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Dietary fat and risk of renal cell carcinoma in the USA: a case–control study

Kaye E. Brock[1]*, Gloria Gridley[2], Brian C.-H. Chiu[3], Abby G. Ershow[4], Charles F. Lynch[5] and Kenneth P. Cantor[2]

[1]*Department of Behavioural and Community Health Sciences, Faculty of Heath Sciences, University of Sydney, Sydney, NSW, Australia*
[2]*Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, NIH, Bethesda, MD, USA*
[3]*Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA*
[4]*Department of Health and Human Services, National Heart Lung and Blood Institute, NIH, Bethesda, MD, USA*
[5]*Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA*

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An increased risk of renal cell carcinoma (RCC) has been linked with obesity. However, there is limited information about the contribution of dietary fat and fat-related food groups to RCC risk. A population-based case–control study of 406 cases and 2434 controls aged 40–85 years was conducted in Iowa (1986–89). For 323 cases and 1820 controls from the present study, information on dietary intake from foods high in fat nutrients and other lifestyle factors was obtained using a mailed questionnaire. Cancer risks were estimated by OR and 95 % CI, adjusting for age, sex, smoking, obesity, hypertension, physical activity, alcohol and vegetable intake and tea and coffee consumption. In all nutrient analyses, energy density estimates were used. Dietary nutrient intake of animal fat, saturated fat, oleic acid and cholesterol was associated with an elevated risk of RCC (OR = 1·9, 95 % CI 1·3, 2·9, $P_{trend} < 0·001$; OR = 2·6, 95 % CI 1·6, 4·0, $P_{trend} < 0·001$; OR = 1·9, 95 % CI 1·2, 2·9, $P_{trend} = 0·01$; OR = 1·9, 95 % CI 1·3, 2·8, $P_{trend} = 0·006$, respectively, for the top quartile compared with the bottom quartile of intake). Increased risks were also associated with high-fat spreads, red and cured meats and dairy products (OR = 2·0, 95 % CI 1·4, 3·0, $P_{trend} = 0·001$; OR = 1·7, 95 % CI 1·0, 2·2, $P_{trend} = 0·01$; OR = 1·8, 95 % CI 1·2, 2·7, $P_{trend} = 0·02$; OR = 1·6, 95 % CI 1·1, 2·3, $P_{trend} = 0·02$, respectively). In both the food groups and nutrients, there was a significant dose–response with increased intake. Our data also indicated that the association of RCC with high-fat spreads may be stronger among individuals with hypertension. These findings deserve further investigation in prospective studies.

Kidney cancer: Renal cell carcinoma: Case–control studies: Dietary fat

Although renal cell carcinoma (RCC) accounts for only 3 % of adult malignancies in the USA, its incidence has been increasing in the USA for the last 30 years, with annual increments of 1·6 % in white men and 1·7 % in white women. Thirty years ago, rates of renal cancer were 12 per 100 000 white men and 5 per 100 000 white women. Recent rates are reported as 18 per 100 000 white men and 9 per 100 000 white women[1,2]. The increase cannot be fully explained by early detection of pre-symptomatic tumours. The reported ongoing epidemic of obesity in the USA[3] and/or the increase in hypertension[4] and diabetes[5] may explain part of this increase, which occurred despite a drop in smoking rates[6]. Although obesity[7], hypertension[8] and diabetes[9] have consistently been associated with RCC risk, few studies have tried to disentangle the effects of obesity from increased dietary intake and lack of physical activity[10,11]. An increase in lipid peroxidation may partially explain some of the reasons for RCC risk[12,13]. To evaluate the association between an 'energy-dense' diet and the risk of RCC and to understand the interrelationship between dietary intake of fatty foods and its correlates, we analysed RCC dietary data, along with other established and potential risk factors collected as part of a large population-based case–control study.

Material and methods

Study sample

A population-based case–control study of RCC and five other cancers was conducted in Iowa between 1986 and 1989. Detailed methods are reported elsewhere[14,15]. 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) in July 1985 to December 1987, and without previous diagnosis of a malignant neoplasm. Cases were identified by the State Health Registry of Iowa[16]. An introductory letter was followed by a telephone call in which potential participants were invited to complete a mailed

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

* **Corresponding author:** Kaye E. Brock, fax +61 293519540, email k.brock@usyd.edu.au

questionnaire, designed either for direct respondents or their proxies, sent per request during the telephone contact. Of the 463 eligible RCC cases, the questionnaires were completed for 406 of them (87·7 % response rate). Among these, 287 subjects completed the questionnaire designed for direct respondents and 119 completed a proxy questionnaire. The early version of the direct respondent questionnaire, which did not include a question about possible proxy status, was completed by 81 of the 287 'direct questionnaire' respondents. In the present analysis, these respondents were assumed to be the study subjects 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.

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[17], whereas controls aged 65 years and older were selected randomly from the lists of Iowa residents provided by the US 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[18]. Of the 999 eligible controls under the age of 65 years, 817 (82 %) participated by returning a completed questionnaire, and 1617 of 2036 eligible controls aged 65 years or older participated (79 %). Among the 2432 sent direct reminder questionnaires, control subjects 2064 were completed by the subject, 241 by a proxy and 127 by an undetermined respondent (assumed to be a direct respondent, as described earlier). Proxy questionnaires were sent to two control subjects.

Written informed consent was obtained from all participants. The study was approved by the Institutional Review Boards at the US National Cancer Institute and at 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 usual 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. BMI was calculated as (weight (in kilograms))/(height (in meters))^2 and subjects were classified as normal (BMI < 25 kg/m^2), overweight (BMI 25–29·9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) when they were in their 20s, 40s and 60s.

Of the 2434 controls, 548 did not have sufficient dietary data for analysis. We did not exclude any subject for 'extreme' values on any dietary variable. Sixty-six controls were missing information on BMI and/or a history of hypertension. Of the 406 RCC cases, seventy 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 1820 controls for the dietary analysis. Most of the 548 controls and seventy three cases, who were excluded due to insufficient dietary information, had responded to a truncated telephone questionnaire that did not include diet.

Dietary analysis

Information on usual adult dietary intake was gathered with a food frequency questionnaire 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. Using these data, we calculated the intake per common time period for each item. We then summed these data to derive the 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)[19,20]. Nutrients were then estimated by multiplying the intake of these foods by nutrient density estimates derived from the US Department of Agriculture (USDA) food composition tables[20] and a USDA-National Cancer Institute (NCI) food composition database[19]. An adjustment for total food intake was carried out by the nutrient density method[21]. Each nutrient was individually divided by the subject's total energy intake before the quartiles of intake were calculated. Quartiles of dietary intake by food group or nutrient were calculated based on the distribution among controls. 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) and EPICURE[22].

Multiple logistic regression analysis was used to adjust for confounding by age (continuous), sex, smoking (in eight pack-year categories), proxy status of respondents (direct or proxy respondent), history of high blood pressure (yes, no), BMI at age 40, alcohol intake (as per recent cohort studies[23,24]) and vegetable consumption (Tables 1 and 2). Physical activity, fruit intake, education, family history of kidney cancer, coffee, tea consumption and history of kidney infection were found not to be risk factors and when added to the models of the present analysis had no added effect on RCC risk; thus they were not included as confounders in further analyses. The maximum-likelihood estimate of the OR, with 95 % CI, was used as the measure of association between either dietary fat-related food group variables or nutrients and RCC[25]. Tests for trend across quartiles were performed by assigning the mean value of each respective quartile to the score variable, and then testing linear trend using a likelihood ratio test[25]. To evaluate possible interaction on the association of risk with dietary fat by other established risk factors, we examined stratified models and also tested multiplicative interaction by the log-likelihood ratio test. For example, interaction ($OR_{interaction}$) between blood pressure and fatty spread consumption (continuous) was tested by the log-likelihood ratio test in a logistic model, with main effects adjusting for sex, age, proxy status, smoking, energy, BMI at age 40, alcohol intake and vegetable intake[25]. We previously reported the joint effect of obesity and hypertension on RCC risk in these data[26].

Table 1. Distribution of potential confounding factors (%) and their correlations by dietary fat consumption in controls of Iowa case–control study of renal cell carcinoma and diet

Dietary fat consumption	0–35 g (%)	36–40 g (%)	41–45 g (%)	>45 g (%)	Significance	Correlation coefficient*
Age (years)						
40–54	22	20	26	32		
55–64	24	27	21	27		
65–74	29	26	22	23		
75–85	31	30	22	17		
χ^2 (P)					<0·001	−0·05*
Type of interview						
Direct respondents	28	27	22	23		
Proxy respondents	21	22	24	33		
χ^2 (P)					0·02	
Sex						
Male	27	26	23	23		
Female	28	28	21	23		
χ^2 (P)					NS	
Smoking						
Never	28	29	23	20		
Former	30	25	23	22		
Current	21	25	22	32		
χ^2 (P)					<0·001	0·20*
BMI at age 40 (kg/m^2)						
<25	28	27	22	23		
25–30	26	26	23	25		
>30	24	29	20	27		
χ^2 (P)					NS	
Hypertension						
No	25	25	25	25		
Yes	32	29	18	21		
χ^2 (P)					<0·001	
Alcohol intake (drinks/d)						
Never	22	27	24	27		
One	38	25	23	14		
Two	51	32	14	3		
>Two	72	19	5	4		
χ^2 (P)					<0·001	−0·3*
Vegetable intake (serves/d)						
0–<1	24	23	21	32		
1–1·4	27	26	25	22		
1·5–2	25	31	19	25		
>2	32	27	24	17		
χ^2 (P)					<0·001	−0·1*
Coffee consumption (cups/d)						
0	32	29	29	32		
<0·5	59	60	62	54		
<1	4	6	4	8		
≥1	5	5	5	6		
χ^2 (P)					NS	0·18*
Physical activity						
>1/d	31	26	21	21		
2–6/week	22	28	24	27		
1–4/month	23	28	24	25		
<1/month	27	27	22	24		
χ^2 (P)					0·001	0·13*
Protein intake (g/d)						
0–42	42	28	15	15		
43–45	29	27	23	21		
46–52	22	27	27	25		
>52	18	25	24	34		
χ^2 (P)					<0·001	0·4*
Carbohydrate intake (g/d)						
0–89	12	13	14	61		
90–107	11	16	38	35		
108–119	17	41	36	6		
>119	63	33	3	1		
χ^2 (P)					<0·001	−0·6*

*Correlation was adjusted for energy.

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Results

Table 1 presents the distribution between dietary fat consumption and covariates in the control population. This analysis was done both by percentage distribution by quartile of fat intake and also Pearson's correlation coefficients with dietary fat as a continuous variable, where relevant. The major associations in the controls with dietary fat were with age, proxy status, smoking, hypertension, alcohol consumption, coffee, physical activity, protein and carbohydrate intake and vegetable consumption. It should be noted that energy, as expected, was highly correlated with dietary fat consumption. We therefore present the correlations of the variables adjusted for energy.

In Table 2, smoking, increased BMI at age 40, age, a history of hypertension, low alcohol intake and low vegetable consumption were significant risk factors for RCC in our data. Compared with the controls, the cases were more likely to be current smokers (OR = 1·6 (95 % CI 1·1, 2·2)), obese at age 40 (OR = 1·9 (95 % CI 1·3, 2·9)), to report a history of hypertension (OR = 1·8 (95 % CI 1·4, 2·4)), not drink alcohol and consume vegetables at a low level. The cases were somewhat younger than the controls; thus age was included as a confounder (continuous) in subsequent analyses. Among the direct respondents, OR for smoking, obesity and hypertension and low alcohol and vegetable consumption followed patterns similar to those shown in Table 2 (data not shown). Thus, age, smoking, proxy status, obesity, hypertension and alcohol and vegetable consumption were included as confounders in subsequent analyses. In our data, neither physical activity, coffee/tea consumption nor fruit consumption remained as risk factors after adjustment for these confounders, and thus were not included as covariates in any models.

We compared energy and percentage of contribution of fat, protein and carbohydrate, by sex and case–control status, in our data with those in the NHANES II nutritional survey conducted contemporaneously[20]. This was done as no validation studies were available from 1986, and we wanted some 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 the Iowa study was remarkably similar to those of the NHANES II study sample (i.e. 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 %; Appendix 1).

Table 3 presents analyses of fat-related food groups. High-fat spreads (e.g. mayonnaise, margarine, butter), red meat (bacon, breakfast sausage, beefsteaks, roasts, hamburgers, meat loaf, beef stew, pot pie, hot dogs, lunch meats, bratwurst, ham, pork, meat in pasta dishes), dairy foods (ice cream, cheese, milk) and cured meats (e.g. bacon, hot dogs) were found to be associated with a higher risk of RCC, with

Table 2. Demographic and lifestyle risk factors: Iowa case–control study of renal cell carcinoma

	No. of cases (*n* 323)	Percentage	No. of controls (*n* 1820)	Percentage	OR*	95 % CI
Age (years)						
40–54	61	19	206	11		
55–64	109	34	480	26		
65–74	113	35	707	39		
75–85	40	12	427	24		
Proxy status						
Direct respondent	247	77	1675	92		
Proxy respondent	76	23	145	8		
Sex						
Male	202	62	1211	67		
Female	121	38	609	33		
Smoking						
Never	124	38	796	43	1·0	
Former	108	33	668	37	1·2	0·9, 1·7
Present	91	29	356	20	1·6	1·1, 2·2
BMI at age 40 (kg/m^2)						
< 25	156	40	1108	61	1·0	
25–30	118	37	576	33	1·4	1·0, 1·8
> 30	49	15	136	6	1·9	1·3, 2·9
Hypertension history						
Never	165	51	1176	65	1·0	
Ever	158	49	644	36	1·8	1·4, 2·4
Alcohol consumption (per d)						
Never	280	87	1511	83	1·0	
Once	21	7	149	8	0·8	0·5, 1·0
Twice	14	4	78	4	0·8	0·5, 1·0
> Twice	8	2	82	5	0·4	0·3, 0·6
Vegetable servings (per d)						
< 1·0	68	21	409	22	1·0	
1·0–1·4	99	31	540	30	0·7	0·5, 1·0
1·5–2·0	89	27	517	28	0·7	0·5, 1·0
> 2·0	67	21	354	20	0·4	0·3, 0·6

* Adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, alcohol and vegetable consumption, where relevant.

Table 3. Fat-related food groups and their association with renal cell carcinoma risk: Iowa case–control study
(Odds ratios and 95% confidence intervals)

	Intake (servings/d)			Total sample (*n* 2143)		Self-respondents (*n* 1922)	
Fat-related food groups	Quartiles	Cases (*n* 323)	Controls (*n* 1820)	OR*	95 % CI	OR†	95 % CI
High-fat spreads‡	0–4·8	55	451	1·0		1·0	
	4·9–6·4	73	448	1·4	1·0, 2·1	1·4	0·9, 2·1
	6·5–8·4	83	455	1·4	1·0, 2·0	1·4	1·0, 2·2
	>8·4	112	466	2·0	1·4, 3·0	1·6	1·0, 2·4
P_{trend}					0·001		0·03
Red meat‡	0–0·8	61	455	1·0		1·0	
	0·9–1·2	83	452	1·4	0·9, 1·9	1·4	0·9, 2·1
	1·3–1·7	82	458	1·3	0·9, 1·9	1·4	0·9, 2·0
	>1·7	97	455	1·7	1·0, 2·2	1·5	1·0, 2·4
P_{trend}					0·01		0·05
Dairy‡	0–1·0	63	455	1·0		1·0	
	1·1–2·0	76	455	1·3	0·9, 2·0	1·3	0·9, 2·0
	2·1–3·0	87	455	1·4	1·0, 2·1	1·2	0·7, 1·7
	>3·0	97	455	1·6	1·1, 2·3	1·4	1·0, 2·1
P_{trend}					0·02		0·09
Cured meat‡	0–0·10	49	451	1·0		1·0	
	0·11–0·30	81	431	1·4	1·0, 2·0	1·4	0·9, 2·0
	0·31–0·60	82	437	1·3	0·9, 2·0	1·2	0·8, 1·8
	>0·60	111	501	1·8	1·2, 2·7	1·6	1·1, 2·5
P_{trend}					0·02		0·07

*OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, alcohol and vegetable consumption in total population.
†OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, alcohol and vegetable consumption in direct respondents.
‡High-fat spreads: butter/margarine and mayonnaise; red meat: bacon, breakfast sausage, beef (steaks, roasts, hamburgers, meat loaf), beef stew, pot pie, hot dogs, lunch meats, bratwurst, ham, pork, meat in pasta dishes; dairy: ice cream, cheese, cheese spread, cheese or cream in pasta dishes, whole and skimmed milk; cured meat: bacon, breakfast sausage, hot dogs, bratwurst, lunch meats.

significant trends for high-fat spreads ($P_{trend} = 0{\cdot}001$), red meat ($P_{trend} = 0{\cdot}01$), dairy foods ($P_{trend} = 0{\cdot}02$) and cured meats ($P_{trend} = 0{\cdot}02$). Total meat consumption (data not shown) did not show this significant positive association with RCC risk. Subjects in the highest quartile (compared with the lowest quartile) of consumption of high-fat spreads, red meat, dairy foods and cured meat had significantly increased risks: OR = 2·0 (95 % CI 1·4, 3·0), OR = 1·7 (95 % CI 1·0, 2·2), OR = 1·6 (95 % CI 1·1, 2·3) and OR = 1·8 (95 % CI 1·2, 2·7), respectively. Similar risks were seen when analyses were limited to self-respondents (Table 3).

Table 4 presents energy density nutrient values for the macronutrients. Total energy was not significantly associated with the risk of RCC ($P_{trend} = 0{\cdot}31$; top quartile *v.* bottom quartile of intake: OR = 1·3, 95 % CI 0·8, 2·0). There was no association between increased protein intake and RCC (OR = 1·2, 95 % CI 0·7, 1·6, high *v.* low quartile). The significantly reduced risks and trends for carbohydrate consumption disappeared when adjusted for fat intake (OR = 1·1, 95 % CI 0·6, 2·0, high *v.* low quartile; protein: OR = 0·7, 95 % CI 0·5, 1·2, high *v.* low quartile). However, increased fat intake was associated with significant risk of RCC (OR = 2·0 (95 % CI 1·3, 3·0), $P_{trend} = 0{\cdot}001$), even after adjustment for protein or carbohydrate intake. As was found for the food group associations, results from the analyses limited to direct respondents were similar to those from the total study sample.

Table 5 presents results of the analyses for the types of fat nutrients, using energy density estimates for these fat nutrient variables. For saturated fat, animal fat, oleic acid and cholesterol, there were significant dose–response increases in the risk for RCC, with the risk increasing as the intake of each type of fat increased. Those in the highest quartile of each type of fat nutrient had a significant twofold risk: OR = 2·6 (95 % CI 1·6, 4·0, $P_{trend} < 0{\cdot}001$), OR = 1·9 (95 % CI 1·3, 2·9, $P_{trend} < 0{\cdot}001$), OR = 1·9 (95 % CI 1·2, 2·9, $P_{trend} = 0{\cdot}01$) and OR = 1·9 (95 % CI 1·3, 2·8, $P_{trend} = 0{\cdot}006$), respectively. Increasing intake of vegetable fat and polyunsaturated fat (linoleic acid) showed little association with RCC risk. Results from the analyses limited to direct respondents were similar to those from the total study sample. As the nutrients related to the types of fat were highly correlated with one another (Appendix 2), the individual fat-related nutrients were not further adjusted for each other, nor for protein or carbohydrate.

In an attempt to disentangle food group findings from energy-adjusted nutrient findings, we adjusted dairy intake for cholesterol (and vice versa). The risks for both dairy and cholesterol remained unchanged and significant. By contrast, the risk for cured meat was reduced by adjusting for cholesterol (but not vice versa; $OR_{cured\ meat} = 1{\cdot}4$ (95 % CI 0·9, 2·3) and $OR_{cholesterol} = 2{\cdot}2$ (95 % CI 1·3, 3·7), for the highest compared with the lowest intake quartile).

Table 6 shows the interaction between hypertension and high-fat spreads for the risk of RCC. As this interaction was interesting but only marginally significant for the high-fat spreads food group ($P = 0{\cdot}06$), we also investigated the interaction between hypertension and the other fat-related food groups and nutrients. We found similar interactions that were only marginally significant for saturated fat and oleic acid (data not shown). When we investigated other potential interactions, none were found with age, sex, tobacco, BMI, alcohol intake or vegetable intake for the association between fat intake and RCC risk.

Table 4. Macronutrients and their association with renal cell carcinoma risk from a case–control study in Iowa
(Odds ratios and 95% confidence intervals)

Nutrients	Percentage energy	Cases	Controls	Total sample (*n* 2123) OR*	Total sample (*n* 2123) 95 % CI	Self-respondents (*n* 1922) OR*	Self-respondents (*n* 1922) 95 % CI	Total sample (*n* 2123) OR†	Total sample (*n* 2123) 95 % CI	Self-respondents (*n* 1922) OR†	Self-respondents (*n* 1922) 95 % CI	Total sample (*n* 2123) OR‡	Total sample (*n* 2123) 95 % CI	Self-respondents (*n* 1922) OR‡	Self-respondents (*n* 1922) 95 % CI	Total sample (*n* 2123) OR§	Total sample (*n* 2123) 95 % CI	Self-respondents (*n* 1922) OR§	Self-respondents (*n* 1922) 95 % CI
Percentage of energy from fat	<32	47	455	1·0		1·0		1·0		1·0		–		–		1·0		1·0	
	32–35	66	455	1·4	1·0, 2·5	1·5	1·0, 2·5	1·5	0·9, 2·4	1·7	1·0, 2·8	–		–		1·4	0·9, 2·2	1·6	1·0, 2·5
	36–40	100	455	2·3	1·6, 4·2	2·6	1·6, 4·2	2·2	1·4, 3·6	2·4	1·4, 4·1	–		–		2·2	1·4, 3·3	2·4	1·6, 3·8
	>40	110	455	2·0	1·3, 3·0	2·0	1·2, 3·3	2·2	1·3, 3·6	2·4	1·3, 4·3	–		–		2·1	1·4, 3·2	2·2	1·4, 3·6
P_{trend}					0·001		0·001		0·001		0·001						0·001		0·001
Percentage of energy from carbohydrates	<40	100	455	1·0		1·0		1·0		1·0		1·0		1·0		–		–	
	40–44	102	455	1·1	0·9, 1·6	1·2	0·8, 1·7	1·3	0·9, 1·8	1·4	1·0, 2·1	1·3	0·9, 1·8	1·5	1·0, 2·2	–		–	
	45–48	68	455	0·7	0·5, 1·0	0·7	0·4, 1·0	0·9	0·6, 1·4	0·9	0·5, 1·5	0·8	0·5, 1·2	0·8	0·5, 1·3	–		–	
	>48	53	455	0·6	0·4, 0·9	0·5	0·3, 0·9	1·1	0·6, 2·0	1·2	0·6, 2·1	0·7	0·5, 1·2	0·7	0·4, 1·3	–		–	
P_{trend}					0·003		0·001		NS		NS		0·07		0·08				
Percentage of energy from protein	<16	78	455	1·0		1·0		–		–		1·0		1·0		1·0		1·0	
	16–17	79	455	0·8	0·6, 1·3	0·8	0·5, 1·3	–		–		1·0	0·7, 1·5	1·0	0·6, 1·5	1·0	0·7, 1·4	0·9	0·6, 1·4
	18–19	66	455	0·9	0·6, 1·2	0·9	0·6, 1·4	–		–		0·9	0·6, 1·3	1·1	0·7, 1·6	0·8	0·5, 1·2	1·0	0·6, 1·5
	>19	100	455	1·2	0·7, 1·6	1·2	0·8, 1·8	–		–		1·3	0·9, 1·8	1·4	1·0, 2·2	1·2	0·8, 1·7	1·3	0·9, 2·0
P_{trend}					NS		NS						NS		0·07		NS		NS

* OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, energy, alcohol and vegetable consumption.
† OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, energy, alcohol and vegetable consumption, and the model also includes percentage of energy from fat and carbohydrates.
‡ OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, energy, alcohol and vegetable consumption, and the model also includes percentage of energy from protein and carbohydrates.
§ OR adjusted for age, sex, proxy status, smoking, BMI at age 40, blood pressure, energy, alcohol and vegetable consumption, and the model also includes percentage of energy from fat and protein.

Table 5. Fat nutrients and their association with renal cell carcinoma risk: a case–control study in Iowa
(Odds ratios and 95% confidence intervals)

				Total sample (*n* 2143)		Self-respondents (*n* 1922)	
	Percentage of energy	Cases	Controls	OR*	95 % CI	OR†	95 % CI
Percentage of energy from saturated fat	<12	49	455	1·0		1·0	
	12–13	72	455	2·2	1·4, 3·4	2·3	1·4, 3·8
	14–15	98	455	2·6	1·7, 4·0	2·7	1·7, 4·5
	>15	104	455	2·6	1·6, 4·0	2·6	1·6, 4·3
P_{trend}					0·001		0·001
Percentage of energy from animal fat	<18	50	455	1·0		1·0	
	18–21	70	455	1·5	1·0, 2·3	1·5	1·0, 2·4
	22–25	91	455	1·8	1·2, 2·4	1·8	1·2, 2·8
	>25	112	455	1·9	1·3, 2·9	2·0	1·3, 3·1
P_{trend}					0·001		0·002
Percentage of energy from vegetable fat	<11	77	455	1·0		1·0	
	11–13	67	455	0·9	0·6, 1·3	1·1	0·7, 1·7
	14–16	91	455	1·0	0·7, 1·4	1·4	0·9, 2·0
	>16	88	455	1·3	0·9, 1·8	1·0	0·7, 1·6
P_{trend}					NS		NS
Percentage of energy from linoleic acid (polyunsaturated)	<21	74	455	1·0		1·0	
	21–27	65	455	1·4	0·9, 2·1	1·4	0·9, 2·2
	28–37	93	455	1·6	1·1, 2·4	1·7	1·1, 2·6
	>37	91	455	1·5	1·0, 2·2	1·5	1·0, 2·3
P_{trend}					0·04		NS
Percentage of energy from oleic acid (monounsaturated)	<6	67	455	1·0		1·0	
	6–7	84	455	1·8	1·2, 2·7	1·9	1·2, 3·0
	8–10	78	455	2·0	1·3, 3·0	2·4	1·5, 3·8
	>10	94	455	1·9	1·2, 2·9	1·9	1·2, 3·1
P_{trend}					0·01		0·01
Percentage of energy from cholesterol	<1·2	53	455	1·0		1·0	
	1·2–1·6	92	455	1·8	1·2, 2·7	1·9	1·2, 2·9
	1·7–2	82	455	1·8	1·2, 2·7	2·0	1·3, 3·0
	>2	96	455	1·9	1·3, 2·8	1·9	1·2, 3·0
P_{trend}					0·006		0·01

* OR adjusted for sex, age, proxy status, smoking, BMI at age 40, hypertension, alcohol, vegetable consumption and energy.
† OR direct respondent analysis adjusted for sex, age, smoking, BMI at age 40, hypertension, alcohol, vegetable consumption and energy.

Discussion

Results from this population-based case–control study provide evidence for a link between high dietary saturated fat, animal fat, oleic acid and cholesterol intake and an excess risk of RCC. In initial macronutrient analysis, once the effect of fat was taken into account, neither protein, carbohydrate nor total energy intake was significantly associated with RCC. Increased risks were associated with high-fat spreads, red and cured meats and dairy products. In both the fat-related food groups and nutrients, there was a significant dose–response with increased intake. Our data also indicated that the association of RCC with fatty foods may be stronger among individuals with hypertension.

Our findings of a significant effect of animal and saturated fat intake, cholesterol, high-fat spreads, dairy products and red and cured meat are consistent with indications from very early ecological observations noted both in the USA[27] and internationally[28], where average national intake of animal products was significantly correlated with national RCC mortality in

Table 6. Interaction between blood pressure and high-fat spreads consumption on renal cell carcinoma risk*
(Odds ratios and 95% confidence intervals)

	Normal blood pressure				Hypertensive			
Quartiles (frequency/d)	Cases (*n* 165)	Controls (*n* 1176)	OR†	95 % CI	Cases (*n* 158)	Controls (*n* 644)	OR†	95 % CI
High-fat spreads food group								
0–4·8	32	282	1·0	Reference	23	169	1·3	0·7, 2·5
>4·8–6·4	38	285	1·1	0·6, 1·9	35	163	1·9	1·1, 3·4
>6·4–8·4	38	296	1·1	0·6, 1·9	45	159	2·6	1·5, 4·6
>8·5	57	313	1·5	0·9, 2·5	55	153	3·6	2·1, 6·3

* Interaction between blood pressure and high-fat spread consumption was tested by the likelihood ratio test in a logistic model adjusted for age (continuous), smoking, proxy status, sex, blood pressure, BMI at age 40, alcohol and vegetable consumption ($OR_{interaction}$). $OR_{interaction}$ = 1·2 (95% CI 0·99, 1·6), $P_{interaction}$ = 0·06.
† OR adjusted for sex, age, proxy status, BMI at age 40, smoking, alcohol and vegetable intake.

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thirty-two countries ($r^2 = 0{\cdot}8$). Our data showing an increased risk for selected fats in the diet are similar to those of a US case–control study, collected in a similar time period, which reported an OR of 2·2 (95 % CI 1·2, 3·9) for saturated fat, an OR = 1·8 (95 % CI 1·0, 3·1) for animal fat and yet little association with animal protein (OR = 1·3 (95 % CI 0·8, 2·3))[29]. An Italian case–control study (with hospital controls) reported a significant twofold association, similar to ours, between margarine and oils and RCC risk[30]. Out of the eleven case–control[27,29–38] and six cohort studies[39–44], four medium-sized case–control studies (all but one with population controls)[29,30,32,33] and one cohort study[40] reported a specific association of intake of some form of fat with RCC risk.

Similar to past case–control findings, our data show a stronger association with red meat than with total meat consumption. Eight of the case–control studies reported positive significant associations with high intakes of meat, some specifically with animal protein[29,30,34–36], beef[11,29,34], red meat[35,36], fried meat[35,37], processed meat[11] and poultry[38]. Our data also showed some association with cured/processed meat. In a pooled case–control study from four countries[37] and in a California study[10], cured meat was not found to be a risk factor.

Our finding of selected types of dietary fat as the major nutrient associated with RCC risk is not in total accord with the few other studies that investigated the role of macronutrients, where either protein[30,36], fat[33] or total energy[32] was determined to be a risk factor, after mutual adjustment. In an attempt to elucidate the macronutrient involved, case–control data from five countries were combined and a risk for RCC of 1·7 for the highest *v.* the lowest quartile of total energy intake was reported[37]. In subsequent cohort studies, only one investigated macronutrients and a null effect was reported for total energy[40]. Most cohort studies have shown little association of RCC risk with high-fat foods[39–43], except for a Japanese study in which 'a fondness for fatty foods' was associated with RCC risk[44], although it must be noted that the numbers of RCC cases in these studies were small (*n* 14–122).

The disparity between case–control and cohort studies may have two origins. First, cohort studies to date have had very limited numbers of RCC cases as it is a rare cancer. Thus, they may not have had adequate power to detect an effect. Second, it is also possible that the effect we have observed could be due to recall bias. Only further investigations in large cohort studies or consortia will resolve this issue.

Several types of putative mechanisms may shed light on these findings. First, as diabetes may also be related to RCC risk, one explanation for an association with specific types of fat in the diet is that high insulin levels may increase the risk of RCC[5,9], as certain types of fat in the diet have previously been thought to be associated with high insulin levels and development of type 2 diabetes[9], although these associations are now in question[45]. In animal models, insulin directly stimulates carcinogenesis and neoplastic differentiation by promoting DNA synthesis[46]. A second mechanism is hormonal, as animal studies indicate that the deposition of lipids in the kidney may be regulated by hormones and the kidney is rich in prolactin receptors[47]. Thus, there is a possibility that fat intake, obesity, diabetes and hypertension could all be intermediate steps in a causal pathway to RCC. An overriding hypothesis that incorporates all these steps has recently been proposed as a 'lipid peroxidation hypothesis' to explain the associations of specific types of fats in the diet, obesity and hypertension with RCC[12,13,48]. This hypothesis is supported by observations in both experimental chemically induced models[48,49] and human renal cell tissue[50].

The possible interaction between diets high in specific types of fat and hypertension is of interest. We previously reported the joint effect of obesity and hypertension on RCC risk in these data and speculated that the increase in RCC risk related to obesity may be rather mild unless blood pressure was poorly controlled[26]. Unhealthy diets that are high in certain types of fat may be associated with poorly controlled blood pressure, which could partly explain these observations. Also in line with the 'lipid peroxidation hypothesis'[12,13], we speculated that diets high in specific types of fat may play a synergistic role with hypertension for RCC risk.

The strengths of the present study include the use of a well-established tumour registry to ascertain cases[2], a randomly selected control sample representative of the general population and reasonable participation rates among the cases and controls. Additional strengths of the present study were our ability to adjust for a wide variety of potential confounding factors and the high prevalence of fat intake among the present study subjects. A difficulty in sorting out the effects of specific high-energy nutrients lay in their high intercorrelation. Although we did not find total energy to be a significant confounder in the present 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 the present study deserve a mention. Height, weight at various ages and hypertension were self-reported. It is possible that the risk associated with our high-fat spread food group was higher in individuals with hypertension, but the present study had limited power to detect the interaction between consumption of this food group and hypertension. Larger studies are necessary to test this hypothesis. In addition, the dietary questionnaire was retrospective and limited to fifty-five items, was not validated and portion sizes were not asked. The questions about meat were limited and did not ascertain inner and outer doneness and various forms of meat preparation. The questionnaire asked about past diet and responses may be subject to recall bias. If 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, 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[51]. Dietary changes due to hypertension or other conditions were not ascertained. 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 and saturated fat have steadily declined over the last 20 years in the USA[52]. Thus, the present results may not be as relevant in the society today, or may reflect a latency effect. Given that 99 % of the participants in the

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present study were white, 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 drop in smoking rates. It would therefore be worthwhile to further evaluate these findings in larger prospective studies.

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Appendix 1. Nutritional distributions: Iowa case–control study compared with National Health and Nutrition Examination Survey II (NHANES II)

	Male cases (*n* 202)		Male controls (*n* 1211)		NHANES II males		Female cases (*n* 121)		Female controls (*n* 609)		NHANES II females	
	Mean daily intake	Percentage	Mean daily intake	Percentage	Mean daily intake	Percentage	Mean daily intake	Percentage	Mean daily intake	Percentage	Mean daily intake	Percentage
kJ	8345·4		8983·8		8005·2		5636·4		5502		5552·4	
Protein	338	17	395	18	324	17	215	16	223	17	212	16
Fat	795	40	842	40	724	38	497	37	432	33	463	35
Carbohydrate	854	43	902	42	858	45	631	47	655	50	648	49

Appendix 2. Pearson correlation coefficients between fat-related nutrients in the control population

	Fat	Saturated fat	Oleic acid	Linoleic acid	Vegetable fat	Animal fat	Cholesterol
Total fat	1·0						
Saturated fat	0·99	1·0					
Oleic acid (monounsaturated)	0·99	0·98	1·0				
Linoleic acid (polyunsaturated)	0·88	0·81	0·87	1·0			
Vegetable fat	0·79	0·71	0·79	0·93	1·0		
Animal fat	0·94	0·97	0·94	0·71	0·54	1·0	
Cholesterol	0·79	0·78	0·79	0·61	0·48	0·82	1·0