Meat and fish consumption and the risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition

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What's new?

Kidney cancer strikes different populations with different frequency, with developed nations seeing more cases. In this paper, the authors investigate whether certain elements of diet might correlate with increased incidence of renal cell carcinoma. Using data from the European Prospective Investigation into Cancer and Nutrition (EPIC), they assessed the amount of meat and fish consumed in populations representing a wide range of dietary habits. They then correlated this data with renal cell carcinoma incidence. They found no effect from eating fish; consuming red and processed meats did increase risk in women, but not in men.

Renal cell cancer (RCC) incidence varies worldwide with a higher incidence in developed countries and lifestyle is likely to contribute to the development of this disease. We examined whether meat and fish consumption were related to the risk of RCC in the European Prospective Investigation into Cancer and Nutrition (EPIC). The analysis included 493,179 EPIC participants, recruited between 1992 and 2000. Until December 2008, 691 RCC cases have been identified. Meat and fish consumption was assessed at baseline using country-specific dietary assessment instruments; 24-hour recalls were applied in an 8% subsample for calibration purposes. Cox proportional hazards regression was used to calculate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI). Women with a high consumption of red meat (HR = 1.36, 95% CI 1.14–1.62; calibrated, per 50 g/day) and processed meat (HR = 1.78, 95% CI 1.05–3.03; calibrated, per 50 g/day) had a higher risk of RCC, while no association existed in men. For processed meat, the association with RCC incidence was prominent in premenopausal women and was lacking in postmenopausal women (p interaction = 0.02). Neither poultry nor fish consumption were statistically significantly associated with the risk of RCC. The results show a distinct association of red and processed meat consumption with incident RCC in women but not in men. A biological explanation for these findings remains unclear.

According to the Globocan statistics (www.globocan.iarc.fr), kidney cancer is the ninth most common cancer in Europe, affecting approximately 100,000 European men and women each year. Renal cell cancers (RCC), which account for about 85% of all kidney cancers,[1] are more common in countries with so-called Western lifestyle.[2] Due to the geographical variation in the incidence of RCC even in Europe (*e.g.*, higher reates in Eastern than Northern European countries),[3] environmental and lifestyle factors are thought to be important risk factors. Smoking is estimated to account for 20–30% of RCC cases in men and 10–20% in women,[1] and obesity up to 30% in Europe.[4] Among dietary factors, case-control studies have often reported inverse associations between fruit and vegetable consumpiton and RCC,[1] but results from cohort studies are inconsistent.[5,6] A meta-analysis of case-control studies reported a direct association of total, red, and processed meat as well as poultry consumption with risk of RCC.[7] However, as for fruits and vegetables, only few prospective studies have been published. A pooled analysis of 13 prospective studies reported that none of the examined types of meat (red and processed meat, and poultry) were significantly related to the risk of RCC.[8]

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large European-wide cohort, in which 691 RCC cases have been observed. With its standardized dietary and nondietary assessment procedures, it offers the opportunity to examine the association between meat consumption and RCC in a cohort with a wide range of dietary habits.

Material and Methods

Population

EPIC is a large prospective cohort study with 521,457 participants conducted since 1992 in 23 centers in 10 European countries [Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Great Britain (Cambridge, Oxford), Greece, Italy (Florence, Varese, Ragusa, Turin, Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmö, Umea), The Netherlands (Bilthoven, Utrecht)]. In most centers, the participants were recruited

from the general population. However, French participants were female members of a health insurance for school and university employees. Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, civil servants, but also the general population. In Utrecht and Florence, participants in mammographic screening programs were recruited for the study. In Oxford, half of the cohort consisted of "health conscious" subjects from England, Wales, Scotland and Northern Ireland, which includes a high percentage of vegans, ovo-lacto vegetarians, fish eaters (consuming fish but no meat), and meat eaters. The cohorts of France, Norway, Utrecht and Naples include women only.[9]

The EPIC cohort consists of 493,179 participants without prevalent cancers. Of these, we excluded participants with incomplete dietary, nondietary or follow-up information, or with a ratio for energy intake versus estimated energy expenditure in the top and bottom percentile ($n = 15{,}854$), self-reported ($n = 8$) and secondary kidney cancer cases ($n = 86$). Thus, the analytic cohort included 477,231 participants (335,014 women and 142,217 men).

Exposure assessment

Diet over the previous 12 months was assessed using dietary assessment instruments that were specifically developed for each participating country based on a common core protocol.[9] Questions were structured by meals on the questionnaires used in Italy, Spain and Malmö (Sweden), and by broad food groups in the other centers. Participants were asked to report their average consumption of each food item over the previous twelve months, according to precoded categories ranging from never or less than once per month to six or more times per day. Individual average portions were estimated in Germany, Italy, The Netherlands and Spain, whereas standard portions were assigned to all subjects in Denmark, the United Kingdom and Umeå, and a combination of methods for estimating portion size was used in Malmo and in Norway. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC.[10,11] For this analysis, meats were grouped into red meat (beef, pork, mutton/lamb, horse, goat), processed meat (all meat products, including ham, bacon, sausages; small part of minced meat that has been bought as ready-to-eat product), white meat [poultry, including chicken, hen, turkey, duck, goose, rabbit (domestic)] and fish (fish, fish products, crustaceans, molluscs, fish in crumbs). Processed meat mainly refers to processed red meat but may contain small amounts of processed white meat as well, for example, in sausages.

Lifestyle questionnaires were used to collect information on education, medical history, tobacco and alcohol consumption, and physical activity. Height and weight were measured at the baseline examination, except for Norway, and Oxford, where self-reported height and weight was assessed via questionnaire.[9]

Outcome assessment

Cancer diagnoses were based on population registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. An active follow-up through study subjects as well as next-to-kin information, the use of health insurance records and cancer and pathology registries were used in France, Germany and Greece. Mortality data were also obtained from either the cancer or mortality registries at the regional or national level. Censoring dates for complete follow-up were between December 2004 and December 2008 in the EPIC centers, with the exception of Germany, Greece and France, where the end of the follow up was considered to be the last known contact, date of diagnosis, or date of death, whichever came first. At at end of follow-up, vital status was known for 98.4% of all EPIC subjects.

The diagnosis of RCC was based on the second revision of the International Classification of Diseases for Oncology (ICD-O-2) and included all first incident cases coded as RCC.

Statistical analysis

Cox proportional hazards regression was used to examine the association of meat and fish consumption with RCC entering meat and fish consumption as categorical variables using predefined categories of intake into the models (red and processed meat combined 0–19.9, 20–39.9, 40–79.9, 80–159.9 and $\geq$160 g/day; red meat, processed meat, and fish: 0–9.9, 10–19.9, 20–39.9, 40–79.9 and $\geq$ 80 g/day; poultry 0–4.9, 5–9.9, 10–19.9, 20–39.9 and $\geq$40 g/day). Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. In our regression models, we adjusted for cigarette smoking [never, former (three categories), current (four categories), other, missing], smoking duration in 10-year categories, education (no degree or primary school completed, technical or professional school completed, secondary school completed, university degree, not specified/missing), physical activity (active, moderately active, moderately inactive, inactive, missing/unknown), history of hypertension (self-report) and body mass index (continuous variable). In an additional model we also included other dietary variables: energy intake from fat, energy intake from other sources than fat and alcohol, alcohol consumption, fruit intake and vegetable intake (all continuous variables). Additionally adjusting for menopausal status and use of hormone therapy did not materially change the observed hazard ratios (HRs) and was not included in the final model.

To improve the comparability of dietary data across the participating centers, dietary intakes from the questionnaires were calibrated using a standardized 24-hour dietary recall,[12,13] thus, partly correcting for over and underestimation of dietary intakes.[14,15] In brief, an 8% random sample of

each center's participants provided a 24-hour dietary recall. Dietary intakes were calibrated using a fixed effects linear model in which gender- and center-specific 24-hour dietary recall data were regressed on the questionnaire data controlling for weight, height, age, day of the week and season of the year. Calibrated and uncalibrated data was used to estimate the association of meat and fish consumption with RCC risk on a continuous scale.

Subanalyses were performed by sex, smoking status, duration of follow-up and menopausal status. Tests for trend were conducted using integer scores for categories of meat and fish intake. We tested for interaction by including a cross-product term along with the main effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated using the likelihood ratio test. Heterogeneity between countries was assessed using likelihood chi-square tests. We also examined whether the associations differed in the first 2 years and the succeeding years of follow-up. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

During the follow-up until the end of 2008 (median follow-up time 11.6 years), 691 RCC cases [388 in men (median follow-up 11.8 years), 303 in women (median follow-up 11.5 years)] were observed. Men and women with low red and processed meat intake were younger than participants in the top four categories of intake (Table 1). Energy intake was higher, whereas fruit and vegetable consumption was lower with increasing red and processed meat consumption, in particular among men. Low consumers of red and processed meat were less frequently current smokers, physically inactive and less likely to have a history of hypertension. These individuals also tended to drink more alcohol had a higher BMI.

Consumption of both red and processed meat were associated with a statistically significantly higher RCC risk in the crude model, but the association was distinctly attenuated in the multivariable model (Table 2). After multivariable adjustment, statistically significant interaction between red meat consumption and sex was observed (Table 2). Women in the top category of red meat consumption had a higher risk compared to women in the lowest intake category [HR = 2.03, 95% confidence intervals (CI) 1.14–3.63], whereas no significant association was observed in men. Using corrected (calibrated) continuous consumption data (Table 3), the risk estimate in women per 50 g/day increase in red meat was HR = 1.36 (95% CI 1.14–1.62). Excluding the first 2 years of follow-up did not materially change this association (HR = 1.35, 95% CI 1.10–1.66 per 50 g/day). Mutual adjustment of meat types and fish did not materially alter the observed associations (results not shown).

A similar observation was made for processed meat consumption, such that the association was statistically significant among women, but not among men (Tables 2 and 3), although the interaction by sex was not statistically significant. Excluding the first 2 years of follow-up attenuated the association between processed meat consumption and risk of RCC in women (HR = 1.10, 95% CI 0.58–2.08; per 50 g); the association was stronger during the first 2 years of follow-up (HR = 1.78, 95% CI 0.86–3.69). The relationship between processed meat and RCC incidence was restricted to pre (and peri)menopausal women, while no association existed in postmenopausal women (Table 3), which was still seen after excluding the first 2 years of follow-up (HR = 4.12, 95% CI 1.12–15.2; calibrated, per 50 g/day; data not shown).

Neither white meat nor fish consumption was statistically significantly associated with risk of RCC (Tables 2 and 3).

We did not observe statistically significant interactions by smoking (all p-interactions > 0.05; Table 3), although never smokers with high red meat consumption tended to have a higher risk of RCC, which is possibly explained by the higher percentage of never smoking women. Indeed, when further stratifying by sex, we observed a positive association between red meat consumption and RCC only among never (HR = 1.48; 95% CI 1.18–1.87; calibrated, per 50 g/day) and formerly (1.54; 0.99–2.40) smoking women, but not among currently smoking women (1.13; 0.77–1.66); no associations by smoking status were seen among men (data not shown).

We observed statistically significant heterogeneity by country in the association between red meat intake and RCC risk, which was not significant any longer after removing the Greek cohort, which contributed only a small number of cases, from the analysis (data not shown). There was no heterogeneity by country for processed meat, white meat or fish consumption.

Discussion

In our analysis that included 691 cases from 10 European countries, we observed a higher risk of RCC among women with a high consumption of red and processed meat, but not among men. The strong association of processed meat and RCC was confined to premenopausal women. White meat and fish consumption were not associated with RCC risk.

So far, several studies have examined the association between meat consumption and risk of RCC, but the results of these studies are heterogeneous. A pooled analysis of 13 cohort studies and 1,478 RCC cases, observed no association of red and processed meat with risk of RCC.[8] The largest study so far, a cohort with more than 1,800 RCC cases, showed a statistically significant positive association between red meat consumption and risk of RCC, such that individuals in the highest quintile of red meat intake (mean intake: 66.8 g/1,000 kcal) had a higher risk (HR = 1.19; 95% CI 1.01–1.40) compared with those in the lowest quintile (mean intake: 9.7 g/1,000 kcal).[16] Among compounds found in meat, they observed a positive association of benzo-a-pyrene (BaP), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), and heme iron with risk of RCC. In a US case-control study, BaP intake was also positively related to risk of RCC.[17] Meat is, depending on the type of meat and cut, also rich in protein and different types of fat, but neither protein nor fat intake was associated with RCC risk in a previous analysis of this cohort[18]; similarly, there were no associations in the Pooling project.[8] Similar to our results, the Pooling Project also observed

Table 1. Baseline characteristics of study participants by gender and categories of red and processed meat consumption in EPIC

Variable	All participants Median (Q1–Q3)	Categories of red and processed meat intake (g/day)				
		0–19.9 Median (Q1–Q3)	20–39.9 Median (Q1–Q3)	40–79.9 Median (Q1–Q3)	80–159.9 Median (Q1–Q3)	160+ Median (Q1–Q3)
Men (*n*)	142,217	10,356	10,452	36,508	63,437	21,464
Age at recruitment (years)	52.7 (45.7–59.6)	46.3 (36.6–57.3)	54.3 (46.6–61.4)	52.9 (45.8–60.2)	53.2 (46.9–59.3)	52.4 (46.5–57.6)
Total energy intake (kcal/day)	2344 (1938–2808)	1978 (1625–2409)	1895 (1562–2300)	2111 (1767–2498)	2426 (2074–2831)	2914 (2514–3378)
Alcohol intake (g/day)	13.0 (4.2–30.0)	8.0 (1.6–18.3)	7.8 (1.8–19.6)	9.9 (2.9–24.1)	15.4 (5.9–33.0)	19.7 (7.7–40.8)
Vegetable intake (g/day)	151 (94–248)	237 (159–343)	171 (89–307)	148 (84–265)	141 (91.9–222)	150 (101–224)
Fruit intake (g/day)	156 (82–280)	205 (117–333)	197 (100–332)	174 (90–308)	144 (76–259)	133 (67–241)
BMI (kg/m^2)	26.1 (24.0–28.6)	24.1 (22.2–26.4)	25.8 (23.8–28.2)	26.1 (24.0–28.4)	26.4 (24.3–28.7)	26.8 (24.5–29.3)
Smoking status (%)						
Never	33.0	49.5	36.2	35.5	30.4	26.5
Former	36.3	34.6	39.0	37.4	36.3	34.0
Current	29.4	14.4	22.1	25.1	32.3	39.0
Physical activity (%)						
Inactive	29.7	8.8	28.9	30.0	31.7	35.0
Active	26.5	48.8	27.5	25.6	25.2	22.3
History of hypertension (%)	20.0	11.8	21.6	21.1	20.3	20.7
Education (%)						
≤ Primary school	18.8	18.9	25.5	22.1	17.2	14.8
University degree	24.2	25.2	18.5	20.4	25.1	30.1
Women (*n*)	335,014	44,211	49,622	129,797	102,273	9,111
Age at recruitment (years)	51.0 (44.9–57.5)	47.4 (36.3–56.2)	51.8 (45.8–59.0)	51.4 (45.5–57.7)	51.2 (45.7–57.2)	50.5 (45.5–56.2)
Total energy intake (kcal/day)	1870 (1546–2252)	1676 (1366–2037)	1645 (1355–1975)	1813 (1525–2153)	2094 (1779–2460)	2538 (2173–2974)
Alcohol intake (g/day)	3.6 (0.6–11.1)	3.0 (0.4–10.1)	2.3 (0.4–8.5)	3.2 (0.6–10.4)	5.1 (0.9–13.2)	6.3 (1.1–17.5)
Vegetable intake (g/day)	185 (118–286)	243 (158–351)	181 (108.0–290)	170 (109–266)	182 (121–273)	215 (140–324)
Fruit intake (g/day)	209 (120–323)	235 (137–360)	218 (124–335)	204 (117–319)	201 (116.4–310)	204 (109–319)
BMI (kg/m^2)	24.1 (21.9–27.2)	22.8 (20.9–25.4)	24.1 (21.8–27.3)	24.3 (22.0–27.4)	24.4 (22.1–27.5)	25.1 (22.4–28.7)
Smoking status (%)[1]						
Never	55.7	61.1	58.2	54.8	53.5	51.7
Former	22.5	25.0	22.0	22.3	22.1	21.2
Current	19.5	12.0	17.1	20.5	22.1	24.5
Physical activity (%)[1]						
Inactive	23.9	11.0	24.8	26.7	26.3	26.9

Table 1. Baseline characteristics of study participants by gender and categories of red and processed meat consumption in EPIC (Continued)

Variable	All participants Median (Q1–Q3)	Categories of red and processed meat intake (g/day)				
		0–19.9 Median (Q1–Q3)	20–39.9 Median (Q1–Q3)	40–79.9 Median (Q1–Q3)	80–159.9 Median (Q1–Q3)	160+ Median (Q1–Q3)
Active	22.6	36.8	23.0	20.2	20.6	21.8
History of hypertension (%)	17.4	12.8	18.6	17.6	18.3	21.0
Education (%)[1]						
≤ Primary school	21.4	20.4	24.2	21.7	20.1	22.7
University degree	13.9	17.3	12.3	13.0	14.5	13.6

[1]Percentages do not add up to 100% because not all subgroups are shown.

a suggestion of an interaction with sex, such that the risk estimate was 1.20 (95% CI 0.93–1.55; >80 g/day *vs.* 20–<60 g/day) among women and 0.88 (0.72–1.07) among men.[8] In addition, in a US case-control study a stronger association between red and processed meat consumption and RCC risk was observed in women than in men.[19] Also, we have previously reported a higher risk of histologically confirmed pancreatic cancer among women, but not men with high red meat consumption.[20]

It is unlikely that the effect observed in our cohort is explained by meat consumption or meat preparation preferences because male EPIC participants consume more meat on average and more meat that is fried, grilled, or barbecued than women.[21] Unfortunately, cooking methods in EPIC are only available for an 8% subsample and we cannot evaluate whether those who have a high consumption of grilled, barbecued or fried meat have a higher risk of RCC. Searching for reasonable explanations for the differential effects of red and processed meat in women and men inevitably highlights the differences in sex hormones and their metabolism. This is even more convincing since the strongest effect of processed meat is seen in premenopausal women, who have high serum 17ß-estradiol concentrations (with their amplitudes following the menstrual cycle). Interestingly, in premenopausal women, the estrogen metabolite 4-hydroxyestradiol was related to increased lipid peroxidation of polyunsaturated fatty acids measured as etheno DNA adducts in lymphocytes[22] and lipid peroxidation was suggested as an important mechanism in renal carcinogenesis.[23] Processed meat, especially sausages, which contribute the major part of processed meat intake, are rich in saturated but also rich in mono and polyunsaturated fatty acids.[24,25] However, a possible mechanistic link between meat intake and RCC risk based on estrogen concentrations and metabolism remains speculation unless supported by scientific findings. Also, differences in dietary reporting and/or reporting accuracy between men and women might have also partly contributed to the observed differences in the association between meat consumption and risk of RCC. In addition, confounding by sex-specific variables could provide an explanation for the findings in women. However, a comparison of adjustment variables applied in comparable studies gives no clear indication for such an explanation.

Our analysis has several strengths such as the prospective design, the assessment of a variety of potential confounders, and the possibility to, at least partly, correct for measurement error in the analysis of meat/fish intake and cancer risk. To correct for measurement error the 24-hour diet recall values were regressed on the dietary questionnaire values for the main food groups. This approach aims at correcting for systematic over and underestimation of dietary intakes.[26] Still, the error structure in the reference method is not entirely independent of that in the food frequency questionnaire[27,28] and, therefore, the calibrated HR may still be affected by measurement error. A consequence is that the true associations might still be underestimated.

Our study has some limitations. First, the observed associations are based on the assessment of dietary habits at the

Table 2. Association between meat and fish consumption by consumption categories and renal cell cancer in EPIC

	Model 1			Model 2		Model 3		Men, model 3			Women, model 3		
Intake (g/day)	N_{cases}	HR	95% CI	HR	95% CI	HR	95% CI	N_{cases}	HR	95% CI	N_{cases}	HR	95% CI
Red and processed meat													
0–19.9	34	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	14	1.00	(ref.)	20	1.00	(ref.)
20–39.9	57	1.02	(0.65, 1.59)	0.98	(0.63, 1.52)	0.96	(0.62, 1.51)	23	1.12	(0.55, 2.27)	34	0.89	(0.50, 1.57)
40–79.9	236	1.35	(0.92, 2.00)	1.26	(0.85, 1.86)	1.24	(0.84, 1.83)	116	1.45	(0.78, 2.70)	120	1.11	(0.67, 1.84)
80–159.9	284	1.35	(0.91, 2.00)	1.21	(0.81, 1.79)	1.19	(0.79, 1.77)	167	1.05	(0.56, 1.98)	117	1.41	(0.83, 2.38)
160 +	80	1.61	(1.03, 2.53)	1.39	(0.88, 2.18)	1.34	(0.83, 2.16)	68	1.19	(0.60, 2.38)	12	1.94	(0.88, 4.27)
p-trend			*0.02*		*0.11*		*0.18*			*0.69*			*0.02*
p-interaction[1]													*0.006*
Red meat													
0–9.9	44	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	22	1.00	(ref.)	22	1.00	(ref.)
10–19.9	82	1.41	(0.97, 2.06)	1.36	(0.93, 1.99)	1.35	(0.92, 1.97)	43	1.48	(0.86, 2.53)	39	1.25	(0.73, 2.14)
20–39.9	189	1.47	(1.04, 2.07)	1.39	(0.99, 1.96)	1.38	(0.98, 1.95)	95	1.20	(0.73, 1.96)	94	1.60	(0.99, 2.60)
40–79.9	238	1.51	(1.07, 2.13)	1.39	(0.98, 1.96)	1.38	(0.97, 1.96)	129	1.10	(0.67, 1.80)	109	1.80	(1.10, 2.96)
80 +	138	1.64	(1.12, 2.39)	1.46	(1.00, 2.13)	1.46	(0.99, 2.15)	99	1.12	(0.66, 1.91)	39	2.03	(1.14, 3.63)
p-trend			*0.02*		*0.12*		*0.13*			*0.61*			*0.01*
p-interaction[1]													*0.01*
Processed meat													
0–9.9	100	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	45	1.00	(ref.)	55	1.00	(ref.)
10–19.9	119	1.20	(0.90, 1.59)	1.17	(0.88, 1.55)	1.16	(0.87, 1.54)	52	1.16	(0.75, 1.81)	67	1.17	(0.81, 1.70)
20–39.9	195	1.22	(0.93, 1.60)	1.16	(0.89, 1.52)	1.14	(0.87, 1.50)	109	1.18	(0.78, 1.79)	86	1.10	(0.76, 1.59)
40–79.9	192	1.32	(0.99, 1.74)	1.22	(0.92, 1.62)	1.18	(0.88, 1.58)	118	1.03	(0.67, 1.58)	74	1.44	(0.96, 2.17)
80 +	85	1.46	(1.03, 2.06)	1.31	(0.93, 1.86)	1.23	(0.84, 1.79)	64	0.97	(0.58, 1.61)	21	2.14	(1.18, 3.88)
p-trend			*0.04*		*0.14*		*0.31*			*0.62*			*0.03*
p-interaction[1]													*0.10*
White meat													
0–4.9	157	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	80	1.00	(ref.)	77	1.00	(ref.)
5–9.9	130	0.95	(0.75, 1.22)	0.95	(0.74, 1.21)	0.95	(0.74, 1.21)	74	1.13	(0.81, 1.59)	56	0.78	(0.55, 1.12)
10–19.9	196	1.02	(0.81, 1.28)	1.01	(0.81, 1.26)	1.01	(0.81, 1.27)	103	1.07	(0.78, 1.47)	93	0.96	(0.69, 1.32)
20–39.9	134	0.94	(0.73, 1.20)	0.93	(0.73, 1.19)	0.94	(0.73, 1.21)	84	1.05	(0.76, 1.47)	50	0.83	(0.56, 1.22)
40 +	74	0.88	(0.65, 1.19)	0.86	(0.64, 1.17)	0.88	(0.65, 1.20)	47	1.00	(0.67, 1.49)	27	0.77	(0.47, 1.26)
p-trend			*0.47*		*0.40*		*0.50*			*0.96*			*0.38*
p-interaction[1]													*0.61*
Fish													
0–9.9	139	1.00	(ref.)	1.00	(ref.)	1.00	(ref.)	68	1.00	(ref.)	71	1.00	(ref.)
10–19.9	129	0.95	(0.74, 1.21)	0.95	(0.74, 1.21)	0.95	(0.74, 1.22)	70	1.01	(0.72, 1.41)	59	0.90	(0.63, 1.28)
20–39.9	217	1.04	(0.83, 1.32)	1.04	(0.82, 1.31)	1.05	(0.83, 1.32)	133	1.13	(0.83, 1.54)	84	0.96	(0.67, 1.37)
40–79.9	151	1.06	(0.82, 1.39)	1.06	(0.81, 1.38)	1.08	(0.83, 1.41)	83	1.02	(0.71, 1.46)	68	1.16	(0.77, 1.74)
80 +	55	1.01	(0.70, 1.44)	0.98	(0.68, 1.41)	1.01	(0.70, 1.47)	34	1.18	(0.74, 1.88)	21	0.80	(0.44, 1.48)
p-trend			*0.63*		*0.70*		*0.58*			*0.56*			*0.88*
p-interaction[1]													*0.53*

Model 1: adjusted for age, center and sex.
Model 2: adjusted for age, center, sex, education, BMI, history of hypertension, smoking status, duration of smoking.
Model 3: adjusted for age, center, sex (if appropriate), education, BMI, history of hypertension, smoking status, duration of smoking, energy intake from fat sources, energy intake from non-fat sources, alcohol consumption, fruit consumption, vegetable consumption.
[1]Interaction between meat/fish consumption and sex.

Table 3. Association between meat and fish consumption and renal cell cancer by subgroups in EPIC

	Red and processed meat (per 100 g/day)		Red meat (per 50 g/day)		Processed meat (per 50 g/day)		White meat per 50 g/day)		Fish (per 50 g/day)	
Variable	**Observed HR (95% CI)**	**Calibrated HR (95% CI)**	**Observed HR (95% CI)**	**Calibrated HR (95% CI)**	**Observed HR (95% CI)**	**Calibrated HR (95% CI)**	**Observed R (95% CI)**	**Calibrated HR (95% CI)**	**Observed HR (95% CI)**	**Calibrated HR (95% CI)**
All	1.12 (0.94–1.33)	1.15 (0.98–1.35)	1.05 (0.92–1.18)	1.07 (0.97–1.19)	1.08 (0.95–1.23)	1.21 (0.92–1.60)	0.86 (0.68–1.08)	0.62 (0.34–1.12)	1.07 (0.94–1.22)	1.29 (0.94–1.77)
Sex										
Male	0.95 (0.76–1.18)	0.98 (0.80–1.21)	0.94 (0.80–1.10)	0.98 (0.87–1.11)	1.01 (0.86–1.18)	1.08 (0.77–1.50)	0.88 (0.66–1.17)	0.57 (0.30–1.10)	1.09 (0.94–1.28)	1.40 (0.98–1.99)
Female	1.58 (1.18–2.11)	1.79 (1.32–2.43)	1.28 (1.04–1.58)	1.36 (1.14–1.62)	1.31 (1.03–1.66)	1.78 (1.05–3.03)	0.83 (0.56–1.23)	0.84 (0.25–2.88)	1.03 (0.84–1.28)	0.86 (0.39–1.93)
p-interaction	*0.006*	*0.002*	*0.01*	*0.002*	*0.10*	*0.06*	*0.61*	*0.79*	*0.33*	*0.53*
Menopausal status										
Premenopausal	2.15 (1.01–4.60)	2.65 (1.20–5.84)	1.36 (0.77–2.40)	1.37 (0.93–2.00)	1.70 (0.99–2.92)	4.15 (1.23–14.1)	0.47 (0.15–1.44)	0.11 (0.00–4.45)	1.01 (0.57–1.80)	0.83 (0.09–7.38)
Perimenopausal	1.48 (1.04–2.10)	1.65 (1.15–2.38)	1.19 (0.93–1.53)	1.27 (1.03–1.58)	1.33 (1.00–1.77)	1.76 (0.96–3.24)	0.88 (0.55–1.39)	1.08 (0.33–3.60)	1.04 (0.80–1.34)	0.91 (0.36–2.26)
Postmenopausal	1.46 (0.60–3.52)	1.68 (0.70–4.02)	1.60 (0.91–2.80)	1.62 (1.06–2.46)	0.78 (0.34–1.76)	0.56 (0.11–2.93)	1.04 (0.36–2.99)	0.73 (0.03–18.35)	1.00 (0.60–1.69)	0.50 (0.03–7.62)
p-interaction	*0.18*	*0.18*	*0.79*	*0.98*	*0.09*	*0.02*	*0.34*	*0.30*	*0.66*	*0.07*
Smoking status										
Never smokers	1.26 (0.93–1.70)	1.33 (0.99–1.78)	1.21 (0.99–1.48)	1.25 (1.06–1.47)	1.04 (0.83–1.32)	1.12 (0.67–1.89)	0.78 (0.52–1.17)	0.75 (0.26–2.14)	1.09 (0.86–1.37)	1.43 (0.79–2.62)
Former smokers	1.04 (0.75–1.44)	1.04 (0.77–1.39)	0.96 (0.75–1.22)	0.96 (0.80–1.16)	1.09 (0.86–1.37)	1.27 (0.78–2.07)	1.16 (0.85–1.59)	1.08 (0.52–2.27)	1.07 (0.85–1.34)	1.31 (0.74–2.31)
Current smokers	1.09 (0.81–1.47)	1.16 (0.87–1.55)	1.01 (0.81–1.24)	1.05 (0.89–1.23)	1.10 (0.88–1.37)	1.20 (0.77–1.86)	0.70 (0.44–1.11)	0.26 (0.08–0.88)	1.06 (0.84–1.32)	1.22 (0.69–2.16)
p-interaction	*0.81*	*0.58*	*0.58*	*0.40*	*0.93*	*0.98*	*0.16*	*0.65*	*0.54*	*0.13*

All results are adjusted for age, center, sex (if appropriate), education, BMI, history of hypertension, smoking status (if appropriate), duration of smoking, energy intake from fat sources, energy intake from nonfat sources, alcohol consumption, fruit consumption, vegetable consumption.

recruitment of the study participants. Dietary habits might have changed and our results may, thus, not reflect the true association between meat/fish consumption and risk of RCC. Our results point out some degree of reverse causation such that the association for processed meat consumption was attenuated after excluding the first 2 years of follow-up, although no such effect was seen for red meat consumption. Participants with undetected cancers might have changed their diet, which influences the observed associations. The EPIC study population is in its majority a convenience population sample and, therefore, the representativeness regarding to the general population might be limited, in particular with respect to women. However, selective participation usually does not impair etiological conclusions because the effect measures such as relative risk estimates are internally valid, given that the cases are true cases and the follow-up is not selective regarding important confounders.[29,30] Finally, we cannot exclude that some of the observed statistically significant findings are due to chance given the number of associations we analysed. Residual and unknown confounding might also in part explain our results.

In conclusion, our data support an association between red and processed meat consumption and risk of RCC only in women. This adds to the conflicting literature in this area. The literature provides some support for a higher susceptibility in women with high estradiol concentrations as compared to men; however, the full explanation for these findings is not clear.

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