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


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]
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 the 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.
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 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*

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort sample</th>
<th>Person-years</th>
<th>Stomach adenocarcinoma‡</th>
<th>Total meat</th>
<th>Red meat</th>
<th>Poultry</th>
<th>Processed meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>74504</td>
<td>625111</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Italy</td>
<td>47531</td>
<td>280660</td>
<td>52</td>
<td>8</td>
<td>31</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Spain</td>
<td>41413</td>
<td>276926</td>
<td>32</td>
<td>6</td>
<td>21</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>87352</td>
<td>466048</td>
<td>52</td>
<td>21</td>
<td>23</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>40047</td>
<td>249585</td>
<td>29</td>
<td>9</td>
<td>9</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Greece</td>
<td>26856</td>
<td>100514</td>
<td>16</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Sweden</td>
<td>53769</td>
<td>419510</td>
<td>59</td>
<td>17</td>
<td>34</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Denmark</td>
<td>57016</td>
<td>382701</td>
<td>53</td>
<td>24</td>
<td>16</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>481518</td>
<td>3110034</td>
<td>348</td>
<td>101</td>
<td>166</td>
<td>116</td>
<td>120</td>
</tr>
</tbody>
</table>

*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).

‡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*

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>51.7 (10.2)</td>
<td>49.4 (12.1)</td>
<td>52.4 (8.8)</td>
<td>.001</td>
<td>50.4 (11.8)</td>
<td>52.0 (9.3)</td>
<td>.001</td>
<td>50.4 (12.6)</td>
<td>51.3 (9.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Mean alcohol intake, g/d (range)</td>
<td>6.0 (0–339)</td>
<td>4.7 (0–339)</td>
<td>8.7 (0–298)</td>
<td>.001</td>
<td>5.6 (0–339)</td>
<td>6.4 (0–310)</td>
<td>.001</td>
<td>4.1 (0–310)</td>
<td>7.5 (0–339)</td>
<td>.001</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>25.5 (4.3)</td>
<td>25.4 (4.1)</td>
<td>25.9 (4.4)</td>
<td>.001</td>
<td>25.4 (4.0)</td>
<td>26.2 (4.5)</td>
<td>.001</td>
<td>25.2 (4.5)</td>
<td>25.9 (4.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Ever tobacco smoker, %</td>
<td>49.2</td>
<td>44.7</td>
<td>53.5</td>
<td>&lt;.001</td>
<td>49.3</td>
<td>47.3</td>
<td>&lt;.001</td>
<td>44.9</td>
<td>51.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Secondary school education or higher, %</td>
<td>48.9</td>
<td>57.5</td>
<td>46.3</td>
<td>&lt;.001</td>
<td>54.8</td>
<td>47.1</td>
<td>&lt;.001</td>
<td>52.7</td>
<td>44.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean leisure physical activity, MET-h/wk (SD)</td>
<td>82.7</td>
<td>84.2 (48.7)</td>
<td>79.1 (49.8)</td>
<td>&lt;.001</td>
<td>79.8 (47.6)</td>
<td>82.5 (50.9)</td>
<td>&lt;.001</td>
<td>86.1 (50.5)</td>
<td>81.7 (48.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Perform manual activity at work, %</td>
<td>11.8</td>
<td>9.0</td>
<td>15.1</td>
<td>&lt;.001</td>
<td>9.8</td>
<td>11.2</td>
<td>&lt;.001</td>
<td>10.5</td>
<td>11.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean energy intake, Kcal/day (SD)</td>
<td>2136 (632)</td>
<td>1909 (576)</td>
<td>2411 (652)</td>
<td>&lt;.001</td>
<td>2010 (609)</td>
<td>2310 (656)</td>
<td>&lt;.001</td>
<td>1937 (575)</td>
<td>2404 (674)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean total vegetable intake, g/d (SD)</td>
<td>217 (149)</td>
<td>222 (160)</td>
<td>230 (147)</td>
<td>&lt;.001</td>
<td>207 (153)</td>
<td>262 (153)</td>
<td>&lt;.001</td>
<td>290 (188)</td>
<td>187 (121)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean non-citrus fresh fruit intake, g/d (SD)</td>
<td>191 (153)</td>
<td>194 (162)</td>
<td>187 (149)</td>
<td>&lt;.001</td>
<td>181 (153)</td>
<td>219 (161)</td>
<td>&lt;.001</td>
<td>246 (188)</td>
<td>163 (126)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean citrus fruit intake, g/d (SD)</td>
<td>54.7 (72.7)</td>
<td>47.1 (69.5)</td>
<td>54.1 (68.3)</td>
<td>&lt;.001</td>
<td>41.0 (59.2)</td>
<td>69.0 (84.2)</td>
<td>&lt;.001</td>
<td>73.8 (92.2)</td>
<td>43.0 (59.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*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.
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>
<thead>
<tr>
<th>Type of meat</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total meat</td>
<td>91.0 (0–78)</td>
<td>127.4 (78–119)</td>
<td>152.3 (119–166)</td>
<td>186.7 (166–1196)</td>
</tr>
<tr>
<td>Red meat</td>
<td>34.3 (0–26)</td>
<td>51.5 (26–52)</td>
<td>66.5 (52–84)</td>
<td>84.6 (84–1087)</td>
</tr>
<tr>
<td>Poultry</td>
<td>10.2 (0–7)</td>
<td>15.5 (7–16)</td>
<td>21.9 (16–29)</td>
<td>34.0 (29–690)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>19.1 (0–16)</td>
<td>46.9 (16–34)</td>
<td>64.8 (34–59)</td>
<td>85.6 (59–731)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Cancer site/type and type of meat</th>
<th>No. of cases</th>
<th>Observed quartiles/tertiles†</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>1.05 (0.75 to 1.49)</td>
<td>1.59 (1.12 to 2.24)</td>
<td>1.50 (1.01 to 2.23)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.22 (0.87 to 1.71)</td>
<td>1.27 (0.89 to 1.82)</td>
<td>1.50 (1.02 to 2.22)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.29 (0.93 to 1.80)</td>
<td>1.30 (0.92 to 1.83)</td>
<td>1.47 (1.04 to 2.10)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.10 (0.76 to 1.58)</td>
<td>1.16 (0.79 to 1.69)</td>
<td>1.62 (1.08 to 2.41)</td>
</tr>
<tr>
<td>Cardia</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>0.82 (0.43 to 1.57)</td>
<td>1.15 (0.60 to 2.19)</td>
<td>1.00 (0.48 to 2.08)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.56 (0.80 to 3.02)</td>
<td>1.48 (0.73 to 3.02)</td>
<td>1.17 (0.53 to 2.60)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.37 (0.72 to 2.61)</td>
<td>1.67 (0.88 to 3.19)</td>
<td>1.57 (0.80 to 3.09)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.19 (0.61 to 2.34)</td>
<td>1.04 (0.51 to 2.12)</td>
<td>1.14 (0.52 to 2.49)</td>
</tr>
<tr>
<td>Noncardia</td>
<td>159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>1.49 (0.89 to 2.48)</td>
<td>1.95 (1.15 to 3.30)</td>
<td>2.19 (1.22 to 3.93)</td>
</tr>
<tr>
<td>Red meat</td>
<td>0.90 (0.56 to 1.44)</td>
<td>1.29 (0.79 to 2.10)</td>
<td>1.65 (0.97 to 2.82)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.17 (0.71 to 1.94)</td>
<td>1.51 (0.92 to 2.46)</td>
<td>1.65 (1.00 to 2.74)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.02 (0.00 to 1.71)</td>
<td>1.02 (0.59 to 1.77)</td>
<td>1.92 (1.11 to 3.33)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>1.05 (0.59 to 1.87)</td>
<td>1.48 (0.82 to 2.70)</td>
<td>1.24 (0.61 to 2.51)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.29 (0.73 to 2.30)</td>
<td>1.52 (0.83 to 2.78)</td>
<td>1.23 (0.61 to 2.51)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.02 (0.57 to 1.80)</td>
<td>1.06 (0.58 to 1.93)</td>
<td>1.46 (0.81 to 2.62)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.62 (0.84 to 3.11)</td>
<td>1.67 (0.84 to 3.33)</td>
<td>1.78 (0.84 to 3.77)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>116</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>0.80 (0.44 to 1.46)</td>
<td>1.76 (1.00 to 3.07)</td>
<td>1.34 (0.69 to 2.58)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.11 (0.65 to 1.91)</td>
<td>0.95 (0.51 to 1.75)</td>
<td>1.74 (0.93 to 3.24)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.33 (0.76 to 2.34)</td>
<td>1.50 (0.84 to 2.67)</td>
<td>1.87 (1.05 to 3.33)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>0.75 (0.39 to 1.45)</td>
<td>0.88 (0.45 to 1.70)</td>
<td>1.47 (0.76 to 2.82)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total meat</td>
<td>0.96 (0.48 to 1.93)</td>
<td>1.79 (0.86 to 3.75)</td>
<td>N/A</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.73 (0.86 to 3.48)</td>
<td>1.67 (0.75 to 3.72)</td>
<td>N/A</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.29 (0.67 to 2.49)</td>
<td>1.93 (0.99 to 3.76)</td>
<td>0.05</td>
</tr>
<tr>
<td>Processed meat</td>
<td>2.08 (0.96 to 4.47)</td>
<td>3.54 (1.57 to 7.99)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*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): 91.37/50.29 and 142.66/93.70. The cutoff points for the processed meat tertiles, in grams/day, were (men/women): 25.18/12.60 and 49.15/30.48. Quartiles and tertiles are full-cohort sex specific.
positive association between total meat intake (OR for a 100-g/d
increase in intake = 5.32; 95% CI = 2.10 to 13.4) and pro-
cessed 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 statisti-
cally significant.

**DISCUSSION**

This is the largest cohort study to examine associations be-
tween 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 esoph-
ophageal 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 statisti-
cally 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 pro-
spective studies found that cardia tumors are not associated with
H. pylori infection (6). The mechanisms involved in the relation-
ships 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 nitrate 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

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**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.

<table>
<thead>
<tr>
<th>Type of meat</th>
<th>H. pylori antibody status</th>
<th>No. of control subjects</th>
<th>Case patients with stomach adenocarcinoma</th>
<th>Case patients with gastric cardia adenocarcinoma</th>
<th>Case patients with gastric noncardia adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
<td>OR (95% CI) P†</td>
<td>No.</td>
<td>OR (95% CI) P†</td>
</tr>
<tr>
<td>Total meat</td>
<td>Negative</td>
<td>372</td>
<td>40 1.60 (0.26 to 9.96) .76</td>
<td>22 3.05 (0.26 to 35.1) .43</td>
<td>12 0.21 (0.001 to 38.0) .14</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>769</td>
<td>201 2.57 (1.25 to 5.25) .54</td>
<td>47 0.52 (0.12 to 2.32) .43</td>
<td>113 5.22 (1.20 to 13.4) .28</td>
</tr>
<tr>
<td>Red meat</td>
<td>Negative</td>
<td>372</td>
<td>40 1.78 (0.27 to 11.7)  .54</td>
<td>22 1.55 (0.10 to 24.5) .20</td>
<td>12 1.22 (0.01 to 237) .28</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>769</td>
<td>201 1.26 (0.69 to 2.32) .71</td>
<td>47 0.56 (0.16 to 2.00) .14</td>
<td>113 1.93 (0.90 to 4.12) .25</td>
</tr>
<tr>
<td>Poultry</td>
<td>Negative</td>
<td>372</td>
<td>40 1.05 (0.56 to 1.98)  .79</td>
<td>22 1.22 (0.55 to 2.70) .14</td>
<td>12 1.76 (0.34 to 9.19) .79</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>769</td>
<td>201 1.07 (0.84 to 1.36) .70</td>
<td>47 0.75 (0.46 to 1.22) .14</td>
<td>113 1.13 (0.80 to 1.60) .79</td>
</tr>
<tr>
<td>Processed meat</td>
<td>Negative</td>
<td>372</td>
<td>40 0.45 (0.05 to 4.01)  .48</td>
<td>22 0.86 (0.03 to 27.0) .42</td>
<td>12 0.002 (&lt;0.001 to 62.6) .25</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>769</td>
<td>201 2.00 (1.06 to 3.79) .42</td>
<td>47 1.62 (0.47 to 5.55) .14</td>
<td>113 2.67 (1.20 to 5.93) .25</td>
</tr>
</tbody>
</table>

*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.
collect information about family history of gastric cancer. How-

We have emphasized the results that were consistent in the origi-

nal 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
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 pro-
cessed 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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