Meat and fish consumption and risk of pancreatic cancer: Results from the European Prospective Investigation into Cancer and Nutrition

Sabine Rohrmann[1,2], Jakob Linseisen[2,3], Ute Nöthlings[4], Kim Overvad[5], Rikke Egeberg[6], Anne Tjønneland[6], Marie Christine Boutron-Ruault[7,8], Françoise Clavel-Chapelon[7,8], Vanessa Cottet[7,8], Valeria Pala[9], Rosario Tumino[10], Domenico Palli[11], Salvatore Panico[12], Paolo Vineis[13,14], Heiner Boeing[15], Tobias Pischon[15,16], Verena Grote[2], Birigit Teucher[2], Kay-Tee Khaw[17], Nicholas J. Wareham[18], Francesca L. Crowe[19], Ioulia Goufa[20,21], Philippos Orfanos[20,21], Antonia Trichopoulou[20,21], Suzanne M. Jeurnink[22,23], Peter D. Siersema[22], Petra H.M. Peeters[13,24], Magritt Brustad[25], Dagrun Engeset[25], Guri Skeie[25], Eric J. Duell[26], Pilar Amiano[27,28], Aurelio Barricarte[28,29], Esther Molina-Montes[30], Laudina Rodríguez[31], María-José Tormo[28,32], Malin Sund[33,34], Weimin Ye[35,36], Björn Lindkvist[37], Dorthe Johansen[38], Pietro Ferrari[39], Mazda Jenab[39], Nadia Slimani[39], Heather Ward[13], Elio Riboli[13], Teresa Norat[13] and H. Bas Bueno-de-Mesquita[22,23]

[1] Division of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland
[2] Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany
[3] Institute of Epidemiology I, Helmholtz Zentrum München, Neuherberg, Germany
[4] Epidemiology Section, Institute for Experimental Medicine, University of Kiel, Kiel, Germany
[5] Department of Epidemiology, School of Public Health, Aarhus University, Aarhus, Denmark
[6] Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark
[7] Inserm, Centre for Research in Epidemiology and Population Health, U1018, Institut Gustave Roussy, Villejuif, France
[8] Paris South University, UMRS 1018, Villejuif, France
[9] Nutritional Epidemiology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy
[10] Cancer Registry and Histopathology Unit, "Civile-M.P. Arezzo" Hospital, Ragusa, Italy
[11] Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute (ISPO), Florence, Italy
[12] Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy
[13] School of Public Health, Imperial College London, London, United Kingdom
[14] HuGeF Foundation, Torino, Italy
[15] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany
[16] Molecular Epidemiology Group, Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch, Germany
[17] Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
[18] Medical Research Council (MRC) Epidemiology Unit, Cambridge, United Kingdom
[19] Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom
[20] WHO Collaborating Center for Food and Nutrition Policies, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece
[21] Hellenic Health Foundation, Greece

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Correspondence to: Sabine Rohrmann, Institute of Social and Preventive Medicine, University of Zurich, Hirschengraben 84, 8001 Zürich, Switzerland, Tel.: +41-44-6345256, Fax: +41-44-6344909, E-mail: sabine.rohrmann@ifspm.uzh.ch

[22] Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands
[23] National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[24] Julius Center, University Medical Center Utrecht, Utrecht, The Netherlands
[25] Institute of Community Medicine, University of Tromsø, Tromsø, Norway
[26] Unit of Nutrition, Environment and Cancer, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain
[27] Public Health Division of Gipuzkoa, IIS Institute BioDonoastia, Basque Health Department, San Sebastian, Spain
[28] Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiología y Salud Pública-CIBERESP)
[29] Navarre Public Health Institute, Pamplona, Spain
[30] Andalusian School of Public Health, Granada, Spain
[31] Public Health Directorate, Asturias, Spain
[32] Department of Epidemiology, Murcia Regional Health Authority, Murcia, Spain
[33] Department of Surgical and Perioperative Sciences, Nutrition Research, Umeå University, Umeå, Sweden
[34] Department of Surgery and Public Health and Clinical Medicine, Nutrition Research, Umeå University, Umeå, Sweden
[35] Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
[36] The Medical Biobank at Umeå University, Umeå, Sweden
[37] Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[38] Department of Surgery, Skåne University Hospital, SUS, Malmö, Sweden
[39] International Agency for Research on Cancer (IARC-WHO), Lyon, France

Pancreatic cancer is the fourth most common cause of cancer death worldwide with large geographical variation, which implies the contribution of diet and lifestyle in its etiology. We examined the association of meat and fish consumption with risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). A total of 477,202 EPIC participants from 10 European countries recruited between 1992 and 2000 were included in our analysis. Until 2008, 865 nonendocrine pancreatic cancer cases have been observed. Calibrated relative risks (RRs) and 95% confidence intervals (CIs) were computed using multivariable-adjusted Cox hazard regression models. The consumption of red meat (RR per 50 g increase per day = 1.03, 95% CI = 0.93–1.14) and processed meat (RR per 50 g increase per day = 0.93, 95% CI = 0.71–1.23) were not associated with an increased pancreatic cancer risk. Poultry consumption tended to be associated with an increased pancreatic cancer risk (RR per 50 g increase per day = 1.72, 95% CI = 1.04–2.84); however, there was no association with fish consumption (RR per 50 g increase per day = 1.22, 95% CI = 0.92–1.62). Our results do not support the conclusion of the World Cancer Research Fund that red or processed meat consumption may possibly increase the risk of pancreatic cancer. The positive association of poultry consumption with pancreatic cancer might be a chance finding as it contradicts most previous findings.

Introduction

Pancreatic cancer is the fourth most common cause of cancer death worldwide with large geographical variation,[1] and it is one of the cancers with a high fatality rate such that the mortality rate almost equals the incidence rate. In Europe, 48,300 deaths in men and 46,900 deaths in women due to pancreas cancer were estimated for 2008.[2] Because of the large geographical variation in pancreatic cancer incidence, lifestyle factors are very likely important contributors to pancreatic cancer risk. Besides family history of pancreatic cancer,[3] smoking,[4] obesity[5] and diabetes mellitus type 2,[6] no other risk factors were found to be consistently associated with the risk of pancreatic cancer.

Based on the data of 11 cohort studies, a recent meta-analysis found a positive association between red meat consumption and pancreatic cancer in men, but not in women; based on seven cohorts, the same study reported a significantly increased risk of pancreatic cancer with increasing processed meat consumption.[7] However, the results of individual (prospective) studies are fairly inconsistent, with some large cohort studies reporting positive associations between total, red or processed meat consumption and pancreatic cancer risk[8–13]; however, others observing no associations.[14–20] Therefore, we examined meat and fish consumption in relation to pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC), a large European multicenter cohort study.

Material and Methods

Population

EPIC is a large prospective cohort study with more than 500,000 participants conducted since 1992 in 23 centers in ten European countries.[21] In most study centers, the participants were recruited from the general population residing in a given geographical area. Specific cohorts consisted of female members of the health insurance for state school employees (France), women participating in breast cancer screening programs (Naples, Utrecht) or health-conscious individuals (Oxford). The Spanish and Italian cohorts were recruited among blood donors, members of several health insurance

programs, employees of several enterprises, civil servants and also the general population. The cohorts of France, Norway, Utrecht and Naples included women only.[21] All participants signed an informed consent form; EPIC was cleared by the IARC and local ethical review committees.

After exclusion of prevalent cancer cases ($n = 23{,}633$), subjects with incomplete dietary and/or nondietary information ($n = 4{,}981$), missing follow-up information ($n = 1{,}212$), with a ratio for energy intake *versus* energy expenditure in the top and bottom 1% ($n = 9{,}599$), and secondary or unclear pancreatic cancer cases ($n = 126$), the final analytic cohort consisted of 477,202 study participants.

Exposure assessment

Usual diet over the previous 12 months was assessed using dietary questionnaires that were specifically developed for each participating country based on a common core protocol.[21] Questions were structured by meals in the questionnaires used in Italy, Spain and Malmö and by broad food groups in the other centers. Participants were asked to report their average consumption of each food item over the previous 12 months, according to precoded categories. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC.[22] Correlation coefficients for meat intake between 12- and 24-hr recalls and food questionnaires ranged between 0.4 and 0.7, respectively.[23]

For this analysis, meats were grouped into red meat (beef, pork, mutton/lamb, horse and goat), processed meat (all meat products, including ham, bacon and sausages; small part of minced meat that has been bought as ready-to-eat product), white meat [equals poultry, including chicken, hen, turkey, duck, goose and rabbit (domestic) and unclassified poultry] and fish (fish, fish products, crustaceans, molluscs, fish in crumbs and unclassified fish). Processed meat mainly refers to processed red meat but may contain small amounts of processed white meat as well (*e.g.*, in sausages).

Lifestyle questionnaires were used to collect information on education, medical history, tobacco and alcohol consumption and physical activity. Height, weight and waist and hip circumferences were measured at the baseline examination, except for France, Norway and Oxford, where self-reported information was assessed *via* questionnaire.[21] For Umeå and Norway, no information on waist and hip circumferences is available. Detailed information on self-reported history of prevalent diseases such as diabetes mellitus was assessed.

Outcome assessment

In most centers, cancer diagnoses were based on population registries. However, in Germany, Greece and France, information is based on active follow-up through study subjects as well as next-to-kin information, the use of health insurance records and cancer and pathology registries. Mortality data were also obtained from either the cancer or mortality registries at the regional or national level. Cancer cases were identified by the end of the censoring periods ending 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. Pancreatic cancer incidence data were coded according to the International Classification of Diseases-Oncology (ICD-O) 2nd edition and included all first invasive pancreatic cancers that were coded as C25 (C25.0–C25.3 and C25.7–C25.9). All self-reports by the study participants in Greece, Germany and France were then confirmed by a review of the appropriate medical records. Of all 865 exocrine pancreatic tumors, 608 (70%) were microscopically confirmed based on histology of the primary tumor, histology of the metastasis, cytology or autopsy. For 30% of pancreatic tumors, diagnosis was based on clinical symptoms, physical examination and/or imaging results. About 41.7% of the tumors occurred in the head of the pancreas, followed by body (8.0%) and tail (6.5%); the rest of the tumors were of unknown localization. For 51.4% of the tumors, stage was unknown, 8.0% were regional, 13.4% metastatic, 13.2% regional metastases and 13.95 with distant metastases.

Statistical analysis

Cox proportional hazards regression was used to examine the association of meat and fish consumption with pancreatic cancer risk entering food consumption as categorical variables into the models. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment and 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. The analyses were stratified by center, gender and age at recruitment in 1-year categories. Meat and fish consumption was modeled by categories of intake as follows: red meat: 0 to <20, 20 to <40, 40 to <80, >80 g/day; processed meat and fish: 0 to <10, 10 to <20, 20 to <40, >40 g/day; poultry: 0 to <5, 5 to <10, 10 to <20, >20 g/day. In our regression models, we adjusted for height, weight (both continuous), physical activity index[24] (active, moderately active, moderately inactive, inactive, missing), cigarette smoking [never, former (stopped <10 years ago, ≥ 10 years ago), current (1–14, 15–24 and >25 cigarettes per day), other, missing], education (no degree or primary school completed, technical or professional school completed; secondary school completed; university degree; not specified or missing), history of diabetes (yes, no, missing) and total energy intake (continuous). Fruit and vegetable intake and alcohol consumption did not alter the associations and were not included in the final Cox regression models. Adjusting for body mass index or waist–hip ratio instead of weight and height did not appreciably change the risk estimates. We explored meat intake in models with and without adjusting for energy intake. Adjusting for total energy intake takes into account varying energy intake with varying meat

consumption while allowing for substitution with other sources of energy.

The 24-hr diet recalls were used to "calibrate" the FFQ-derived data (hereafter described as calibrated values) across countries and to correct for systematic over- or under-estimation of dietary intakes.[25,26] The 24-hr diet recall values were regressed on the dietary questionnaire values for the main food groups and the subgroups in a linear "calibration model."[27,28] Weight, height, age at recruitment and center were included as covariates, and data were weighted by day of the week and season of the year on which the 24-hr diet recall was collected. Country- and sex-specific calibration models were used to obtain individual calibrated values of dietary exposure for all participants. Cox regression models were then applied using the calibrated values for each individual on a continuous scale. The standard error of the deattenuated coefficient was calculated with bootstrap sampling in the calibration and disease models consecutively.[25] Calibrated and uncalibrated data were used to estimate the association of meat and fish consumption with pancreatic cancer risk on a continuous scale.

Subanalyses were performed by sex and smoking status. We tested for interaction by including cross product terms along with the main effect terms in the Cox regression model. The statistical significance of the cross product terms was evaluated using the likelihood ratio test. Heterogeneity in the association of meat and fish intake with pancreatic cancer between countries was assessed using likelihood χ^2 tests. We also examined whether excluding the first 2 years of follow-up or the exclusion of nonmicroscopically confirmed cases altered the association. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Men and women with high intake of red and processed meat were more often less educated than subjects with low consumption and were more frequently current smokers; they also had a higher BMI and consumed more alcohol (Table 1).

Red or processed meat consumption was not statistically significantly associated with pancreatic cancer risk in the full cohort (Table 2). After the exclusion of nonmicroscopically confirmed cases, the calibrated risk estimate for the association between red meat intake and pancreatic cancer was borderline significant (HR for each 50 g increase per day = 1.08, 95% CI = 0.97–1.21; Table 2). This association was confined to women (HR = 1.68, 95% CI = 1.08–2.61 top *vs.* bottom quartile; men: 0.97, 0.61–1.52; *p*-interaction = 0.31; Supporting Information Table S1). Although the consumption of poultry was not associated with an increased risk of pancreatic cancer when looking at the categorical model (Table 2), the association was statistically significant in the continuous model; however, the association was not statistically significant anymore when we included only the microscopically confirmed cases. Fish consumption was not related to pancreatic cancer risk.

Adjusting for total energy intake takes into account varying energy intake with varying meat consumption while allowing for substitution with other sources of energy. However, in our analysis, energy intake was not associated with pancreatic cancer risk, and the results of the multivariable models with adjustment for energy (see Table 2) are essentially the same as without total energy (data not shown). We neither observed statistically significant heterogeneity in results between countries (data not shown) nor any statistically significant heterogeneity by smoking status (all *p*-interactions $\geq$ 0.05; data not shown). The exclusion of subjects with missing information on smoking status or prevalent diabetes did not alter the observed associations (data not shown).

Discussion

In this large European cohort, we did not observe clear and consistent evidence for an association between meat and fish consumption and the risk of pancreatic cancer. An indication of a positive association of red meat consumption with pancreatic cancer risk was seen in women only after restriction to microscopically confirmed cases, whereas a positive association of poultry consumption with pancreatic cancer risk was not observed anymore in microscopically confirmed cases.

A recent meta-analysis reported an increased risk of pancreatic cancer among men, but not women with high red meat intake; however, there was an overall increased risk for high consumption of processed meat.[7] However, looking at the single studies, the results on red meat consumption and pancreatic cancer risk are pretty inconsistent. Red meat, but not processed meat, was related to an increased risk of pancreatic cancer in women in a Swedish study[10]; however, no elevated risk for red meat intake was observed in the Nurses' Health Study.[18] In the NIH-AARP cohort, no association for red meat consumption was seen in women, but a strong positive relationship was observed in men; however, no association was seen for processed meat consumption.[9] In our analysis, the association with red meat became apparent only among histologically confirmed cases and was confined to women. Quite in contrast to our results, the meta-analysis of Larsson and Wolk[7] reported an increased risk of pancreatic cancer with high red meat consumption among men but not women. Stolzenberg-Solomon *et al.*[9] argued that the difference between men (increased risk) and women (no association) in their study might be due to higher iron stores in men than in women. The observed sex differences might also be due to differences in the preference of meat prepared using methods that produce higher amounts of heterocyclic aromatic amines or polycyclic aromatic hydrocarbons. However, in an analysis of the EPIC 24-hr diet recalls, we have shown that men consume more meat that is fried, grilled or barbecued than women.[29] So far, three studies reported a positive association between well-done meat consumption

Table 1. Baseline information by sex and quartiles of combined red and processed meat consumption in EPIC

		Consumption of red and processed meat (combined)			
	All	**0–19.9 g/day**	**20–39.9 g/day**	**40–79.9 g/day**	**>80 g/day**
Men (*N*)	142,203	10,357	10,451	36,507	84,888
Age at recruitment (years; median, IQR)	52.7 (45.7–59.6)	46.3 (36.6–57.3)	54.3 (46.6–61.5)	52.9 (45.8–60.2)	53 (46.8–58.9)
Body mass index (kg/m^2; median, IQR)	26.1 (24.0–28.6)	24.1 (22.2–26.4)	25.8 (23.8–28.2)	26.1 (24.0–28.4)	26.5 (24.3–28.9)
Alcohol (g/day; median, IQR)	13 (4.2–30.0)	8 (1.6–18.3)	7.8 (1.8–19.6)	9.9 (2.9–24.1)	16.3 (6.3–35.4)
Total energy (kcal/day; median, IQR)	2,344 (1,938–2,808)	1,978 (1,625–2,409)	1,895 (1,562–2,300)	2,111 (1,767–2,498)	2,540 (2,153–2,991)
Highest school level[1] (%)					
None/primary school completed	33.7	10.6	34.3	34.3	36.2
Technical/professional school	24.1	18.4	19.8	22.6	26
Secondary school	13	13.2	14.4	14.7	12.1
University degree	26.5	47.8	27.1	25.4	24.3
Smoking status[1] (%)					
Never smoker	33	49.5	36.2	35.5	29.4
Former smoker	36.3	34.6	38.9	37.4	35.7
Current smoker	29.4	14.4	22.1	25.1	34
Physical activity[1] (%)					
Active	18.8	18.9	25.5	22.1	16.6
Moderately active	30.6	30.5	31.1	31.9	30
Moderately inactive	24.3	24	23.1	24	24.6
Inactive	24.2	25.2	18.5	20.4	26.4
History of diabetes (%)	3.6	2.6	4.4	3.7	3.6
Women (*N*)	334,999	44,209	49,624	129,786	111,380
Age at recruitment (years; median, IQR)	51 (44.9–57.5)	47.4 (36.3–56.2)	51.8 (45.8–59.0)	51.4 (45.5–57.7)	51.2 (45.7–57.1)
Body mass index (kg/m^2; median, IQR)	24.1 (21.9–27.2)	22.8 (20.9–25.4)	24.1 (21.8–27.3)	24.3 (22.0–27.4)	24.5 (22.1–27.6)
Alcohol (g/day; median, IQR)	3.6 (0.6–11.1)	3 (0.4–10.1)	2.3 (0.4–8.5)	3.2 (0.6–10.4)	5.2 (1.0–13.5)
Total energy (kcal/day; median, IQR)	1,870 (1,546–2,252)	1,676 (1,366–2,037)	1,645 (1,355–1,975)	1,813 (1,525–2,153)	2,124 (1,800–2,505)
Highest school level[1] (%)					
None/primary school completed	28.4	14.7	31.5	31.1	29.2
Technical/professional school	21.5	19.2	18.8	22.5	22.5
Secondary school	23.6	21.3	23.1	23.5	24.7
University degree	22.6	36.2	22.7	20	20.3

Table 1. Baseline information by sex and quartiles of combined red and processed meat consumption in EPIC (Continued)

	All	Consumption of red and processed meat (combined)			
		0–19.9 g/day	20–39.9 g/day	40–79.9 g/day	>80 g/day
Smoking status[1] **(%)**					
Never smoker	55.7	61.1	58.2	54.8	53.4
Former smoker	22.5	25	22	22.4	22
Current smoker	19.5	12	17.1	20.5	22.3
Physical activity[1] **(%)**					
Inactive	21.4	20.5	24.2	21.7	20.3
Moderately inactive	31.6	33.2	30.2	30.2	33.4
Moderately active	21.3	23.2	19.7	20.3	22.6
Active	13.9	17.3	12.3	13	14.4
History of diabetes (%)	2.2	1.7	2.5	2.1	2.4

[1]Does not add up to 100% because of missing information.

and risk of pancreatic cancer (reviewed in Ref. 8). As cooking methods in EPIC are only available for an 8% subsample, we cannot evaluate whether those who have a high consumption of grilled, barbecued or fried meat have an increased risk of pancreatic cancer.

So far, poultry consumption has mostly not been found to be associated with an increased risk of pancreatic cancer.[9,11,12,18] In a cohort of Swedish women, a high consumption of white meat was related to a lower risk of pancreatic cancer,[10] whereas one case–control study observed an increased risk of pancreatic cancer among those with a high poultry consumption along with an increased risk of pancreatic cancer for a high intake of other types of meat.[30] In a Dutch cohort, a nonsignificantly increased risk of pancreatic cancer has been observed per 100 g increase in white meat consumption per week [relative risk (RR) = 1.09, 95% CI = 0.97–1.23; microscopically confirmed cases].[15] In the top intake categories, we observed nonsignificantly increased risks of pancreatic cancer, which was also seen in the continuous models. However, the associations were attenuated in the models that included only microscopically confirmed cases.

Our results are consistent with those reported from other cohort studies that did not observe statistically significant associations between fish consumption and pancreatic cancer risk.[10–12,15,18,19]

We did explore meat intake in models with and without total energy intake, both providing essentially identical results. The same was true for models including total energy and fruit and vegetables, which have also been considered important in the development of cancer. The results observed in this study were, thus, robust in a number of different models with different interpretation.

Our study has several strengths, including the large number of incident cases in men and women, whereas some previous studies were confined to women only. Second, by using 24-hr dietary recalls, we were able to compute risk estimates that to a certain extent took measurement error into account. This approach aims at correcting for systematic overestimation and underestimation of dietary intakes.[25] However, the calibrated hazard ratios may still be affected to some extent by measurement error as the error structure in the reference method is not entirely independent of that in the food frequency questionnaire.[31,32] A consequence is that the true associations might still be underestimated. Third, a large proportion of the pancreatic cancer cases in our cohort were microscopically confirmed. The results of this group of cases was, however, slightly different from the results in the complete case set such that an association of red meat consumption became apparent only in this group of cases and an association with poultry consumption was attenuated. Verhage *et al.*[33] argued that cases without pathologic confirmation may reflect different subtypes of pancreatic cancer or may not even be pancreatic cancer cases, and thus, results among the group of microscopically confirmed cases may reflect the most valid estimates of risk. Although we were

Table 2. Association between meat and fish consumption and risk of pancreatic cancer in EPIC

	All cases			First two years of follow-up excluded			Microscopically confirmed cases		
Intake (g/day)	N_{cases}	HR	95% CI	N_{cases}	HR	95% CI	N_{cases}	HR	95% CI
Red meat									
0 to <20	176	1	Ref.	152	1	Ref.	100	1	Ref.
20 to <40	215	1.01	0.82–1.24	190	1.03	0.83–1.29	154	1.1	0.85–1.43
40 to <80	291	0.99	0.80–1.22	267	1.05	0.84–1.32	216	1.07	0.82–1.39
≥80	183	1.07	0.83–1.38	168	1.15	0.88–1.51	154	1.25	0.91–1.71
Per 50 g observed		1.05	0.94–1.17		1.07	0.95–1.20		1.14	1.00–1.29
Per 50 g calibrated		1.03	0.93–1.14		1.06	0.95–1.18		1.08	0.97–1.21
Processed meat									
0 to <10	181	1	Ref.	167	1	Ref.	104	1	Ref.
10 to <20	167	0.98	0.78–1.23	149	0.93	0.73–1.18	109	0.91	0.68–1.21
20 to <40	257	0.93	0.75–1.15	235	0.9	0.72–1.12	199	0.91	0.70–1.19
≥40	260	0.8	0.63–1.02	226	0.74	0.58–0.95	209	0.75	0.56–1.00
Per 50 g observed		0.96	0.83–1.09		0.94	0.81–1.09		0.95	0.82–1.10
Per 50 g calibrated		0.93	0.71–1.23		0.87	0.64–1.19		0.9	0.67–1.25
Poultry									
0 to <5	203	1	Ref.	184	1	Ref.	153	1	Ref.
5 to <10	147	0.94	0.75–1.17	126	0.88	0.69–1.11	108	0.9	0.70–1.17
10 to <20	208	0.9	0.73–1.11	191	0.91	0.73–1.13	138	0.81	0.64–1.04
≥20	307	1.17	0.96–1.43	276	1.16	0.94–1.43	222	1.09	0.87–1.38
Per 50 g observed		1.22	1.02–1.45		1.24	1.04–1.48		1.15	0.93–1.43
Per 50 g calibrated		1.72	1.04–2.84		1.76	1.06–2.93		1.41	0.74–2.67
Fish									
0 to <10	151	1	Ref.	137	1	Ref.	105	1	Ref.
10 to <20	166	1.13	0.90–1.41	147	1.11	0.87–1.41	114	1.06	0.81–1.40
20 to <40	281	1.2	0.97–1.50	252	1.19	0.94–1.49	201	1.21	0.93–1.57
≥40	267	1.16	0.92–1.47	241	1.14	0.89–1.47	201	1.12	0.85–1.49
Per 50 g observed		1.11	0.99–1.25		1.13	1.00–1.27		1.09	0.95–1.25
Per 50 g calibrated		1.22	0.92–1.62		1.27	0.94–1.71		1.16	0.82–1.64

All models were stratified by center, gender and age at recruitment in 1-year categories and adjusted for height, weight (both continuous), physical activity index (active, moderately active, moderately inactive, inactive, missing), cigarette smoking [never, former (two categories), current (three categories), other, missing], education (no degree or primary school completed, technical or professional school completed; secondary school completed; university degree; not specified or missing), history of diabetes (yes, no, missing) and total energy intake (continuous). Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval.

able to adjust for a wide range of potential confounders, we cannot exclude residual confounding, in particular due to passive smoking as passive smoking information has not consistently been collected in all EPIC centers.

In conclusion, we cannot confirm the results of several previous studies that had found an increased pancreatic cancer risk among subjects with high consumption of red or processed meat. The reason for an increased risk in women with high red meat intake when restricting the analyses to microscopically confirmed cases is currently unclear, and this may have been a chance finding. The positive association of poultry consumption with pancreatic cancer in the linear models might also be a chance finding as it disappeared after restriction to microscopically confirmed cases and it contradicts most previous findings.

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