

Fat, protein, and meat consumption and renal cell cancer risk: a pooled analysis of 13 prospective studies

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Fat, Protein, and Meat Consumption and Renal Cell Cancer Risk: A Pooled Analysis of 13 Prospective Studies

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- Background** Results of several case-control studies suggest that high consumption of meat (all meat, red meat, or processed meat) is associated with an increased risk of renal cell cancer, but only a few prospective studies have examined the associations of intakes of meat, fat, and protein with renal cell cancer.
- Methods** We conducted a pooled analysis of 13 prospective studies that included 530 469 women and 244 483 men and had follow-up times of up to 7–20 years to examine associations between meat, fat, and protein intakes and the risk of renal cell cancer. All participants had completed a validated food frequency questionnaire at study entry. Using the primary data from each study, we calculated the study-specific relative risks (RRs) for renal cell cancer by using Cox proportional hazards models and then pooled these RRs by using a random-effects model. All statistical tests were two-sided.
- Results** A total of 1478 incident cases of renal cell cancer were identified (709 in women and 769 in men). We observed statistically significant positive associations or trends in pooled age-adjusted models for intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, total protein, and animal protein. However, these associations were attenuated and no longer statistically significant after adjusting for body mass index, fruit and vegetable intake, and alcohol intake. For example, the pooled age-adjusted RR of renal cell cancer for the highest vs the lowest quintile of intake for total fat was 1.30 (95% confidence interval [CI] = 1.08 to 1.56; $P_{\text{trend}} = .001$) and for total protein was 1.17 (95% CI = 0.99 to 1.38; $P_{\text{trend}} = .02$). By comparison, the pooled multivariable RR for the highest vs the lowest quintile of total fat intake was 1.10 (95% CI = 0.92 to 1.32; $P_{\text{trend}} = .31$) and of total protein intake was 1.06 (95% CI = 0.89 to 1.26; $P_{\text{trend}} = .37$). Intakes of red meat, processed meat, poultry, or seafood were not associated with the risk of renal cell cancer.
- Conclusions** Intakes of fat and protein or their subtypes, red meat, processed meat, poultry, and seafood are not associated with risk of renal cell cancer.

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The incidence of kidney cancer has been increasing worldwide over the past three decades (1). This upward trend is not fully explained by improved detection techniques (2), but may be

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CONTEXT AND CAVEATS

Prior knowledge

Epidemiological studies have produced inconsistent or insufficient evidence regarding associations between intakes of different types of fat, protein, and meat and the risk of renal cell cancer.

Study design

A pooled analysis of 1478 cases of renal cell cancer from 13 prospective studies to examine associations between meat, fat, and protein intakes and the risk of renal cell cancer.

Contribution

None of the types of fat or protein examined was associated with the risk of renal cell cancer after adjustment for several known risk factors in multivariable models.

Implications

Intakes of fat and protein or their subtypes, red meat, processed meat, poultry, and seafood are not associated with risk of renal cell cancer.

Limitations

Some bias due to measurement error was possible. The dietary assessment methods differed across studies. Effects of changes in intakes over time could not be examined because only a baseline measure of dietary intake was available for each study.

From the Editors

explained, in part, by changes in lifestyle factors such as obesity and hypertension, both of which have been shown to increase the risk of renal cell cancer (3,4). It has also been hypothesized that dietary changes may be contributing to this increase, but the association between diet and renal cell cancer risk remains unclear.

An ecologic study (5) has reported that the per capita daily intakes of fat and protein were positively correlated with the incidence of kidney cancer in men and women (total fat intake: $r = .77$ and $.74$, respectively; total protein intake: $r = .55$ and $.70$, respectively). An international review panel sponsored by the World Cancer Research Fund recently summarized the findings from case-control and cohort studies that examined associations between fat and protein intakes and the risk of renal cell cancer (6). The panel found no evidence of an association between total fat intake and the risk of renal cell cancer among the case-control studies; the data from the cohort studies were limited. The panel found evidence among case-control studies, but not among cohort studies, suggesting that protein intake was associated with an increased risk of renal cell cancer. Overall, the panel concluded that there was limited epidemiological evidence that intakes of total fat, protein, meat, poultry, and fish are associated with the risk of renal cell cancer.

Given these inconsistent and insufficient findings, we examined the associations between intakes of different types of fat, protein, and meat and the risk of renal cell cancer using standardized analytic criteria in a pooled analysis of 13 prospective cohort studies (7–18), of which only two (7,12) had reported on some of these associations previously.

Methods

Study Population

The Pooling Project of Prospective Studies of Diet and Cancer (referred to hereafter as the Pooling Project) is an international consortium of cohort studies whose goal is to analyze diet and cancer associations (19). Each of 13 cohort studies included in the analysis reported here met the following predefined inclusion criteria: at least one publication on an association between diet and cancer, identification of at least 25 incident renal cell cancer cases, assessment of long-term dietary intake, and validation of the dietary assessment method or a closely related instrument. Studies that included both men and women (11,13,14,17) were treated as two separate cohorts (one of men and the other of women), and the inclusion criteria were applied to each sex-specific cohort. The Canadian National Breast Screening Study (15) and the Netherlands Cohort Study (11) were each analyzed as case-cohort studies (20). In the Pooling Project, the Nurses' Health Study (9) is analyzed in two cohorts: one corresponds to the 1980–1986 follow-up period (part a) and the other corresponds to follow-up beginning in 1986 (part b) to take advantage of the increased comprehensiveness of the 1986 food frequency questionnaire (FFQ) compared with the 1980 FFQ. For the analyses reported in this article, we used data from the Nurses' Health Study (part b) only because fewer than 25 cases were identified during the 1980–1986 follow-up period. Each of the 13 studies included here was reviewed and approved by the institutional review board of the institution at which the study was conducted.

Case Ascertainment

Incident cases of renal cell cancer were ascertained by follow-up questionnaires and subsequent review of medical records (8,9), linkage to cancer registries (7,10–15), or both (16–18). Some studies (7–10,12–14,16–18) also used linkage to mortality registries to identify outcomes. We defined renal cell cancer cases as those with histologically confirmed renal cell cancer [International Classification of Diseases for Oncology, Second Revision (21) code C64.9 or International Classification of Diseases, Ninth Revision (22) code 189.0] or according to the morphological classification provided by the study investigators. The proportion of renal cell carcinoma, not otherwise specified among our cases (62%), was higher than that reported for surgical series that have reported clear-cell carcinoma as the most common type of renal cell cancer (4%–5%) (23). This difference may be due, in part, to the large number of renal cell cancer case patients in our study who were ascertained before 1997, when the World Health Organization held a workshop on the diagnosis and prognosis of renal cell cancer (23) that prompted more widespread use of the currently used renal cell carcinoma classification system.

Assessment of Dietary Intake

Each study assessed dietary intake at baseline using a validated FFQ or diet history. The number of food items on the questionnaires ranged from 45 in the New York State Cohort to 276 in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. Each study calculated daily nutrient consumption using food

composition databases specific to the study population. We examined intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, *trans*-unsaturated fat, animal fat, plant fat, cholesterol, total protein, animal protein, and plant protein. Each study reported food intake data as either the number of servings consumed per day or the amount (in grams) consumed per day. For the seven studies (7–9,12,13,17) that provided food intake data in servings per day, we converted the intake of each food item to the amount consumed per day (grams per day) based on the intake frequencies and study-specific standard serving sizes that were reported. The intake of each specific food group was calculated by summing the intakes of the related individual food items included in that group as listed on the FFQ for each study. The red meat group included beef, pork, lamb, liver, and veal but not processed meat. The processed meat group included sausage, bacon, hot dog, ham, and luncheon meat. The poultry group included chicken and turkey. The seafood group included all types of fish and shellfish. The numbers of studies included in the analyses of each dietary factor varied because not all studies assessed intake of all of the nutrients or food groups.

The study-specific correlation coefficients comparing the FFQ used in each cohort or a closely related instrument with either multiple dietary records or 24-hour recalls generally exceeded .40 for intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, and total protein (19). The study-specific correlation coefficients have not been examined for food groups, including meat intake, in most of the cohort studies included in these analyses.

Assessment of Non-dietary Factors

Each study collected information on non-dietary factors at baseline using self-administered questionnaires. All 13 studies collected information on age, height, and weight at baseline; we used the baseline height and weight values to calculate body mass index (BMI; weight in kilograms divided by the square of the height in meters). All of the nine cohort studies (7–12,15,17,18) that included women assessed parity and the woman's age at first child's birth. Most of the studies assessed information on smoking habits (12 studies) and history of hypertension (nine studies). When we excluded data from the Swedish Mammography Cohort, which did not collect information on smoking habits, the pooled results were similar to those of analyses in which we did not exclude this study. Thus, we have only presented the pooled results that include this study.

Statistical Analysis

For each study, the exclusion criteria specified by that study were first applied, followed by the exclusion of participants who reported implausible values for energy intake (beyond 3 SDs from the study-specific \log_e -transformed mean energy intake) or who had a history of cancer (excluding nonmelanoma skin cancer) at baseline. We used the Cox proportional hazards model (24) to calculate study-specific relative risks (RRs) as implemented in SAS statistical software (25). We stratified the data by age at baseline (in years) and the year of the returned baseline questionnaire, thereby creating a time metric that simultaneously accounted for age, calendar time, and time since entry into the study. We calculated

person-years of follow-up time from the date of the baseline questionnaire until the date of renal cell cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. We evaluated whether the proportional hazards assumption was satisfied by adding interaction terms between age and each of the main exposures and found that the terms were not statistically significant; thus, the assumption was satisfied.

We analyzed fat and protein intakes as percentages of total daily caloric intake. We categorized intakes of fat, protein, and meat using either study-specific quintiles or uniform absolute intake cut points across studies. We also conducted separate analyses in which we modeled intakes using continuous variables. Study-specific quantiles were chosen to maximize the contrast between the highest and the lowest levels of intake and to ensure a sufficient number of participants in each category. Categories that were based on absolute cut points represented multiples of one serving per day (eg, 112 grams per day for seafood) and were chosen to ensure that the referent category within each study was not so small that it would lead to unstable RR estimates. If no cases were included in the highest intake category for a study, the RR for the highest category could not be estimated for that study and the participants in the highest category were included in the second highest category. To calculate the P_{trend} , we assigned participants the median value of their intake category and treated this variable as a continuous term in the model. In multivariable analyses, we further adjusted for BMI (continuous), history of hypertension (yes, no), pack-years of smoking (continuous), fruit and vegetable consumption (tertiles), energy intake (continuous), alcohol intake (continuous), and, among women, parity and age at first child's birth (fewer than three children and age at first birth <25 years old, fewer than three children and age at first birth \geq 25 years old or nulliparous, three or more children and age at first birth <25 years old, and three or more children and age at first birth \geq 25 years old). For each measured covariate, an indicator variable was used for missing responses if needed.

We combined the study- and sex-specific \log_e RRs using a random-effects model (26). The individual study estimates were weighted by the inverse of their variance. We tested for heterogeneity between studies using the Q statistic (26). Two-sided 95% confidence intervals (CIs) were calculated.

To assess whether associations between renal cell cancer and intakes of total fat, each type of fat, total protein, each type of protein, and each meat group were linear, we examined nonparametric regression curves for each dietary factor using restricted cubic splines (27–29). To test for nonlinearity, we used a likelihood ratio test to compare the model fit in a model with the linear and cubic spline terms selected by a stepwise regression procedure with that in a model with only the linear term, and visually inspected the restricted cubic spline graphs. For these analyses, all studies were combined into a single dataset; the models were stratified by age, the year that the baseline questionnaire was returned, and study; and the risk estimates were adjusted for other covariates in the model. Participants who reported extremely high intakes of each of the main nutrients and food groups (ie, participants whose consumption levels were in the highest 1% of the distribution in each cohort) were excluded from the analysis to reduce the influence of extreme values.

We examined whether associations between renal cell cancer and intakes of total fat, each type of fat, total protein, each type of protein, and each meat group varied by sex, median age at diagnosis (<68, ≥68 years), and smoking habits (never, past, or current smoker) using a mixed-effects meta-regression model (19,30). To evaluate whether BMI (<25, ≥25 kg/m²), history of hypertension (no, yes), and alcohol use (nondrinker, drinker) modified the association, we used a two-sided Wald test of the pooled cross-product term of consumption as a continuous variable with the specific modifier variable modeled as a dichotomous variable. For total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, and total protein, we corrected the RRs for measurement error by regressing intake from the reference dietary assessment method used for each validation study (19) on intake from the study-specific FFQ or a closely related instrument (31,32). In the multivariable measurement error models, we adjusted for age, energy intake, alcohol intake, and BMI. We assumed that age and BMI were measured without error and that each main exposure, energy intake, and alcohol intake were measured with error. The corrected estimates were then pooled using a random-effects model (26). Because the validation studies for most of the cohort studies included in these analyses did not examine foods, we could not conduct measurement error correction analyses for the food groups.

All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant.

Results

A total of 1478 incident renal cell cancers (709 in women and 769 in men) were diagnosed among 530469 women and 244483 men during follow-up periods of up to 7–20 years across the 13 studies (Table 1). Energy intake distributions varied and were plausible across the 13 studies. The median total fat intake ranged from 29% of the total daily caloric intake for the Swedish Mammography Cohort to 43% of total daily caloric intake for the Canadian National Breast Screening Study. Across studies, the median intakes of saturated fat ranged from 10% to 19% of total daily caloric intake, of monounsaturated fat ranged from 10% to 16% of total daily caloric intake, and of polyunsaturated fat ranged from 4% to 8% of total daily caloric intake. Median total protein intakes ranged from 14% to 19% of total daily caloric intake, and the amount of animal protein consumed was approximately two times greater than the amount of plant protein consumed (data not shown). Median intakes for red meat, poultry, seafood, and processed meat varied at least fourfold across studies (Table 1).

In age-adjusted analyses, renal cell cancer risks were 22%–30% higher for the highest vs the lowest quintile of intake for total fat, saturated fat, monounsaturated fat, and polyunsaturated fat (Table 2). These positive associations became weaker after we controlled for other risk factors. For example, in the analyses of total fat, the pooled age-adjusted RR of renal cell cancer for the highest vs the lowest quintile of intake—1.30 (95% CI = 1.08 to 1.56)—was attenuated to 1.23 (95% CI = 1.03 to 1.46) after adjusting for BMI, to 1.25 (95% CI = 1.06 to 1.48) after adjusting for alcohol intake, and to 1.24 (95% CI = 1.02 to 1.51) after adjusting for fruit and vegetable intake. Simultaneous adjustment for BMI, alcohol

intake, and total fruit and vegetable intake resulted in further attenuation of the risk estimates (pooled multivariable RR for the highest vs the lowest quintiles of total fat intake = 1.13; 95% CI = 0.95 to 1.34). Additional adjustment for energy intake, history of hypertension, pack-years of smoking, and, among women, parity and age at first child's birth did not appreciably change these RR estimates. For example, the pooled multivariable RR for the highest vs the lowest quintile of total fat intake was 1.10 (95% CI = 0.92 to 1.32; *P*_{trend} = .31). RR estimates from the multivariable models for total fat, saturated fat, monounsaturated fat, and polyunsaturated fat (Table 2) changed little after further adjustment for physical activity and multivitamin use (data not shown). When we simultaneously adjusted for intakes of saturated fat, monounsaturated fat, and polyunsaturated fat and included total protein intake in the same model to examine the effect of replacing carbohydrate with fat, the results for each type of fat did not change appreciably (Table 2).

The results using absolute intake cut points were similar to those using quintiles (data not shown). For example, for total fat intake, we observed a statistically significant positive trend (*P*_{trend} = .004) in the age-adjusted model but not in the multivariable model (*P*_{trend} = .59). Compared with those who obtained 30% to <35% energy from total fat, the pooled multivariable RR for those who obtained <25% energy from total fat was 1.00 (95% CI = 0.75 to 1.35), for those who obtained 25% to <30% energy from total fat was 0.92 (95% CI = 0.76 to 1.11), for those who obtained 35% to <40% energy from total fat was 1.12 (95% CI = 0.91 to 1.37), and for those who obtained at least 40% energy from total fat was 1.01 (95% CI = 0.82 to 1.25).

Neither animal fat intakes nor plant fat intakes (eight studies included; *n* = 900 cases) were associated with the risk of renal cell cancer in either the age-adjusted or the multivariable quintile (Table 2), continuous (Table 2), or absolute cut point categorical models (data not shown). In addition, we found no association between cholesterol intake and renal cell cancer risk in the multivariable model (all 13 studies included; *n* = 1478 cases) (Table 2). Nor did we find an association between *trans*-unsaturated fat intake and the risk of renal cell cancer in the five studies (the Iowa Women's Health Study, the Women's Health Study, the Nurses' Health Study, the Health Professionals Follow-up Study, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; *n* = 555 cases) that assessed this intake (pooled multivariable RR for the highest vs the lowest quintile of intake = 1.25; 95% CI = 0.94 to 1.66; *P*_{trend} = .46).

The nonparametric regression curves and formal tests showed that the associations between intakes of total fat, individual types of fat, and cholesterol and the risk of renal cell cancer were linear (all *P*_{curvature} >.2). In a multivariable analysis in which intake of each type of fat was modeled as a continuous variable, no associations were observed (Table 2).

For total protein, the pooled age-adjusted RR for the highest vs the lowest quintile of intake was 1.17 (95% CI = 0.99 to 1.38; *P*_{trend} = .02; Table 3). After controlling for the two strongest confounders, BMI and alcohol intake, the pooled multivariable RR for the highest vs the lowest quintile of total protein intake was attenuated and the trend was no longer statistically significant (RR = 1.06; 95% CI = 0.89 to 1.25; *P*_{trend} = .37), as was also observed in

Table 1. Baseline characteristics of the cohort studies and participants included in the pooled analyses of fat, protein, and meat intakes and renal cell cancer risk*

Study, sex (reference)	Follow-up period	Baseline cohort size†	No. of case subjects	Energy, kcal/d	Total fat, % energy per day	Cholesterol, mg/1000 kcal/d	Median intake (10th–90th percentile)				
							Total protein, % energy per day	Red meat‡, g/d	Poultry, g/d	Seafood, g/d	Processed meat, g/d
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, M (16)	1985–1999	26987	187	2721 (1914–3826)	39 (32–46)	197 (141–281)	15 (12–17)	65 (36–113)	8 (0–30)	33 (11–75)	60 (22–142)
Breast Cancer Detection Demonstration Project Follow-up Study, W (18)	1987–1999	42007	49	1185 (707–1950)	35 (24–45)	140 (82–236)	18 (14–23)	23 (4–57)	21 (5–44)	12 (1–36)	6 (0–28)
California Teachers Study, W (10)	1995–2001	100036	35	1498 (941–2283)	32 (22–41)	111 (70–184)	16 (12–20)	15 (0–42)	18 (5–41)	12 (0–35)	3 (0–16)
Canadian National Breast Screening Study, W (15)	1980–2000	49613	81	1970 (1334–2897)	43 (35–51)	187 (141–255)	17 (14–21)	95 (45–176)	16 (8–49)	26 (6–58)	14 (2–35)
Cancer Prevention Study II Nutrition Cohort, W (17)	1992–2001	74138	86	1301 (804–1989)	34 (21–46)	114 (71–186)	16 (13–21)	24 (6–58)	19 (6–43)	14 (3–37)	6 (0–24)
Cancer Prevention Study II Nutrition Cohort, M (17)	1992–2001	66166	220	1718 (1076–2646)	36 (24–46)	124 (78–201)	16 (12–20)	40 (11–96)	21 (6–50)	17(3–45)	13 (0–46)
Health Professionals Follow-up Study, M (9)	1986–2000	47780	116	1906 (1252–2831)	32 (24–40)	145 (95–213)	18 (15–23)	60 (18–136)	39 (20–80)	29 (8–74)	7 (0–23)
Iowa Women’s Health Study, W (7)	1986–2000	34588	117	1721 (1114–2564)	34 (27–41)	159 (104–234)	18 (14–22)	80 (30–167)	22 (11–71)	17 (0–56)	5 (0–17)
Melbourne Collaborative Cohort Study, M (14)	1990–2003	14908	50	2354 (1559–3548)	33 (26–40)	133 (89–194)	18 (15–21)	100 (36–208)	17 (7–59)	22 (6–57)	21 (3–59)
Netherlands Cohort Study, W (11)	1986–1993	62573	68	1651 (1222–2205)	39 (32–46)	140 (98–189)	16 (13–20)	56 (24–97)	11 (0–18)	8 (0–27)	13 (2–33)
Netherlands Cohort Study, M (11)	1986–1993	58279	134	2124 (1557–2805)	39 (31–46)	126 (88–177)	14 (11–17)	64 (32–108)	11 (0–18)	12 (0–33)	18 (4–48)
New York State Cohort, M (13)	1980–1987	30363	62	2019 (1226–3165)	36 (29–41)	195 (154–266)	18 (15–20)	61 (14–130)	—	—	15 (3–65)
Nurses’ Health Study, W (9)	1986–2000	69523	86	1716 (1132–2476)	33 (26–40)	146 (101–204)	18 (15–23)	56 (24–123)	39 (11–80)	25 (8–67)	7 (0–19)
Swedish Mammography Cohort, W (12)	1987–2004	60604	138	1543 (1060–2166)	29 (23–34)	123 (87–169)	16 (13–19)	30 (13–59)	8 (0–16)	18 (8–44)	21 (5–44)
Women’s Health Study, W (8)	1993–2004	38387	49	1672 (1083–2452)	30 (22–38)	127 (86–181)	19 (15–23)	57 (18–129)	59 (20–120)	18 (8–51)	4 (0–13)
Total		774952	1478								

* W = women; M = men; – = data not available.

† Cohort sizes after applying study-specific exclusion criteria and then excluding participants with log_e-transformed energy intake values beyond 3 SDs from the study-specific mean or with a previous cancer diagnosis (other than nonmelanoma skin cancer); the Canadian National Breast Screening Study (15) and the Netherlands Cohort Study (11) were analyzed as case-cohort studies so their baseline cohort size does not reflect the above exclusions.

‡ Excludes processed meat.

Table 2. Pooled relative risks (RRs) and 95% confidence intervals (CIs) of renal cell cancer for fat and cholesterol intakes

Nutrient, model	Quintile of intake					P_{trend}^*	$P_{\text{between-studies heterogeneity}}^{\dagger}$	$P_{\text{between-studies heterogeneity due to sex}}^{\ddagger}$	RR for a 5% increase of total caloric intake from fat and RR for an increase of 100 mg/1000 kcal of cholesterol per day (95% CI)
	1 (lowest)	2	3	4	5 (highest)				
Total fat									
Age adjusted	1.00 (referent)	1.02 (0.82 to 1.27)	1.25 (1.01 to 1.55)	1.09 (0.89 to 1.33)	1.30 (1.08 to 1.56)	.001	.28	.58	1.07 (1.03 to 1.12)
Multivariable†	1.00 (referent)	0.98 (0.79 to 1.21)	1.16 (0.94 to 1.44)	0.98 (0.81 to 1.17)	1.10 (0.92 to 1.32)	.31	.47	.35	1.02 (0.98 to 1.07)
Saturated fat									
Age adjusted	1.00 (referent)	1.13 (0.96 to 1.33)	1.08 (0.91 to 1.28)	1.19 (1.01 to 1.41)	1.23 (1.04 to 1.45)	.02	.42	.79	1.12 (1.02 to 1.23)
Multivariable†	1.00 (referent)	1.07 (0.91 to 1.27)	1.00 (0.84 to 1.20)	1.09 (0.91 to 1.29)	1.05 (0.88 to 1.26)	.55	.88	.50	1.03 (0.94 to 1.12)
Multivariable‡	1.00 (referent)	1.04 (0.86 to 1.26)	0.94 (0.76 to 1.16)	1.02 (0.82 to 1.28)	0.99 (0.77 to 1.27)	.94	.92	.93	0.98 (0.86 to 1.13)
Monounsaturated fat									
Age adjusted	1.00 (referent)	1.07 (0.86 to 1.33)	1.17 (0.99 to 1.38)	1.21 (1.01 to 1.44)	1.30 (1.09 to 1.55)	<.001	.36	.48	1.21 (1.11 to 1.33)
Multivariable†	1.00 (referent)	1.02 (0.83 to 1.26)	1.09 (0.91 to 1.29)	1.08 (0.91 to 1.29)	1.10 (0.92 to 1.32)	.26	.72	.29	1.07 (0.97 to 1.19)
Multivariable‡	1.00 (referent)	1.02 (0.78 to 1.32)	1.07 (0.86 to 1.33)	1.09 (0.82 to 1.43)	1.10 (0.85 to 1.43)	.46	.47	.27	1.17 (0.98 to 1.38)
Polyunsaturated fat									
Age adjusted	1.00 (referent)	1.18 (0.97 to 1.44)	1.11 (0.94 to 1.32)	1.10 (0.92 to 1.30)	1.22 (1.03 to 1.44)	.13	.86	.59	1.09 (0.97 to 1.22)
Multivariable†	1.00 (referent)	1.14 (0.93 to 1.39)	1.06 (0.88 to 1.26)	1.03 (0.86 to 1.23)	1.10 (0.93 to 1.31)	.73	.96	.65	1.01 (0.90 to 1.14)
Multivariable‡	1.00 (referent)	1.11 (0.90 to 1.36)	1.01 (0.82 to 1.25)	0.99 (0.79 to 1.24)	1.05 (0.85 to 1.29)	.76	.75	.89	0.95 (0.81 to 1.10)
Animal fat 									
Age adjusted	1.00 (referent)	0.96 (0.78 to 1.18)	1.00 (0.81 to 1.23)	0.98 (0.79 to 1.21)	1.13 (0.90 to 1.41)	.32	.32	.83	1.04 (0.99 to 1.10)
Multivariable†	1.00 (referent)	0.93 (0.75 to 1.15)	0.94 (0.76 to 1.17)	0.92 (0.74 to 1.14)	1.02 (0.81 to 1.27)	.88	.40	.78	1.01 (0.96 to 1.07)
Multivariable‡	1.00 (referent)	0.94 (0.75 to 1.17)	0.93 (0.74 to 1.18)	0.91 (0.71 to 1.17)	1.02 (0.77 to 1.34)	.63	.39	.43	1.01 (0.93 to 1.10)
Plant fat 									
Age adjusted	1.00 (referent)	0.93 (0.72 to 1.21)	1.05 (0.85 to 1.29)	0.94 (0.75 to 1.18)	1.05 (0.85 to 1.29)	.62	.47	.92	1.00 (0.94 to 1.06)
Multivariable†	1.00 (referent)	0.95 (0.72 to 1.25)	1.05 (0.85 to 1.30)	0.95 (0.75 to 1.19)	1.03 (0.83 to 1.28)	.77	.49	.92	0.99 (0.93 to 1.05)
Multivariable‡	1.00 (referent)	0.97 (0.73 to 1.29)	1.09 (0.87 to 1.36)	1.00 (0.78 to 1.29)	1.13 (0.87 to 1.48)	.65	.38	.96	1.01 (0.92 to 1.10)
Cholesterol									
Age adjusted	1.00 (referent)	1.01 (0.85 to 1.20)	1.08 (0.91 to 1.27)	1.17 (0.99 to 1.37)	1.18 (1.00 to 1.39)	.01	.46	.84	1.13 (1.04 to 1.23)#
Multivariable†	1.00 (referent)	0.98 (0.82 to 1.16)	1.01 (0.85 to 1.20)	1.07 (0.90 to 1.27)	1.02 (0.86 to 1.21)	.50	.43	.76	1.03 (0.94 to 1.14)#

* P_{trend} (two-sided) was calculated using the Wald test statistic.† For the highest category, P values (two-sided) for between-studies heterogeneity were calculated using the Q test statistic. P values (two-sided) for between-studies heterogeneity due to sex were calculated using the Wald test statistic.‡ Models were adjusted for age, history of hypertension (yes/no), body mass index (continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first child's birth <25 years and parity of ≥ 3), and age at first child's birth ≥ 25 years and parity of ≥ 3), fruit and vegetable consumption (tertiles), alcohol intake (continuous), and total energy intake (continuous).

§ Saturated fat (quintiles), monounsaturated fat (quintiles), polyunsaturated fat (quintiles), and total protein (continuous) were in the same model in the quintile analyses. Saturated fat (continuous), monounsaturated fat (continuous), polyunsaturated fat (continuous), and total protein (continuous) were in the same model in the continuous analyses.

|| Animal fat and plant fat were not available in the Breast Cancer Detection Demonstration Project Follow-Up Study, the California Teachers Study, the Cancer Prevention Study II Nutrition Cohort, the Melbourne Collaborative Cohort Study, and the Swedish Mammography Cohort.

¶ Animal fat (quintiles), plant fat (quintiles), and total protein (continuous) were in the same model.

For cholesterol intakes, RR is for an increase of 100 mg/1000 kcal/d.

Table 3. Pooled relative risks (RRs) and 95% confidence intervals (CIs) of renal cell cancer for protein intake

Type of protein, model	Quintile of intake					P_{trend}^*	$P_{\text{between-studies heterogeneity}}^{\dagger}$	$P_{\text{between-studies heterogeneity due to sex}}^{\ddagger}$	RR for a 5% increase of total caloric intake from protein (95% CI)
	1 (lowest)	2	3	4	5 (highest)				
Total protein									
Age adjusted	1.00 (referent)	0.99 (0.83 to 1.17)	1.11 (0.94 to 1.31)	1.15 (0.97 to 1.35)	1.17 (0.99 to 1.38)	.02	.69	.89	1.13 (1.04 to 1.24)
Multivariable†	1.00 (referent)	0.97 (0.82 to 1.16)	1.07 (0.91 to 1.27)	1.09 (0.92 to 1.29)	1.06 (0.89 to 1.26)	.37	.70	.82	1.07 (0.97 to 1.17)
Animal proteins									
Age adjusted	1.00 (referent)	0.86 (0.70 to 1.06)	1.08 (0.89 to 1.32)	1.20 (0.99 to 1.46)	1.17 (0.97 to 1.43)	.004	.89	.71	1.17 (1.07 to 1.29)
Multivariable†	1.00 (referent)	0.84 (0.68 to 1.04)	1.04 (0.85 to 1.27)	1.12 (0.92 to 1.36)	1.05 (0.85 to 1.28)	.14	.88	.87	1.09 (0.99 to 1.21)
Multivariable	1.00 (referent)	0.84 (0.68 to 1.04)	1.03 (0.84 to 1.26)	1.11 (0.90 to 1.36)	1.04 (0.84 to 1.29)	.51	.96	.83	1.09 (0.98 to 1.21)
Plant proteins									
Age adjusted	1.00 (referent)	1.09 (0.89 to 1.34)	0.94 (0.73 to 1.20)	1.03 (0.82 to 1.28)	0.88 (0.68 to 1.14)	.08	.14	.86	0.81 (0.62 to 1.05)
Multivariable†	1.00 (referent)	1.13 (0.92 to 1.40)	0.99 (0.76 to 1.27)	1.11 (0.86 to 1.43)	0.96 (0.74 to 1.24)	.44	.20	.97	0.92 (0.69 to 1.22)
Multivariable	1.00 (referent)	1.15 (0.93 to 1.41)	1.01 (0.79 to 1.28)	1.14 (0.88 to 1.48)	0.99 (0.78 to 1.26)	.91	.36	.94	0.99 (0.73 to 1.34)

* P_{trend} (two-sided) was calculated using the Wald test statistic.

† For the highest category. P values (two-sided) for between-studies heterogeneity were calculated using the Q test statistic. P values (two-sided) for between-studies heterogeneity due to sex were calculated using the Wald test statistic.

‡ Models were adjusted for age, history of hypertension (yes/no), body mass index (continuous), pack-years of smoking (continuous), combination of parity and age at first child's birth (<25 years and parity of 1 or 2; or nulliparous; age at first child's birth <25 years and parity of ≥3; and age at first child's birth ≥25 years and parity of ≥3), fruit and vegetable consumption (tertiles), alcohol intake (continuous), and total energy intake (continuous).

§ Animal protein and plant protein were not available in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, the Breast Cancer Detection Demonstration Project Follow-Up Study, the California Teachers Study, the Melbourne Collaborative Cohort Study, and the Swedish Mammography Cohort.

|| Animal protein (quintile) and plant protein (quintile) were in the same model.

the full multivariable model (RR = 1.06; 95% CI = 0.89 to 1.26; $P_{\text{trend}} = .37$) (Table 3). When we additionally adjusted for total fat intake, physical activity, and multivitamin use, the results did not change (data not shown). Intakes of neither animal protein nor plant protein were associated with the risk of renal cell cancer (eight studies included, $n = 1019$ cases).

The nonparametric regression curves and formal tests showed that the associations between intakes of total protein, animal protein, and plant protein and the risk of renal cell cancer were linear (all $P_{\text{curvature}} > .5$). When we modeled intakes of total protein, animal protein, and plant protein as continuous variables (Table 3) or as categorical variables based on uniform absolute intake cut points across studies (data not shown), we found no associations.

We corrected the study-specific RRs for possible bias due to measurement error in total fat, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, and total protein intakes in the 12 cohort studies that assessed these nutrients in their FFQ validation studies (33–41) (A. Wolk, DMSC: personal communication). We also included energy intake, age, BMI, and alcohol intake as covariates in the measurement error correction analyses. BMI was not adjusted for in two studies (the California Teachers Study and the Netherlands Cohort Study—men) because BMI information was not routinely collected in their validation studies, and alcohol intake was not adjusted for in two studies that did not assess alcohol intake in their validation studies. We did not include total fruit and vegetable intake in this measurement error correction analysis even though it was one of the strongest confounders in the fat analyses because the validity of total fruit and vegetable intake was not assessed for most of the studies included in our analyses. The pooled corrected adjusted RRs for intakes of total fat, saturated fat, polyunsaturated fat, and cholesterol were similar to the pooled uncorrected adjusted RRs. For example, the pooled corrected adjusted RR for a 5% increment of energy intake from total fat was 1.11 (95% CI = 1.00 to 1.22), which was similar to the pooled uncorrected adjusted RR based on the same 12 studies (RR = 1.05; 95% CI = 1.01 to 1.10). The pooled corrected RRs for a 5% increment of energy intake from monounsaturated fat was 1.32 (95% CI = 1.02 to 1.69) and from total protein was 1.21 (95% CI = 0.93 to 1.58), which were slightly higher than the respective pooled uncorrected adjusted RRs (RR for 5% increment of energy intake from monounsaturated fat = 1.15; 95% CI = 1.04 to 1.27 and RR for 5% increment of energy intake from total protein = 1.08; 95% CI = 0.99 to 1.19).

Intakes of red meat, processed meat, poultry, and seafood were not associated with the risk of renal cell cancer regardless of whether RRs were estimated by the categorical (Table 4), continuous (Table 4), or quartile (data not shown) models. There was a suggestion that the association between red meat intake and renal cell cancer risk differed by sex ($P_{\text{heterogeneity due to sex}} = .06$). The pooled multivariable RR for at least four servings (≥ 80 grams per day) of red meat per week vs 1 to less than three servings (20 to <60 grams per day) of red meat per week for women was 1.20 (95% CI = 0.93 to 1.55; $P_{\text{trend}} = .58$) and for men was 0.88 (95% CI = 0.72 to 1.07; $P_{\text{trend}} = .70$). The nonparametric regression curves and formal tests showed that the associations between each of these food groups and renal cell cancer risk were linear (all $P_{\text{curvature}} > .1$).

Because participants who were diagnosed with renal cell cancer shortly after they completed the FFQ may have altered their diet due to preclinical symptoms, we also conducted analyses in which participants who were diagnosed during the first 4 years of follow-up were excluded. In these analyses, there were still no associations between intakes of total fat, each type of fat, total protein, each type of protein, or each meat group and the risk of renal cell cancer (data not shown).

We also conducted analyses in which we excluded the nonconsumers of each type of meat (4% of participants in the aggregated dataset did not consume red meat, 16% did not consume processed meat, 7% did not consume poultry, and 6% did not consume seafood) and modeled intake using categories based on uniform absolute intake cut points across studies. The P_{trend} values did not change appreciably in these analyses (data not shown).

The associations between intakes of total fat, each type of fat, total protein, each type of protein, and each meat group and the risk of renal cell cancer were not modified by BMI (<25 , ≥ 25 kg/m²), history of hypertension (no, yes), median age at diagnosis (<68 , ≥ 68 years), or alcohol use (nondrinker, drinker) (all $P_{\text{interaction}} > .07$). However, smoking status (never, past, or current smoker) modified the association with polyunsaturated fat intake ($P_{\text{interaction}} = .008$). We observed a slightly more positive but nonstatistically significant association between polyunsaturated fat intake and renal cell cancer risk for current smokers compared with the associations for never and past smokers (data not shown). The associations for the other dietary factors were not modified by smoking status.

Discussion

In our pooled analysis of 1478 cases of renal cell cancer from 13 prospective studies, none of the types of fat or protein examined was associated with the risk of renal cell cancer after we adjusted for several known risk factors in multivariable models. The results were consistent regardless of whether intakes of these nutrients were modeled as study-specific quintiles, as continuous variables, or by using uniform absolute cut points. In general, there was no statistically significant heterogeneity between the studies or by sex. Intakes of red meat, processed meat, poultry, and seafood were also not associated with the risk of renal cell cancer.

Dietary fat has been hypothesized to increase the risk for cancers of the colon, pancreas, and prostate by increasing the release of bile acids (42), cholecystokinin (43), and prostaglandins (44). However, specific mechanisms have not been identified for renal cell cancer. Our findings for intakes of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol concur with those of a large multicenter case-control study of 1185 renal cell cancer cases that reported no associations for these nutrients (45). Other case-control studies have reported no association between intakes of vegetable fat (46), dairy fat (47), or cholesterol (46) and the risk of renal cell cancer; however, the findings in one study (46) differed depending on the amount of time between diagnosis and the study interview. In that study, intakes of saturated fat and animal fat were associated with a statistically significantly increased risk of incident renal cell cancer among case subjects who were interviewed for dietary information less than

Table 4. Pooled relative risks (RRs) and 95% confidence intervals (CIs) of renal cell cancer for meat consumption*

Type of meat, model	Intake category (g/d)				P_{trend} †	$P_{\text{between-studies heterogeneity}}$ ‡	$P_{\text{between-studies heterogeneity due to sex}}$ ‡	RR for an increase of 2 servings/week (95% CI)
	<20	20 to <60	60 to <80	≥80§				
Red meat								
No. of cases	216	621	241	400				
Age adjusted	0.96 (0.81 to 1.13)	1.00 (referent)	1.10 (0.94 to 1.28)	1.05 (0.91 to 1.21)	.18	.52	.02	1.04 (0.99 to 1.09)
Multivariable	1.01 (0.85 to 1.20)	1.00 (referent)	1.07 (0.91 to 1.25)	0.99 (0.85 to 1.16)	.93	.75	.06	1.00 (0.95 to 1.06)
Processed meat								
No. of cases	<4	4 to <8	8 to <12	12 to <27				
Age adjusted	335	201	145	386				
Multivariable	1.04 (0.83 to 1.29)	1.00 (referent)	1.01 (0.81 to 1.27)	1.10 (0.91 to 1.32)	.05	.83	.34	1.02 (1.00 to 1.05)
Poultry	<14	14 to <20	20 to <60	≥60§, ¶				
No. of cases	624	225	373	185				
Age adjusted	1.14 (0.96 to 1.35)	1.00 (referent)	1.16 (0.95 to 1.42)	1.28 (0.88 to 1.87)	.44	.04	.97	1.03 (0.94 to 1.11)
Multivariable	1.14 (0.96 to 1.36)	1.00 (referent)	1.16 (0.95 to 1.42)	1.25 (0.83 to 1.88)	.60	.02	.79	1.01 (0.93 to 1.10)
Seafood	<11	11 to <16	16 to <48	≥48§, ¶				
No. of cases	337	163	663	212				
Age adjusted	1.09 (0.90 to 1.31)	1.00 (referent)	1.03 (0.86 to 1.22)	1.05 (0.82 to 1.34)	.67	.70	.50	1.00 (0.91 to 1.10)
Multivariable	1.06 (0.88 to 1.28)	1.00 (referent)	1.03 (0.86 to 1.23)	1.05 (0.82 to 1.35)	.52	.69	.55	1.01 (0.92 to 1.11)

* Multivariable models were adjusted for age, history of hypertension (yes/no), body mass index (continuous), pack-years of smoking (continuous), combination of parity and age at first birth (age at first child's birth <25 years and parity of 1 or 2; age at first child's birth ≥25 years and parity of 1 or 2, or nulliparous; age at first child's birth <25 years and parity of ≥3; and age at first child's birth ≥25 years and parity of ≥3), fruit and vegetable consumption (tertiles), alcohol intake (continuous), and total energy intake (continuous).

† P_{trend} (two-sided) was calculated using the Wald test statistic.

‡ For the highest category, P values (two-sided) for between-studies heterogeneity were calculated using the Q test statistic. P values (two-sided) for between-studies heterogeneity due to sex were calculated using the Wald test statistic.

§ 80 g/d (2.8 oz) of red meat is equivalent to 4 servings/week; 27 g/d (1 oz) of processed meat is equivalent to 1 serving/d; 60 g/d (2.1 oz) of poultry is equivalent to 3 servings/week; and 48 g/d (1.7 oz) of total sea-food is equivalent to 3 servings/week.

|| New York State Cohort was excluded because seafood and poultry intakes were not assessed.

¶ Netherlands Cohort Study—women was excluded from the highest category because no case subjects were included in this category.

1 year after diagnosis, but not among those who were interviewed more than 1 year after diagnosis.

Most case-control studies have reported non-statistically significant positive associations between intakes of total protein or animal protein and the risk of renal cell cancer (45,46,48). However, to our knowledge, no potential mechanism for these associations has been clearly identified. Among healthy individuals, a higher protein intake, particularly from plant sources, is thought to help prevent hypertension (49), a risk factor for renal cell cancer. However, individuals with active renal disease tend to have lower protein intakes because excess protein intake among these individuals results in the accumulation of nitrogenous waste products and inorganic ions, which is related to the severity of their uremic symptoms (50). In this study, we found no associations between intakes of total protein, animal protein, or plant protein and the risk of renal cell cancer in multivariable analyses.

We also found no associations between intakes of red meat, processed meat, poultry, or seafood and the risk of renal cell cancer. By contrast, a recent meta-analysis (51) of case-control studies reported positive associations between intakes of all meat, red meat, poultry, or processed meat and the risk of kidney cancer. In that meta-analysis, the odds ratio of kidney cancer for the highest vs the lowest intake category of all meat was 1.27 (95% CI = 1.12 to 1.43; 11 studies), of red meat was 1.30 (95% CI = 1.03 to 1.63; six studies), of poultry was 1.21 (95% CI = 1.01 to 1.48; four studies), and of processed meat was 1.18 (95% CI = 1.01 to 1.40; four studies). The discordant results between our pooled analysis of prospective studies and the meta-analysis of case-control studies may be due to the combination of publication, selection, and recall biases in the case-control investigations or to limitations in our analyses. For example, in a case-control study, if individuals who had healthy lifestyles were more likely to participate as control subjects than those who were less health conscious and who may have higher fat, protein, and meat intakes, spurious positive associations for these dietary factors could be observed.

Our study has limitations. Intakes of fat, protein, and meat may be measured with error when assessed by FFQs. However, the validation studies of the FFQs used by the studies included in our analysis showed that correlations between fat and protein intakes estimated by the FFQ and intakes estimated from either multiple dietary records or 24-hour dietary recalls generally exceeded .4 (19). We were able to calculate measurement error-corrected results by calibrating the measures of fat and protein intake to a common standard, to the extent that the reference instruments used by the studies are comparable. However, we cannot rule out the possibility that errors in the FFQs and in the referent methods were correlated, which would result in incomplete removal of all bias due to measurement error (32,52-54). Nevertheless, findings from a biomarker study (55) suggest that for energy-adjusted nutrients, the standard measurement error correction methodology is likely to come close to a full adjustment for this bias. In particular, Kipnis et al. (55) found that in the Observing Protein and Energy Nutrition study, the attenuation factor for protein density from the biomarker method was similar to that from the standard method of regressing 24-hour dietary recalls on the FFQ. We were unable to conduct measurement error correction analyses for the meat groups because most

of the validation studies for these cohort studies did not evaluate food intake.

Another limitation was that the dietary assessment methods differed across studies because the FFQs were designed for use in their study-specific populations. To minimize the influence of these differences, we modeled dietary variables using study-specific quantiles. However, this approach does not take into account true differences in intakes across studies. Therefore, we also performed analyses in which we categorized dietary variables using uniform absolute intake cut points. The results were similar regardless of the approach used, which suggests that our results are robust.

Because we had only a baseline measure of dietary intake for each study, we could not investigate the effects of changes in intake during follow-up or of intakes during earlier age periods or over a lifetime. We were not able to examine intakes of fatty fish or dark fish separately from those of total seafood, or intake of fish oil separately from that of polyunsaturated fat, because most of the studies in our analyses lacked information about these specific foods or nutrients. We did not have information about method used to cook meat, which can influence the amount of carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons that are generated (56-58). Finally, although we did not have information about some risk factors for renal cell cancer, including family history of renal cell cancer, environmental exposures (eg, asbestos), medications (eg, phenacetin), or advanced kidney disease, the lack of associations between intakes of fat, protein, and meat and renal cell cancer is not likely to be fully explained by these factors because they would have been both widespread in the study populations and strongly associated with fat, protein, and meat intakes.

Our analysis has several strengths. Because of the prospective design and high rates of follow-up (19), recall bias and selection bias are unlikely to account for our findings. In addition, because of the large number of case subjects in our study and the wide range of fat, protein, and meat intakes, we were able to achieve more precise risk estimates than those of the individual prospective studies. This analysis used existing data from several cohorts, most of which had insufficient numbers of case subjects to examine these associations separately. Because we analyzed the primary data from each study, we were able to model fat, protein, and meat intakes and confounding factors uniformly across the studies to eliminate potential sources of heterogeneity in the results across studies. In addition, we were able to correct the RRs for measurement error by using data from study-specific validation studies.

In conclusion, our data do not support the hypotheses that intakes of fat, protein, or meat from animal sources are associated with an increased risk of renal cell cancer. However, our study could not evaluate the potential roles of specific types of fish, fish oil, and heterocyclic amines in renal cell carcinogenesis. Further epidemiological and mechanistic studies on these foods and components are warranted.

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