidation hypothesis'. This mechanism not only explains the positive effects of smoking and fat on RCC risk, but also explains the associations of dietary antioxidants with kidney function. This hypothesis is supported by observations in both experimental chemically induced models and human renal cell tissue[18,19].

Strengths of our present study include the use of a well-established tumour registry to ascertain cases[57], a randomly selected control sample representative of the general population and high participation rates among cases and controls. In addition, we assessed external validity by comparing energy and percentage contribution of fat, protein and carbohydrate, by sex and case–control status, in our data with that in the NHANES II. The dietary composition of total energy and distribution of macronutrients among both male and female controls from this study in Iowa was remarkably similar to the NHANES II study sample. Additional strengths were our ability to investigate dietary fibre and to adjust for a wide variety of potential confounding factors including fat intake, which had a high prevalence among our study subjects. In addition, this study investigated a wide range of micronutrients. Although we did not find total energy to be a significant confounder in our study, we controlled for energy intake in the analysis of nutrients in order to adjust for potential general over- or under-reporting of all foods.

In addition to limitations inherent in case–control studies of past diet, other limitations of this study deserve mention. The dietary questionnaire was limited to fifty-five items, was not validated, nor had reliability measured, and portion sizes were not asked. The questions about vegetables and fruits were limited and did not ascertain various forms of cooked preparation, despite asking about consumption of 'raw' vegetables. The questionnaire asked about past diet, and responses may have been subject to recall bias. When differences in dietary recall occur non-differentially with respect to case–control status, estimates of risk are typically biased towards the null. If recall is differential, then risk estimates could be biased in either direction. It is known that although diet has some consistency over time, reported food intakes may not accurately reflect past behaviour[58]. Dietary changes may also have occurred in the food supply (marketplace) over the past 20 years. Survey data suggest that the amount and proportion of energy from total fat and saturated fat have steadily declined over the last 20 years in the USA. Little is known about changes in fruit and vegetables intake although carbohydrate intake has increased[59]. Given that 99 % of the participants in our study were Whites, the present results may have limited generalisability to other racial/ethnic groups. Some observed associations may have been due to chance.

While RCC is not common in the general population, it is increasing, both in the USA and worldwide, despite a decrease in smoking rates in affected populations. It would therefore be worthwhile to further evaluate these findings in larger representative prospective studies, especially in older, non-smoking populations.

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References

1. McLaughlin JK, Lipworth L, Tarone RE, *et al.* (2006) Renal cancer. In *Cancer Epidemiology and Prevention*, 3rd ed., pp. 1087–1100 [D Schottenfeld and JF Fraumeni Jr, editors]. New York, NY: Oxford University Press.
2. Devesa SS, Silverman DT, McLaughlin JK, *et al.* (1990) Comparison of the descriptive epidemiology of urinary tract cancers. *Cancer Causes Control* **1**, 133–141.
3. Moore LE, Wilson RT & Campleman SL (2005) Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. *Cancer Invest* **23**, 240–255.
4. Flegal KM (1999) The obesity epidemic in children and adults: current evidence and research issues. *Med Sci Sports Exerc* **31**, S509–S514.
5. Fields LE, Burt VL, Cutler JA, *et al.* (2004) The burden of adult hypertension in the United States 1999 to 2000: a rising tide. *Hypertension* **44**, 398–404.
6. Boyle JP, Thompson TJ, Gregg EW, *et al.* (2010) Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr* **8**, 29.
7. Anonymous (2004) The 2004 United States Surgeon General's Report: the health consequences of smoking. *NSW Public Health Bull* **15**, 5–6.
8. Parker AS, Cerhan JR, Janney CA, *et al.* (2003) Smoking cessation and renal cell carcinoma. *Ann Epidemiol* **13**, 245–251.
9. Bergstrom A, Hsieh CC, Lindblad P, *et al.* (2001) Obesity and renal cell cancer – a quantitative review. *Br J Cancer* **85**, 984–990.
10. Brock KE, Gridley G, Lynch CF, *et al.* (2007) Obesity and hypertension interact to increase risk of renal cell carcinoma in Iowa, USA. *Obes Res Clin Pract* **1**, 147–153.
11. Chow WH, Gridley G, Fraumeni JF, *et al.* (2000) Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* **343**, 1305–1311.

12. Pan SY, DesMeules M, Morrison H, *et al.* (2006) Obesity, high energy intake, lack of physical activity, and the risk of kidney cancer. *Cancer Epidemiol Biomarkers Prev* **15**, 2453–2460.
13. Grossman E, Messerli FH, Boyko V, *et al.* (2002) Is there an association between hypertension and cancer mortality? *Am J Med* **112**, 479–486.
14. Zucchetto A, Dal Maso L, Tavani A, *et al.* (2007) History of treated hypertension and diabetes mellitus and risk of renal cell cancer. *Ann Oncol* **18**, 596–600.
15. Galeone C, Pelucchi C, Talamini R, *et al.* (2007) Fibre intake and renal cell carcinoma: a case–control study from Italy. *Int J Cancer* **121**, 1869–1872.
16. Hu J, La Vecchia C, DesMeules M, *et al.* (2008) Nutrient and fiber intake and risk of renal cell carcinoma. *Nutr Cancer* **60**, 720–728.
17. Hu J, La Vecchia C, Negri E, *et al.* (2009) Dietary vitamin C, E, and carotenoid intake and risk of renal cell carcinoma. *Cancer Causes Control* **20**, 1451–1458.
18. Gago-Dominguez M & Castelao JE (2006) Lipid peroxidation and renal cell carcinoma: further supportive evidence and new mechanistic insights. *Free Radic Biol Med* **40**, 721–733.
19. Gago-Dominguez M, Castelao JE, Yuan JM, *et al.* (2002) Lipid peroxidation: a novel and unifying concept of the etiology of renal cell carcinoma (United States). *Cancer Causes Control* **13**, 287–293.
20. Greenland S, Gago-Dominguez M & Castelao JE (2004) The value of risk-factor ("black-box") epidemiology. *Epidemiology* **15**, 529–535.
21. Brock KE, Gridley G, Chiu BC, *et al.* (2009) Dietary fat and risk of renal cell carcinoma in the USA: a case–control study. *Br J Nutr* **101**, 1228–1238.
22. Cantor KP, Lynch CF & Johnson D (1993) Reproductive factors and risk of brain, colon, and other malignancies in Iowa (United States). *Cancer Causes Control* **4**, 505–511.
23. Lynch CF, Logsden-Sackett N, Edwards SL, *et al.* (1994) The driver's license list as a population-based sampling frame in Iowa. *Am J Public Health* **84**, 469–472.
24. Hartge P, Cahill JI, West D, *et al.* (1984) Design and methods in a multi-center case–control interview study. *Am J Public Health* **74**, 52–56.
25. Dixon LB, Zimmerman TP, Kahle LL, *et al.* (2003) Adding carotenoids to the NCI Diet History Questionnaire Database. *J Food Comp Anal* **16**, 269–280.
26. Dresser CM (1983) From nutrient data to data base for a health and nutrition examination survey:organization, coding, and values-real or imputed. *Proceedings of the Eighth National Nutrient Data Bank Conference.*
27. Hu FB, Stampfer MJ, Rimm E, *et al.* (1999) Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol* **149**, 531–540.
28. Preston D, Lubin J, Pierce DA, *et al.* (1996) *Epicure [2·0].* Seattle, WA: HiroSoft International Corporation.
29. Greving JP, Lee JE, Wolk A, *et al.* (2007) Alcoholic beverages and risk of renal cell cancer. *Br J Cancer* **97**, 429–433.
30. Lee JE, Hunter DJ, Spiegelman D, *et al.* (2007) Alcohol intake and renal cell cancer in a pooled analysis of 12 prospective studies. *J Natl Cancer Inst* **99**, 801–810.
31. Breslow NE & Day NE (1980) Statistical methods in cancer research. Volume I – the analysis of case–control studies. *IARC Sci Publ* 5–338.
32. Handa K & Kreiger N (2002) Diet patterns and the risk of renal cell carcinoma. *Public Health Nutr* **5**, 757–767.
33. Bravi F, Bosetti C, Scotti L, *et al.* (2006) Food groups and renal cell carcinoma: a case–control study from Italy. *Int J Cancer* **120**, 681–685.
34. Grieb SM, Theis RP, Burr D, *et al.* (2009) Food groups and renal cell carcinoma: results from a case–control study. *J Am Diet Assoc* **109**, 656–667.
35. Talamini R, Baron AE, Barra S, *et al.* (1990) A case–control study of risk factor for renal cell cancer in northern Italy. *Cancer Causes Control* **1**, 125–131.
36. Boeing H, Schlehofer B & Wahrendorf J (1997) Diet, obesity and risk for renal cell carcinoma: results from a case control-study in Germany. *Z Ernahrungswiss* **36**, 3–11.
37. Bosetti C, Rossi M, McLaughlin JK, *et al.* (2007) Flavonoids and the risk of renal cell carcinoma. *Cancer Epidemiol Biomarkers Prev* **16**, 98–101.
38. Hsu CC, Chow WH, Boffetta P, *et al.* (2007) Dietary risk factors for kidney cancer in Eastern and Central Europe. *Am J Epidemiol* **166**, 62–70.
39. Hu J, Mao Y & White K (2003) Diet and vitamin or mineral supplements and risk of renal cell carcinoma in Canada. *Cancer Causes Control* **14**, 705–714.
40. Maclure M & Willett W (1990) A case–control study of diet and risk of renal adenocarcinoma. *Epidemiology* **1**, 430–440.
41. McLaughlin JK, Gao YT, Gao RN, *et al.* (1992) Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* **52**, 562–565.
42. Wakai K, Hirose K, Takezaki T, *et al.* (2004) Foods and beverages in relation to urothelial cancer: case–control study in Japan. *Int J Urol* **11**, 11–19.
43. Wolk A, Gridley G, Niwa S, *et al.* (1996) International renal cell cancer study. VII. Role of diet. *Int J Cancer* **65**, 67–73.
44. Yuan JM, Gago-Dominguez M, Castelao JE, *et al.* (1998) Cruciferous vegetables in relation to renal cell carcinoma. *Int J Cancer* **77**, 211–216.
45. Bertoia M, Albanes D, Mayne ST, *et al.* (2010) No association between fruit, vegetables, antioxidant nutrients and risk of renal cell carcinoma. *Int J Cancer* **126**, 1504–1512.
46. Lee JE, Giovannucci E, Smith-Warner SA, *et al.* (2006) Intakes of fruits, vegetables, vitamins A, C, and E, and carotenoids and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev* **15**, 2445–2452.
47. Rashidkhani B, Akesson A, Lindblad P, *et al.* (2005) Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. *J Nutr* **135**, 1757–1762.
48. Rashidkhani B, Lindblad P & Wolk A (2005) Fruits, vegetables and risk of renal cell carcinoma: a prospective study of Swedish women. *Int J Cancer* **113**, 451–455.
49. van Dijk BA, Schouten LJ, Kiemeney LA, *et al.* (2005) Vegetable and fruit consumption and risk of renal cell carcinoma: results from the Netherlands cohort study. *Int J Cancer* **117**, 648–654.
50. Weikert S, Boeing H, Pischon T, *et al.* (2006) Fruits and vegetables and renal cell carcinoma: findings from the European prospective investigation into cancer and nutrition (EPIC). *Int J Cancer* **118**, 3133–3139.
51. Boffetta P, Couto E, Wichmann J, *et al.* (2010) Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* **102**, 529–537.
52. Lee JE, Mannisto S, Spiegelman D, *et al.* (2009) Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. *Cancer Epidemiol Biomarkers Prev* **18**, 1730–1739.
53. Bosetti C, Scotti L, Maso LD, *et al.* (2007) Micronutrients and the risk of renal cell cancer: a case–control study from Italy. *Int J Cancer* **120**, 892–896.
54. van Dijk BA, Schouten LJ, Oosterwijk E, *et al.* (2008) Carotenoid and vitamin intake, von Hippel-Lindau gene

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mutations and sporadic renal cell carcinoma. *Cancer Causes Control* **19**, 125–134.
55. Moore LE, Hung R, Karami S, *et al.* (2008) Folate metabolism genes, vegetable intake and renal cancer risk in central Europe. *Int J Cancer* **122**, 1710–1715.
56. Gibson TM, Weinstein SJ, Mayne ST, *et al.* (2010) A prospective study of one-carbon metabolism biomarkers and risk of renal cell carcinoma. *Cancer Causes Control* **21**, 1061–1069.
57. Ries LAG, Harkins D, Krapcho M, *et al.* (2006) *SEER Cancer Statistics Review, 1975–2003*. Bethesda, MD: National Cancer Institute. http://seer.cancer.gov/csr/1975_2003/ (based on November 2005 SEER data submission, posted to the SEER web site, 2006).
58. Dwyer JT, Gardner J, Halvorsen K, *et al.* (1989) Memory of food intake in the distant past. *Am J Epidemiol* **130**, 1033–1046.
59. Kant AK & Graubard BI (2007) Secular trends in the association of socio-economic position with self-reported dietary attributes and biomarkers in the US population: National Health and Nutrition Examination Survey (NHANES) 1971–1975 to NHANES 1999–2002. *Public Health Nutr* **10**, 158–167.