Meat Intake and Risk of Stomach and Esophageal Adenocarcinoma Within the European Prospective Investigation Into Cancer and Nutrition (EPIC)

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Background: **Dietary factors are thought to have an important role in gastric and esophageal carcinogenesis, but evidence from cohort studies for such a role is lacking. We examined the risks of gastric cancer and esophageal adenocarcinoma associated with meat consumption within the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort.** ***Methods:*** **A total of 521 457 men and women aged 35–70 years in 10 European countries participated in the EPIC cohort. Dietary and lifestyle information was collected at recruitment. Cox proportional hazard models were used to examine associations between meat intake and risks of cardia and gastric noncardia cancers and esophageal adenocarcinoma. Data from a calibration substudy were used to correct hazard ratios (HRs) and 95% confidence intervals (CIs) for diet measurement errors. In a nested case–control study, we examined interactions between *Helicobacter pylori* infection status (i.e., plasma *H. pylori* antibodies) and meat intakes. All statistical tests were two-sided.** ***Results:*** **During a mean follow-up of 6.5 years, 330 gastric adenocarcinoma and 65 esophageal adenocarcinomas were diagnosed. Gastric noncardia cancer risk was statistically significantly associated with intakes of total meat (calibrated HR per 100-g/day increase = 3.52; 95% CI = 1.96 to 6.34), red meat (calibrated HR per 50-g/day increase = 1.73; 95% CI = 1.03 to 2.88), and processed meat (calibrated HR per 50-g/day increase = 2.45; 95% CI = 1.43 to 4.21). The association between the risk of gastric noncardia cancer and total meat intake was especially large in *H. pylori*-infected subjects (odds ratio per 100-g/day increase = 5.32; 95% CI = 2.10 to 13.4). Intakes of total, red, or processed meat were not associated with the risk of gastric cardia cancer. A positive but non–statistically significant association was observed between esophageal adenocarcinoma cancer risk and total and processed meat intake in the calibrated model. In this study population, the absolute risk of development of gastric adenocarcinoma within 10 years for a study subject aged 60 years was 0.26% for the lowest quartile of total meat intake and 0.33% for the highest quartile of total meat intake.** ***Conclusion:*** **Total, red, and processed meat intakes were associated with an increased risk of gastric noncardia cancer, especially in *H. pylori* antibody-positive subjects, but not with cardia gastric cancer. [J Natl Cancer Inst 2006;98:345–54]**

The incidences of esophageal adenocarcinoma and gastric cardia cancer have risen steadily in the United States *(1)* and Europe *(2)* over the last 3 decades; the incidence of cardia cancer increased less than that of esophageal adenocarcinoma. By contrast, during the same period, the incidences of gastric noncardia cancer and esophageal squamous cell carcinoma declined in most

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countries *(3)*. Overall, gastric and esophageal cancers are the second and sixth most common causes of cancer death in the world, respectively *(3)*.

These similar incidence trends suggest that esophageal adenocarcinoma and gastric cardia cancer share, at least in part, some etiologic factors despite their epidemiologic differences *(4)*. Gastric cardia cancer and esophageal adenocarcinoma are associated with gastroesophageal reflux disease, Barrett's esophagus, and obesity *(5)*. Infection with *Helicobacter pylori* is an established risk factor for gastric noncardia cancer but not for gastric cardia cancer *(6)*, and *H. pylori* infection has been associated with a reduced risk of esophageal adenocarcinoma *(7)*. Tobacco smoking is causally associated with cardia and gastric noncardia cancer *(8)* and with both types (i.e., adenocarcinoma and squamous cell carcinoma) of esophageal cancer *(9)*. Dietary factors are also thought to have an important role in gastric and esophageal carcinogenesis, but evidence from cohort studies for such a role, particularly among Western populations, is lacking.

Meat consumption is a dietary factor that has been linked to several cancers. High meat consumption has been associated with increased risks of colorectal cancer *(10)*, breast cancer *(11)* and, possibly, prostate cancer *(12)*. However, a comprehensive review on nutrition and cancer published in 1997 *(13)* concluded that there was insufficient evidence that total meat consumption or consumption of cured meat was related to the risk of gastric cancer and that judgment about associations with the risk of esophageal cancer was not possible because the evidence was limited. Since then, several new cohort studies on dietary factors and the risk of gastric cancer have contributed to the available evidence, all showing either no association *(14,15)* or a weak but non–statistically significant association *(16)* between total meat, beef, or pork intake and the risk of gastric cancer. Processed meat intake was statistically significant and positively associated with the risk of gastric cancer in two cohort studies *(15,17)* but not in three other studies *(14,18,19)*, and none of the studies took into account the anatomical site of the cancer (gastric cardia cancer versus gastric noncardia cancer). Associations between intakes of meat and processed meat and the risk of esophageal cancer have not yet been analyzed in a cohort study among a Western population.

The goal of this study was to examine associations between meat and processed meat intake and the risks of stomach and esophageal adenocarcinomas within the European Prospective Investigation Into Cancer and Nutrition (EPIC) *(20)*, a large prospective cohort that includes participants with large differences in meat consumption *(21)*. Furthermore, we examined, for the first time, whether *H. pylori* infection modifies these associations by conducting a nested case–control study within the EPIC cohort.

Subjects and Methods

Study Subjects

EPIC, a prospective study that has been described in detail elsewhere *(20,22)*, was designed to investigate the relationships between dietary, lifestyle, genetic, and environmental factors and the incidence of cancer. EPIC cohorts are recruited through 23 research centers located in 10 European countries: Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Greece, Italy (Florence, Turin, Varese, Naples, Ragusa), The Netherlands (Bilthoven, Utrecht), Norway, Spain (Granada, Murcia, Asturias, Navarra, San Sebastian), Sweden (Malmo, Umeå), and the United Kingdom (Norfolk, Oxford). The EPIC cohorts include a total of 521 457 subjects (368 010 women and 153 447 men), most of whom were recruited between 1992 and 1998 when they were 35–70 years old, usually from the general population residing in a given geographic area, town, or province. Exceptions were the French cohort, in which participants were recruited from among female members of the health insurance agency for school employees; the Utrecht and Florence cohorts, in which participants were recruited from among women attending breast cancer screening programs; parts of the Italian and Spanish cohorts, in which participants were recruited from among blood donors; and most of the Oxford cohort, in which participants were recruited from among vegetarian volunteers. Blood samples (30 mL) were collected from approximately 74% of the EPIC participants. After extraction, blood samples were aliquoted into plastic straws of serum, plasma, white blood cells, and erythrocytes and stored in liquid nitrogen (at −196 °C) in a central repository. Eligible participants gave written informed consent and completed questionnaires on their diet, lifestyle, and medical history. Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer (IARC) and from all local participating centers.

We excluded from this study prevalent cancer cases (138 gastric cancers and 22 esophageal adenocarcinomas) and 2403 subjects who were lost to follow-up, as well as all subjects in the Norway cohort because of the small number of incident cases (two gastric cancer cases from among 37 203 subjects at risk) and the short follow-up.

Diet and Lifestyle Questionnaires

The usual diet over the previous 12 months was measured at EPIC study recruitment with the use of country-specific validated questionnaires *(20,23)*. Most centers adopted a self-administered dietary questionnaire that included 88–266 food items. In Greece, Spain, and Ragusa, the dietary questionnaire was administered at a personal interview. Dietary questionnaires in France, Northern Italy, Spain, The Netherlands, Germany, and Greece were quantitative, estimating individual average portion size. Those in Denmark, Naples, and Umeå were semiquantitative, with the same standard portion size assigned to all participants. In Malmö and the United Kingdom, diet was measured by a dietary questionnaire combined with a food record. A separate lifestyle questionnaire included questions on education level, lifetime history of smoking and alcohol consumption, occupation, reproductive history, use of hormones, history of previous illness including surgical operations, and physical activity level.

Follow-Up and Identification of Cancer Cases

The follow-up was based on information in population cancer registries, except in France, Germany Greece, and Naples, where a combination of methods including health insurance records, cancer and pathology hospital registries, and active follow-up were used. Mortality data were collected from regional or national mortality registries. Follow-up began on the date of EPIC recruitment and ended on the date of diagnosis of gastric or esophageal cancer, the date of death, or date of the last complete follow-up, whichever came first. A total of 398 incident gastric cancer cases and 188 incident esophageal cancer cases were reported to the central database at IARC for the period up to

December 31, 1999 or September 30, 2002, depending on the study center. Cancer of the stomach included cancers coded as C16 according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death *(24)*. Validation and confirmation of the diagnosis and classification of tumor site and of tumor morphology [according to International Classification of Diseases for Oncology, 2nd version, and Lauren classification of histologic type *(25)*] were carried out by a panel of pathologists that included a representative from each country participating in EPIC and a coordinator (FC). The panel reviewed material provided by the centers (original histology slides and/or slices obtained from paraffin blocks of tumor specimens as well as the original pathology reports). Among incident cancer cases, we excluded nonadenocarcinomas of the esophagus (n = 121), gastric lymphomas (n = 26), gastric stump cancers (n = 5), other nonadenocarcinoma gastric cancers (n = 11), and otherwise unspecified malignant neoplasms of the stomach (n = 8). After these exclusions, 348 gastric adenocarcinoma cases and 67 esophageal adenocarcinoma cases were available for the analysis. Of these cases, 56% (n = 195) were validated by a panel of pathologists through review of the available histologic material, 24% (n = 83) were classified according to the pathology report, and 20% (n = 70) were classified on the basis of information reported by the cancer registries to the IARC central database. Gastric cardia tumors included gastroesophageal junction tumors (n = 24).

Nested Case–Control Study of *H. pylori* Infection Status

We conducted a nested case–control study within the EPIC cohort to examine whether the association between meat intake and cancer risk was modified by *H. pylori* infection. Each case subject with incident gastric cancer and an available blood sample was matched by sex, age group (± 2.5 years), center, and date of blood sample collection (± 45 days) to four control subjects with available blood samples who were randomly selected from among subjects in the cohort still at risk at the time of diagnosis of each case.

The concentration of anti-*H. pylori* immunoglobulin G (IgG) antibodies was measured by an enzyme-linked immunosorbent assay. Briefly, dilutions of plasma samples (from 1 : 200 to 1 : 25 600) were incubated for 1 hour in 96-well flat-bottomed microtiter plates (Nunc, Roskilde, Denmark) coated with a whole-cell lysate of *H. pylori* [CCUG strain *(26)*] (1 μg/mL). The wells were washed extensively and incubated for 3 hours with an alkaline phosphatase-conjugated affinity-purified polyclonal goat anti-human IgG (Sigma Chemical Co, St. Louis, MO). After further washings, the presence of bound human IgG antibodies specific for *H. pylori* was detected by adding 1 mg/mL *p*-nitrophenylphosphate (100 μL/well) to the plates. Optical densities were read after 1 hour at 405 and 650 nm. *H. pylori*-specific IgG antibody titers were expressed as arbitrary enzyme-linked immunosorbent assay units (EU) and were determined by interpolation relative to a standard curve constructed by serial dilutions of a standard positive control consisting of a pool of samples from subjects known to be infected with *H. pylori* and to have antibodies, as determined by Western blotting. A cutoff value of 100 EU was defined using serum samples from individuals negative for *H. pylori* infection as determined by clinical, microbiologic, and serologic (western blotting) assays. Serum samples giving EU values above 100 were considered positive for anti-*H. pylori* IgG antibodies.

Calibration of the Dietary Data

We used a detailed computerized 24-hour diet recall (24HR) method *(27)* to obtain a second dietary measurement (between 1995 and 1999) from a random sample of the cohort (7.1% of total cohort; n = 36 994 participants) to calibrate dietary measurements across countries and to correct for systematic over- or underestimation of dietary intakes *(28,29)*. Country- and sex-specific calibration models were used to obtain individual predicted values of dietary exposure for all participants. Calibration models were used for meat intake (total, red, processed, and poultry), total vegetable intake, non-citrus fresh fruit intake, citrus intake, and energy. The 24HR values were regressed on the intake values for meat (total, red, processed, and poultry), total vegetables, non-citrus fresh fruit, and fresh citrus fruit and the values for energy obtained from the main dietary questionnaires. Consumption values of zero in the main dietary questionnaires (reported by 0% to 13% of the participants, depending on the food variable) were excluded from the regression calibration models; instead, a zero was directly imputed as the corrected value. Weight, height, age at study recruitment, and study center were included as additional covariates, and data were weighted by the day of the week and the season of the year in which the 24HR diet recall data were collected. Cox regression models were then run using the predicted (calibrated) values of the meat variable of interest and the calibrated values of the adjusting variables (total vegetables, non-citrus fresh fruit, citrus, and energy) for each individual on a continuous scale, and the other adjusting variables used in the noncalibrated model. The standard error of the deattenuated coefficient was calculated with bootstrap sampling in the calibration and disease models consecutively *(29)*.

Statistical Methods

Analyses were conducted using Cox regression. We confirmed the proportional hazards assumption for meat intake variables in relation to gastric and esophageal adenocarcinomas using the likelihood ratio test, comparing models with and without product terms for the meat variables and follow-up time (years). Data were stratified by study center and age at EPIC study recruitment to control for differences in follow-up procedures and questionnaire design. Age at EPIC study recruitment was used as the time scale variable in all models. Entry time was defined as age at recruitment, and final time was defined as the age at diagnosis for case patients or the age at censoring for at-risk subjects. All models were adjusted for sex, height, weight, educational level, alcohol intake (grams/day) at baseline, smoking status (never, former, or current), number of cigarettes smoked per day (in current smokers only), level of work-related physical activity (no activity, sedentary, standing, manual, or heavy manual), level of leisure-time physical activity (as continuous metabolic equivalents for the energy expended-hour/week), energy intake (Kcal/day), and consumption of total vegetables, non-citrus fresh fruit, and citrus fruit (grams/day). Intakes of total meat, red meat, poultry, and processed meat were estimated, in grams per day, from information reported in the dietary questionnaires. Red meat, poultry, and processed meat intakes were mutually adjusted for in the models. Red meat intake included pork, beef, veal, and lamb. Poultry intake included chicken, turkey, and duck. Processed meat intake included ham, bacon, sausages, processed meat cuts, hamburgers (i.e., beef burgers), meatballs, and pâtés

(21). Intakes were analyzed as continuous variables (per 100-g increase for total meat intake, per 50-g increase for red and processed meat intakes, and per 10-g increase for poultry intake) and as categorical variables using EPIC study-wide sex-specific quartiles for analyses of associations with gastric cancer risk and tertiles for analyses of associations with esophageal adenocarcinoma risk. To calculate *P* values for trends across quartiles (or tertiles), participants were assigned a score ranging from 1 to 4 (or 1 to 3) according to their quartile (or tertile) of intake and this variable was entered as a continuous term in the Cox regression models. Separate analyses were done for men and women, but because no substantial differences by sex emerged, we present the results for both sexes combined in this report. Subsequent analyses were performed after exclusion of case patients who were diagnosed during the first 2 years of follow-up. The Wald statistic *(30)* was used to test for homogeneity of risk for cardia and gastric noncardia tumors.

The odds ratio (OR) for association of meat and processed meat intake in *H. pylori* antibody-positive and -negative subjects in the nested case–control study was estimated by multiple unconditional logistic regression, including matching variables in the model. The statistical significance of interactions between intakes of different meat variables and *H. pylori* infection were assessed using a likelihood ratio test. All statistical tests were two-sided, and *P* values less than .05 were considered statistically significant.

Results

During a mean follow-up of 6.5 years (3 110 034 person-years) starting in 1991, 348 eligible stomach adenocarcinomas and 67 esophageal adenocarcinomas were diagnosed (Table 1). The stomach adenocarcinomas included 101 cancers in the gastric cardia (24 of which were in the gastroesophageal junction), 166 cancers in the distal part of the stomach, and 81 cancers (23%) of unknown location. According to Lauren classification *(25)*, 116 gastric cancers (33.3%) were intestinal, 120 (34.5%) were diffuse, four (1.1%) were mixed, and 108 (31.0%) were unclassified or unknown. We excluded from the analyses individuals who were in the top or bottom 1% of energy intake *(31)* (seven subjects with gastric cancer, one subject with esophageal adenocarcinoma, and 9426 members of the cohort) and individuals with missing dietary information (11 subjects with gastric cancer, one subject with esophageal adenocarcinoma, and 6486 members of the cohort). The final sample for analyses included 330 gastric cancer patients (56% of whom were men) and 65 esophagus adenocarcinoma patients (77% of whom were men). A total of 241 gastric cancer patients with available blood samples and 1141 matched control subjects were included in the nested case–control study. Table 1 also shows the mean intakes of red meat, processed meat, and poultry by country, which were estimated using the 24HR data collected in the calibration study. Processed meat consumption varied between countries by approximately 10-fold, and red meat consumption varied by two- to threefold.

Baseline characteristics of the participants according to meat intake levels are reported in Table 2. Subjects with the highest intake of red meat were more likely to have ever smoked than subjects with the lowest intake of red meat, and subjects with the highest intake of processed meat had lower intakes of citrus and non-citrus fruits and vegetables than subjects with the lowest intake of processed meat. Table 3 shows the mean intake levels of red meat, processed meat, and poultry within each study-wide quartile of intake. For both men and women, the mean intake of red meat in the highest intake quartile was more than twofold higher than that in the lowest intake quartile. For men, the mean intake of processed meat in the highest intake quartile was 4.5 times higher than that in the lowest intake quartile, and for women, it was 3.5 times higher.

Table 4 shows the hazard ratios (HRs) for risks of gastric cancer and esophageal adenocarcinoma associated with total meat intake. In the observed uncalibrated analysis, there was a statistically significant positive association between total meat intake and the risk of gastric cancer (P_{trend} = .01). The calibrated hazard ratio for a 100-g/day increase in intake was 2.03 (95% CI = 1.28 to 3.22). The positive association between total meat intake and the risk of gastric cancer was restricted to gastric noncardia cancers (calibrated HR for a 100-g/day increase in intake = 3.52; 95% CI = 1.96 to 6.34); there was no association between total meat intake and the risk of cardia cancer (*P* for heterogeneity = .01). No differences between the hazard ratios of intestinal and diffuse types for total meat intakes were observed. We also observed a non–statistically significant positive association between total meat intake and the risk of esophageal adenocarcinoma for the whole cohort (calibrated HR for a 100-g/day increase in intake = 1.84; 95% CI = 0.78 to 4.39). In the uncalibrated model, we observed a positive association of borderline statistical significance between red meat intake and gastric cancer risk for the highest level of consumption (P_{trend} = .05); the calibrated hazard ratio was not statistically significant. This positive association between red meat intake and gastric cancer risk was restricted to noncardia tumors (calibrated HR for a 50-g/day increase in intake = 1.73; 95% CI = 1.03 to 2.88; *P* for heterogeneity = .19). A non–statistically significant positive association between red meat intake and esophageal adenocarcinoma was observed in the uncalibrated model, but not in the calibrated model.

We observed a statistically significant positive association between poultry consumption and the risk of gastric cancer for the highest category of intake in the uncalibrated analysis (Table 4). However, this association disappeared in the calibrated model. We also observed a statistically significant positive association between poultry intake and esophageal adenocarcinoma (calibrated HR for a 10-g/day increase in intake = 1.14; 95% CI = 1.00 to 1.30). We found a statistically significant positive association between processed meat intake and gastric cancer risk (P_{trend} = .02), with a 62% increase in risk for the highest versus the lowest quartile of intake. This association between processed meat and the risk of gastric cancer was observed only for noncardia tumors (calibrated HR for a 50-g/day increase in intake = 2.45; 95% CI = 1.43 to 4.21; *P* for heterogeneity = .02). Processed meat intake was also positively associated with the risk of esophageal adenocarcinoma (HR for the highest versus the lowest tertile of intake = 3.54; 95% CI = 1.57 to 7.99; P_{trend} = .002), but the association was not statistically significant in the calibrated model. In this study population, the absolute risk of development of gastric adenocarcinoma within 10 years for a study subject aged 60 years was 0.26% for the lowest quartile of total meat intake and 0.33% for the highest quartile of total meat intake.

To eliminate the potential effects of early undiagnosed gastric or esophageal cancers, we repeated our analyses after excluding case patients whose cancers were diagnosed during the 2 first years of follow-up because these individuals might have

Table 1. Countries participating in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort*

Country	Cohort sample	Person-years	Stomach adenocarcinoma‡					Esophageal adenocarcinoma	Mean (SD) daily intake (g/d)†							
									Total meat		Red meat		Poultry		Processed meat	
			Gastric§	Cardia§	Noncardia	Intestinal§	Diffuse§		Men	Women	Men	Women	Men	Women	Men	Women
France‖	74 504	625 111	11	4	4	3	3	0	N/A	104.5 (85.4)	N/A	46.1 (68.2)	N/A	24.3 (51.5)	N/A	28.8 (46.4)
Italy	47 531	280 660	52	8	31	26	16	2	132.6 (112.1)	86.9 (85.2)	58.5 (90.7)	38.5 (64.2)	35.6 (72.0)	24.2 (58.7)	33.2 (51.9)	21.0 (36.3)
Spain	41 413	276 962	32	6	21	13	13	0	184.5 (149.0)	99.9 (91.7)	85.5 (123.4)	37.9 (67.7)	37.5 (80.0)	27.1 (55.8)	54.2 (68.6)	30.5 (44.2)
United Kingdom	87 352	466 048	52	21	23	13	9	25	87.1 (99.1)	57.4 (70.2)	33.0 (70.7)	19.3 (44.3)	22.8 (53.2)	18.8 (48.8)	30.0 (55.1)	18.1 (38.0)
The Netherlands	40 047	249 585	29	9	9	6	12	4	160.9 (127.3)	92.0 (73.6)	64.9 (90.4)	40.1 (55.1)	18.2 (53.8)	13.7 (39.7)	76.7 (85.7)	37.4 (51.1)
Greece	26 856	100 514	16	2	4	4	9	0	76.5 (99.5)	45.5 (67.3)	46.8 (80.9)	26.9 (53.0)	16.0 (44.9)	11.6 (37.2)	8.4 (32.2)	5.0 (21.4)
Germany	53 030	309 303	44	10	24	15	23	2	155.8 (124.1)	86.6 (81.4)	51.7 (87.7)	29.6 (56.6)	17.0 (55.9)	13.1 (42.1)	84.7 (89.9)	42.5 (55.7)
Sweden	53 769	419 150	59	17	34	23	27	13	134.4 (99.4)	90.0 (72.8)	53.6 (75.5)	34.9 (54.3)	10.0 (39.2)	9.2 (32.8)	64.0 (77.1)	42.1 (53.1)
Denmark	57 016	382 701	53	24	16	13	8	21	140.4 (96.2)	85.2 (69.5)	69.2 (83.8)	43.2 (58.1)	17.4 (50.5)	15.6 (42.0)	51.6 (64.2)	24.5 (39.0)
Total	481 518	3 110 034	348	101	166	116	120	67	139.8 (118.9)	88.9 (80.2)	59.8 (90.6)	37.9 (60.4)	20.6 (57.5)	17.6 (46.3)	55.1 (74.4)	30.4 (47.1)

*Study centers per country: France (North-East, North-West, South, South coast); Italy (Florence, Varese, Ragusa, Turin, Naples); Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), United Kingdom (Cambridge, Oxford [general and health-conscious population]); The Netherlands (Bilthoven, Utrecht); Germany (Heidelberg, Potsdam); Sweden (Malmö, Umeå); Denmark (Aarhus, Copenhagen). SD = standard deviation; N/A = not applicable.

†Based on the 24-hour recall dietary questionnaire of the calibration study participants (13 437 men and 21 674 women).

‡Excludes nonadenocarcinoma gastric cancers ($n = 45$) and gastric stump cancers ($n = 5$).

§Includes gastroesophageal junction tumors. Cardia and noncardia classifications do not include tumors of unknown ($n = 75$) or mixed ($n = 6$) locations. Intestinal and diffuse classifications do not include unknown ($n = 94$), unclassified ($n = 14$), or mixed ($n = 4$) morphologies.

‖Only women.

Table 2. Baseline characteristics of the participants in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort overall and according to quartiles of intake of red meat, poultry, and processed meat*

Characteristic	Whole cohort ($n = 465 586$)	Red meat intake, g/d			Poultry intake, g/d			Processed meat intake, g/d		
		Quartile 1 [M: 0–26, W: 0–17] ($n = 116 534$)	Quartile 4 [M: 84–1087, W: 61–584] ($n = 116 399$)	P†	Quartile 1 [M: 0–7 M, W: 0–5] ($n = 116 396$)	Quartile 4 [M: 29–690, W: 26–690] ($n = 116 398$)	P†	Quartile 1 [M: 0–16, W: 0–9] ($n = 116 355$)	Quartile 4 [M: 59–731, W: 37–771] ($n = 116 396$)	P†
Mean age, years (SD)	51.7 (10.2)	49.4 (12.1)	52.4 (8.8)	<.001	50.4 (11.8)	52.0 (9.3)	<.001	50.4 (12.6)	51.3 (9.1)	<.001
Median alcohol intake, g/d (range)	6.0 (0–339)	4.7 (0–339)	8.7 (0–298)	<.001	5.6 (0–339)	6.4 (0–310)	<.001	4.1 (0–310)	7.5 (0–339)	<.001
Mean BMI, kg/m^2 (SD)	25.5 (4.3)	24.5 (4.1)	25.9 (4.4)	<.001	24.5 (4.0)	26.2 (4.5)	<.001	25.2 (4.5)	25.9 (4.4)	<.001
Ever tobacco smoker, %	49.2	44.7	53.5	<.001	49.3	47.3	<.001	44.9	51.6	<.001
Secondary school education or higher, %	48.9	57.5	46.3	<.001	54.8	47.1	<.001	52.7	44.6	<.001
Mean leisure physical activity, MET-h/wk (SD)	82.7 (49.6)	84.2 (48.7)	79.1 (49.8)	<.001	79.8 (47.6)	82.5 (50.9)	<.001	86.1 (50.5)	81.7 (48.5)	<.001
Perform manual activity at work, %	11.8	9.0	15.1	<.001	9.8	11.2	<.001	10.5	11.7	<.001
Mean energy intake, Kcal/day (SD)	2136 (632)	1909 (576)	2411 (652)	<.001	2010 (609)	2310 (656)	<.001	1937 (575)	2404 (674)	<.001
Mean total vegetable intake, g/d (SD)	217 (149)	222 (160)	230 (147)	<.001	207 (153)	262 (153)	<.001	290 (188)	187 (121)	<.001
Mean non-citrus fresh fruit intake, g/d (SD)	191 (153)	194 (162)	187 (149)	<.001	181 (153)	219 (161)	<.001	246 (188)	163 (126)	<.001
Mean citrus fruit intake, g/d (SD)	54.7 (72.7)	47.1 (69.5)	54.1 (68.3)	<.001	41.0 (59.2)	69.0 (84.2)	<.001	73.8 (92.2)	43.0 (59.9)	<.001

*Intakes determined from EPIC dietary questionnaire data. M = range of intake among men, W = range of intake among women; SD = standard deviation; BMI = body mass index; MET = metabolic equivalents for the energy expended (ratio of physical activity metabolic rate to a standard metabolic rate of 1).

†For continuous variables, two-sided t tests and Wilcoxon tests were used. For categorical variables, two-sided chi-square tests were used.

Table 3. Mean intake (range) of total meat, red meat, poultry, and processed meat according to sex-specific study-wide quartiles in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort*

	Men				Women			
Type of meat	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Total meat	91.0 (0–78)	127.4 (78–119)	152.3 (119–166)	186.7 (166–1196)	60.5 (0–53)	79.7 (53–86)	94.0 (86–121)	117.9 (121–929)
Red meat	34.3 (0–26)	51.5 (26–52)	66.5 (52–84)	84.6 (84–1087)	22.6 (0–17)	31.2 (17–36)	40.6 (36–61)	52.9 (61–584)
Poultry	10.2 (0–7)	15.5 (7–16)	21.9 (16–29)	34.0 (29–690)	11.6 (0–5)	13.4 (5–14)	18.7 (14–26)	27.2 (26–690)
Processed meat	19.1 (0–16)	46.9 (16–34)	64.8 (34–59)	85.6 (59–731)	13.1 (0–9)	25.8 (9–20)	34.4 (20–37)	45.4 (37–771)

*Mean intake reported as g/day. Ranges are based on values reported on the food questionnaires, and the means were estimated from the 24-hour dietary recall data from the calibration study.

modified their diet during the early, prediagnostic phase of the disease. None of our findings for associations between red meat, processed meat, or poultry and the risk of either gastric cancer or esophageal adenocarcinoma changed after we excluded these case patients. In addition, although the number of cancer cases was small, after stratifying the sample by Northern versus Southern European countries (data not shown) the results were very similar. We also examined associations with different subgroups of red and processed meat, but we did not find that a particular type of either red meat or processed meat was more strongly associated with gastric cancer than other types. Intakes of red and processed meat were highly correlated (Pearson's $r = .65$), whereas the correlation between intakes of processed meat and poultry was very low (Pearson's $r = .05$), and the correlation between intakes of red meat and poultry was moderate (Pearson's $r = .23$).

Finally, we conducted a nested case–control study to examine whether *H. pylori* infection (as assessed by plasma level of antibodies against *H. pylori*) modified the associations between total meat, red meat, poultry, or processed meat intakes and the risk of gastric cancer (Table 5). We observed a statistically significant

Table 4. Multivariable hazard ratio (HR) of stomach and esophageal adenocarcinoma (95% confidence intervals) for observed and calibrated intakes of total meat, red meat, poultry, and processed meat according to anatomic location and histologic type of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort*

Cancer site/type and type of meat	No. of cases	Observed quartiles/tertiles†				Continuous	
		2	3	4	P_{trend}	Observed	Calibrated
Stomach	330						
Total meat		1.05 (0.75 to 1.49)	1.59 (1.12 to 2.24)	1.50 (1.01 to 2.23)	.01	1.30 (1.05 to 1.62)	2.03 (1.28 to 3.22)
Red meat		1.22 (0.87 to 1.71)	1.27 (0.89 to 1.82)	1.50 (1.02 to 2.22)	.05	1.14 (0.97 to 1.33)	1.31 (0.89 to 1.94)
Poultry		1.29 (0.93 to 1.80)	1.30 (0.92 to 1.83)	1.47 (1.04 to 2.10)	.04	1.01 (0.96 to 1.07)	0.95 (0.81 to 1.13)
Processed meat		1.10 (0.76 to 1.58)	1.16 (0.79 to 1.69)	1.62 (1.08 to 2.41)	.02	1.18 (0.97 to 1.43)	1.64 (1.07 to 2.51)
Cardia	94						
Total meat		0.82 (0.43 to 1.57)	1.15 (0.60 to 2.19)	1.00 (0.48 to 2.08)	.75	0.95 (0.63 to 1.43)	0.84 (0.31 to 2.28)
Red meat		1.56 (0.80 to 3.02)	1.48 (0.73 to 3.02)	1.17 (0.53 to 2.60)	.85	1.04 (0.79 to 1.38)	1.09 (0.46 to 2.59)
Poultry		1.37 (0.72 to 2.61)	1.67 (0.88 to 3.19)	1.57 (0.80 to 3.09)	.16	0.96 (0.86 to 1.08)	0.82 (0.60 to 1.14)
Processed meat		1.19 (0.61 to 2.34)	1.04 (0.51 to 2.12)	1.14 (0.52 to 2.49)	.91	0.89 (0.59 to 1.34)	0.76 (0.29 to 1.96)
Noncardia	159						
Total meat		1.49 (0.89 to 2.48)	1.95 (1.15 to 3.30)	2.19 (1.22 to 3.93)	.01	1.67 (1.25 to 2.24)	3.52 (1.96 to 6.34)
Red meat		0.90 (0.56 to 1.44)	1.29 (0.79 to 2.10)	1.65 (0.97 to 2.82)	.03	1.30 (1.04 to 1.63)	1.73 (1.03 to 2.88)
Poultry		1.17 (0.71 to 1.94)	1.51 (0.92 to 2.46)	1.65 (1.00 to 2.74)	.03	1.03 (0.96 to 1.11)	1.01 (0.81 to 1.27)
Processed meat		1.02 (0.60 to 1.71)	1.02 (0.59 to 1.77)	1.92 (1.11 to 3.33)	.01	1.36 (1.06 to 1.74)	2.45 (1.43 to 4.21)
Intestinal	109						
Total meat		1.05 (0.59 to 1.87)	1.49 (0.82 to 2.70)	1.24 (0.61 to 2.51)	.33	1.31 (0.90 to 1.92)	2.14 (0.87 to 5.23)
Red meat		1.29 (0.73 to 2.30)	1.52 (0.83 to 2.78)	1.23 (0.61 to 2.51)	.46	1.03 (0.76 to 1.40)	1.10 (0.50 to 2.44)
Poultry		1.02 (0.57 to 1.80)	1.06 (0.58 to 1.93)	1.46 (0.81 to 2.62)	.21	1.03 (0.93 to 1.13)	0.94 (0.70 to 1.27)
Processed meat		1.62 (0.84 to 3.11)	1.67 (0.84 to 3.33)	1.78 (0.84 to 3.77)	.18	1.27 (0.93 to 1.75)	2.11 (1.08 to 4.14)
Diffuse	116						
Total meat		0.80 (0.44 to 1.46)	1.76 (1.00 to 3.07)	1.34 (0.69 to 2.58)	.09	1.23 (0.85 to 1.80)	1.52 (0.67 to 3.43)
Red meat		1.11 (0.65 to 1.91)	0.95 (0.51 to 1.75)	1.74 (0.93 to 3.24)	.13	1.13 (0.84 to 1.51)	1.10 (0.54 to 2.23)
Poultry		1.33 (0.76 to 2.34)	1.50 (0.84 to 2.67)	1.87 (1.05 to 3.33)	.03	1.05 (0.97 to 1.14)	1.04 (0.78 to 1.39)
Processed meat		0.75 (0.39 to 1.45)	0.88 (0.45 to 1.70)	1.47 (0.76 to 2.82)	.10	1.04 (0.75 to 1.43)	1.40 (0.69 to 2.85)
Esophagus	65						
Total meat		0.96 (0.48 to 1.93)	1.79 (0.86 to 3.75)	N/A	.10	1.56 (1.11 to 2.19)	1.84 (0.78 to 4.39)
Red meat		1.73 (0.86 to 3.48)	1.67 (0.75 to 3.72)		.23	1.13 (0.84 to 1.51)	0.75 (0.26 to 2.13)
Poultry		1.29 (0.67 to 2.49)	1.93 (0.99 to 3.76)		.05	1.12 (1.06 to 1.20)	1.14 (1.00 to 1.30)
Processed meat		2.08 (0.96 to 4.47)	3.54 (1.57 to 7.99)		.002	1.16 (0.82 to 1.65)	1.44 (0.64 to 3.22)

*Reference categories are the lowest quartile and tertile for quartile and tertile analyses, respectively. For continuous analysis, HRs are for a daily intake increase of 100 g (total meat), 50 g (red and processed meat), or 10 g (poultry). The full-cohort analysis was stratified by center and age at EPIC study entry and adjusted by sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, vegetable intake, citrus fruit intake, and non-citrus fruit intake. Red meat, poultry, and processed meat intakes were mutually adjusted. N/A = not applicable.

†For esophageal cancer, tertiles were used instead of quartiles because of the small sample size. The cutoff points for the total meat tertiles, in grams/day, were (men/women): 92.64/64.56 and 148.88/107.96. The cutoff points for the red meat tertiles, in grams/day, were (men/women): 34.15/22.98 and 72.61/51.18. The cutoff points for the poultry tertiles, in grams/day, were (men/women): 9.13/7.50 and 21.98/20.35. The cutoff points for the processed meat tertiles, in grams/day, were (men/women): 21.58/12.60 and 49.15/30.48. Quartiles and tertiles are full-cohort sex specific.

Table 5. Nested case–control study of the risk of stomach adenocarcinoma by calibrated intakes of total meat, red meat, poultry, and processed meat according to anatomic location among *Helicobacter pylori* antibody-positive and -negative subjects in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort*

Type of meat	*H. pylori* antibody status	No. of control subjects	Case patients with stomach adenocarcinoma			Case patients with gastric cardia adenocarcinoma			Case patients with gastric noncardia adenocarcinoma		
			No.	OR (95% CI)	P†	No.	OR (95% CI)	P†	No.	OR (95% CI)	P†
Total meat	Negative	372	40	1.60 (0.26 to 9.96)	.76	22	3.03 (0.26 to 35.1)	.43	12	0.21 (0.001 to 38.0)	.14
	Positive	769	201	2.57 (1.25 to 5.25)		47	0.52 (0.12 to 2.32)		113	5.32 (2.10 to 13.4)	
Red meat	Negative	372	40	1.78 (0.27 to 11.7)	.54	22	1.55 (0.10 to 24.5)	.20	12	1.22 (0.01 to 237)	.28
	Positive	769	201	1.26 (0.69 to 2.32)		47	0.56 (0.16 to 2.00)		113	1.93 (0.90 to 4.12)	
Poultry	Negative	372	40	1.05 (0.56 to 1.98)	.71	22	1.22 (0.55 to 2.70)	.14	12	1.76 (0.34 to 9.19)	.79
	Positive	769	201	1.07 (0.84 to 1.36)		47	0.75 (0.46 to 1.22)		113	1.13 (0.80 to 1.60)	
Processed meat	Negative	372	40	0.45 (0.05 to 4.01)	.48	22	0.86 (0.03 to 27.0)	.42	12	0.002 (<0.001 to 62.6)	.25
	Positive	769	201	2.00 (1.06 to 3.79)		47	1.62 (0.47 to 5.55)		113	2.67 (1.20 to 5.93)	

*Odds ratios (ORs) are for a daily intake increase of 100 g (total meat), 50 g (red and processed meat), or 10 g (poultry). Adjusted by sex, age at EPIC study entry, study center, date of blood extraction, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, vegetable intake, and citrus and non-citrus fruit intake. Red meat, poultry, and processed meat intakes were mutually adjusted. CI = confidence interval.

†From two-sided likelihood ratio test for interaction with *H. pylori* infection status.

positive association between total meat intake (OR for a 100-g/day increase in intake = 5.32; 95% CI = 2.10 to 13.4) and processed meat intake (OR for a 50-g/day increase in intake = 2.67; 95% CI = 1.20 to 5.93) and risk of gastric noncardia cancer in *H. pylori* antibody-positive subjects. There was no association between total and processed meat intake and gastric noncardia tumors in *H. pylori* antibody-negative subjects; however, the 95% confidence intervals were wide and the number of *H. pylori* antibody-negative case patients was low. Poultry intake was not associated with gastric noncardia cancer risk in *H. pylori* antibody-positive subjects. Tests for interaction were not statistically significant.

Discussion

This is the largest cohort study to examine associations between intakes of fresh and processed meats and the incidence of cardia and gastric noncardia cancer in Western countries and the first study to examine intakes of these foods and risk of esophageal adenocarcinoma. This is also the first cohort study, to our knowledge, to explore modification of the effects of meat intake by *H. pylori* infection status. We observed positive and statistically significant associations between intakes of total, red, and processed meat and the risk of gastric noncardia cancer. All of these associations seemed to be restricted to the *H. pylori*-infected subjects. Furthermore, there was no association between poultry intake and the risk of gastric noncardia cancer. Cardia gastric cancer was not associated with meat intake of any type. We observed non–statistically significant positive associations between the risk of esophageal adenocarcinoma and intakes of total meat and processed meat and a potential association with poultry intake. In this study population, the absolute risk of development of gastric adenocarcinoma within 10 years for a study subject aged 60 years was 0.26% for the lowest quartile of total meat intake and 0.33% for the highest quartile of total meat intake.

The finding that *H. pylori* infection modifies the associations between total and processed meat intakes and the risk of gastric noncardia cancer may explain the different effect of meat intake between cardia and noncardia tumors. A meta-analysis of prospective studies found that cardia tumors are not associated with *H. pylori* infection *(6)*. The mechanisms involved in the relationships among meat intake, *H. pylori* infection, and gastric cancer risk have yet to be fully elucidated. Red meat is an important source of iron, and it has been suggested that iron is an essential growth factor for *H. pylori (32)*. However, other, unknown factors must play a role in the cancer risk because, although the intake of red meat has increased in most European countries during the last decades, the prevalence of *H. pylori* infection and the incidence of gastric noncardia cancer has decreased over the same period *(3)*.

Few cohort studies have explored associations between meat and processed meat intakes and the risk of gastric cancer. With respect to fresh meat intake and gastric cancer risk, three cohort studies *(14,15,33)* observed no associations with total meat, beef, or pork intakes, whereas one study *(16)* found a weak but non–statistically significant association. Processed meat (such as bacon or sausage) was statistically significantly and positively associated with gastric cancer in two cohort studies *(15,17)* but not in three other studies *(14,18,19)*. However, none of these studies distinguished between cardia and noncardia tumors. Results from case–control studies have also been inconsistent *(13)*. Some studies *(34,35)* observed a statistically significant positive association between red meat intake and gastric cancer risk, whereas other studies *(36–38)* found a positive but non–statistically significant association. However, the two largest studies *(39,40)* found no association between red meat intake and gastric cancer risk. With respect to esophageal cancer, the effect of meat and processed meat intake has never been analyzed in a cohort study for a Western population, and the evidence from case–control studies is limited and inconsistent *(13)*.

Several plausible mechanisms have been suggested to explain the possible causal relationship between meat intake and cancer risk *(41)*. These mechanisms involve potential effects of high levels of heme (a red organic pigment containing ferrous iron) in red meats, of fat and protein, of nitrite and nitrosamines, and of salt, as well as of heterocyclic amines and polycyclic aromatic hydrocarbons. One study *(41)* showed that red meat intake had a consistent dose response on the endogenous formation of *n*-nitroso compounds measured in fecal samples, whereas white meat intake had no effect. This effect seems to be associated with the content of heme, rather than with the content of protein or inorganic iron *(42)*. Processed meat is a mixed category that

consists mainly of pork and beef products and is an important source of salt, nitrites, and exogenous nitrosamines in the human diet *(43)*. Nitrosamines have been shown to cause a wide range of tumors in more than 40 animal species and may be specifically involved in the etiology of gastric cancer and esophageal cancer *(44)*, although so far, there is no conclusive epidemiologic evidence that these compounds are related to cancer risk in humans. Although the levels of sodium nitrite in foods have decreased during the last 20 years *(43)*, it is still widely used as a food preservative in cured meat. Nitrites and nitrates can nitrosate amines and amides, thus forming potentially carcinogenic *N*-nitroso compounds *(45)*. Nitrosating agents *(46)* are overproduced under chronic inflammatory conditions, a common step in the gastric precancerous process. In addition, salt is thought to induce an inflammatory process that leads to damage of the protective stomach mucosa *(13)*. *H. pylori* infection may interact with salt, enhancing carcinogenesis after the gastric epithelium is damaged *(13)*. It has also been suggested that the effect of salt on stomach inflammation could be stronger if nitrosamine compounds are involved *(13)*.

Any effect of meat on cancer risk could be associated also with the content of heterocyclic amines and polycyclic aromatic hydrocarbons. Heterocyclic amines *(47)* and polycyclic aromatic hydrocarbons *(48)* are formed by cooking meat at a high temperature or over an open flame. We could not assess the associations of these chemicals with the risks of gastric cancer and esophageal adenocarcinoma because only some of the EPIC dietary questionnaires recorded detailed information about the method used to cook meat or the frequency of intake of more-well-done versus less-well-done meat or of browned meats. However, on the basis of the information obtained from the 24HR dietary recall, we know that the frequency of use of high-temperature cooking methods (i.e., grilling, frying, or barbecuing) varied from 15% in the EPIC cohort of Italy to 49% in the EPIC cohort of The Netherlands *(49)*. Regarding our finding of a possible association between poultry intake and the risk of esophageal adenocarcinoma, we are not able to find an explanation. White meat (i.e., poultry) is not a source of the endogenous formation of *N*-nitroso compounds *(41)*, and the frequency of use of high-temperature cooking methods for chicken in most of the EPIC countries was lower than 30%, although it varied from 8.3% in France to 88.3% in Germany *(49)*.

Our study has several potential limitations. First, we did not collect information about family history of gastric cancer. However, a Japanese study *(50)* that was designed to assess the influence of this information observed no differences in lifestyle and risk factor patterns between gastric cancer patients with and without a family history of this disease. Second, our results could also be affected by measurement error in dietary intake, a common limitation of epidemiologic studies. The wide range of intakes of meat and processed meat reported in the EPIC study reduced, but did not eliminate, potential effects of measurement error. Because the magnitude of the distortion in the estimated relative risk depends on the ratio of the inter-individual variation to the intra-individual measurement error *(51)*, regression dilution should have been lessened by the inclusion of a diverse range of intakes. In addition, our results for the association between meat intake and cancer risk were calibrated against a more detailed method of dietary assessment (the 24HR dietary recall). We have emphasized the results that were consistent in the original categorical and the continuous calibrated models and note that the study is based mostly in confirmed adenocarcinoma cases validated by a panel of pathologists.

In conclusion, despite the relatively low number of cardia and gastric noncardia cancer and esophageal adenocarcinoma cases in our study and the need for more cases and years of follow-up, our results suggest that meat intake is associated with the risk of gastric noncardia cancer and adenocarcinoma of the esophagus. We observed a statistically significant increase in gastric noncardia cancer risk associated with the intake of total, red, and processed meat. The associations with total and processed meat seemed to be restricted to *H. pylori* antibody-positive subjects. Cardia cancer was not associated with any type of meat intake. Given the low 5-year relative survival rates of European patients with gastric cancer or esophageal cancer (23% and 10%, respectively) *(52)*, identification and better control of risk factors represent the most effective ways for reducing the burden of these tumors.

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Notes

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