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Meat Intake and Risk of Gastric and Esophageal Adenocarcinoma in the European Prospective Investigation Into Cancer and Nutrition (EPIC) Study

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ABSTRACT

Whether meat consumption increases the risk of gastric cancer (GC) and esophageal cancer or not remains unclear. Moreover, the number of prospective studies evaluating the associations by anatomical and histological types of GC is limited. We aimed to assess the associations of red, processed, and white meat with all gastric adenocarcinomas by anatomical site and histological type, and with esophageal adenocarcinoma (EAC), using data from the European Prospective Investigation into Cancer and Nutrition study of 450,112 individuals (131,426 men/318,686 women). Over 14.1 years of follow-up, 876 GC and 215 EAC cases were identified. Among the GC cases, 233 were located in cardia and 329 in non-cardia regions. Histologically, 624 were classified as intestinal type and 208 as diffuse type. The associations between meat intake and risk of GC or EAC were assessed using

Abbreviations: BMI, body mass index; CGC, cardia gastric cancer; CI, confidence interval; DNA, deoxyribonucleic acid; EAC, esophageal adenocarcinoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; GC, gastric cancer; HR, hazard ratios; IARC, International Agency for Research and Cancer; MA, meta-analysis; NCGC, non-cardia gastric cancer; PH, proportional hazards; PUFA, polyunsaturated fatty acid; Q1, first quartile; Q4, fourth quartile; SD, standard deviation; UK, United Kingdom.

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multivariable Cox models. A 30 g/day increase in processed meat consumption was associated with a 9% (95% CI: 2–17) increase in GC risk and a 13% (95% CI: 0–27) increase in EAC risk. Additionally, a 20 g/day increase in white meat intake was associated with a 12% (95% CI: 2–24) increase in non-cardia GC risk. Processed meat was also associated with intestinal GC (11%, 95% CI: 2–20) and higher consumption with diffuse GC. Only processed meat was associated with GC among men while processed and white meat were both positively associated with GC among women. In conclusion, processed meat may increase the risk of GC and EAC, although further research is needed to clarify the effects of white meat consumption.

1 | Introduction

Gastric and esophageal cancers are the 5th and 11th most common cancers worldwide, accounting for more than 660,000 and 445,000 deaths respectively in 2022 [1]. From a histopathological perspective, approximately 90% of gastric cancers (GC) are adenocarcinomas [2]. Recent studies have shown that esophageal adenocarcinoma (EAC) is increasing in Western countries, probably because of changes in lifestyle profiles across these countries [3]. It is projected that by 2030, 1 in 100 men in the Netherlands and the United Kingdom (UK) will be diagnosed with EAC in their lifetime [4]. Due to the accumulated evidence supporting a common origin of EAC and GC arising from similar gastric stem or progenitor cell populations, both cancers are increasingly being considered as related in terms of treatment, particularly in approaches based on molecular profiles [5, 6].

Helicobacter pylori infection is a well-established risk factor of non-cardia gastric cancer (NCGC), most notably for its implication in the etiology of the intestinal type [7]. Other established risk factors for GC are tobacco smoking, occupational exposure to dusty and high-temperature environments, alcohol consumption, foods preserved by salting, and body fatness, the latter associated with cardia gastric cancer (CGC) [8]. The link between other diet-related exposures, like processed meat consumption, and risk of GC is still not settled. In the up-to-date systematic reviews based on prospective studies, the association between processed meat and GC was classified as weak; no associations were found with other types of meat, and evidence by GC subtypes was lacking [2, 9]. Moreover, prospective cohort studies on the association between meat intake and GC among European countries are scarce in recent years [10, 11].

In regard to EAC, gastroesophageal reflux disease, and modifiable factors such as greater body fatness and tobacco smoking have been clearly identified as risk factors.[8] However, similar to GC, there is still limited evidence assessing the association between processed meat consumption and EAC, which highlights the need for further high-level quality and well-designed studies [12].

In a first evaluation of data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, we reported an increased risk of NCGC for red and processed meat, and a null association with CGC and EAC [13]. With the present study we aim to re-assess the relationship between meat intake and risk of GC and EAC, following the inclusion of additional cases after an extended follow-up period. Although no apriori hypothesis regarding sex differences was proposed, a subgroup analysis by sex was conducted in an exploratory way to see if differential patterns could be identified that would indicate more targeted future research.

2 | Methods

2.1 | Study Design and Population

The EPIC is a multi-center cohort study comprising 521,324 participants across 10 European countries. This cohort was designed to investigate the role of diet, lifestyle, and environmental factors in cancer etiology. Recruitment procedures and data collection of the EPIC study have been described elsewhere [14]. The study collected information on diet, lifestyle factors, anthropometric measurements, medical history, and blood samples at baseline.

For the analysis, we excluded participants from Greece ($n = 28{,}561$) due to administrative reasons, prevalent cancer cases ($n = 24{,}550$), participants with missing follow-up information ($n = 3137$), participants lacking lifestyle or dietary information, and those with an extreme ratio of energy intake to estimated energy requirement, defined below the 1th or above the 99th percentile of the distribution ($n = 14{,}964$). After all exclusions, our study included available data from 450,112 individuals (131,426 men and 318,686 women).

2.2 | Follow-Up and Case Ascertainment

In most participating countries, incident cases and vital status were assessed via record linkages to the regional or national cancer registries and national mortality registries. In France and Germany, cancer cases were identified based on cancer and pathology registries, health insurance records, and an active follow-up by contacting the participants or their next-of-kin. The follow-up for cancer endpoints and vital status was available until 2015.

Among incident gastric and esophageal cases, we only considered malignant adenocarcinomas as cancer endpoints, which were defined by anatomic site and histologic code according to the International Classification of Disease for Oncology (ICD-O), Third edition. CGCs included tumors topographically coded as C16.0, non-cardia GCs (NCGC) included codes C16.1 to C16.6, as well as C16.8 (overlapping lesion of stomach) and C16.9 (not otherwise specified). We also classified GCs according to the two main histologic types of the Lauren classification [15, 16]: subjects with the morphology codes 8145/3 and 8490/3 were defined as diffuse type, while subjects with morphology codes 8144/3, 8211/3, 8260/3, 8480/3, and 8481/3 were defined as intestinal type. Esophageal cases included topography codes C15.0–C15.9. Subjects with code C16_ or C15_ not considered as cases for the analysis were censored at the date of diagnosis.

What's New?

Limited evidence links processed meat intake and non-cardia gastric cancer, while esophageal adenocarcinoma is increasing in Western countries, where diets are typically high in red and processed meats. Using data from over 450,000 participants from a large prospective study, the authors examined meat consumption and the risk of gastric and esophageal adenocarcinomas. Higher processed meat intake was associated with an increased risk of gastric cancer, especially intestinal-type gastric cancer, and esophageal adenocarcinoma. There also was a positive association between white meat intake and gastric cancer risk in women. This study adds new evidence for gastric and esophageal cancer prevention related to meat consumption.

2.3 | Diet and Lifestyle Information

Questionnaires on sociodemographic characteristics and lifestyle were collected at baseline. These questionnaires included information about the level of educational attainment, smoking habits, alcohol consumption, and reproductive history. Baseline anthropometry was measured using standardized procedures at baseline in most of the centers, except for Oxford (UK), France, and Norway, which collected self-reported data [17]. The usual diet over the previous 12 months of recruitment was collected using country-specific validated questionnaires [14, 18]. Most countries adopted extensive quantitative or semiquantitative food frequency questionnaires (FFQs), while some used diet-history questionnaires alone or combined with FFQs.

In this study, intake of red meat, processed meat, and white meat was estimated in grams/day from the dietary questionnaires reported at baseline. Red meat intake included pork, beef, veal, and lamb and unclassified red meat. Processed meat included ham, bacon, sausages, processed meat cuts, hamburgers, meatballs, pâtés, and unclassified processed meat. White meat included chicken, hen, turkey, duck, goose, rabbit, and unclassified poultry or combined [19].

2.4 | Statistical Analysis

We estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between meat intake and risk of GC or EAC using the Cox Proportional Hazard (PH) models with age as the underlying time scale. The entry time was defined as the age of recruitment and the exit time was defined as the age at diagnosis, loss to follow-up, or the end of follow-up, whichever came first. The survival models were stratified by age at recruitment and center, and adjusted for sex and total energy intake (Kcal/day). Furthermore, the multivariable models were also adjusted for potential confounders as follows: attained level of education (none or primary school, technical or professional school, secondary school, longer education including university degree, and unknown), BMI (underweight $<18.5\,kg/m^2$, normal weight 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2 and obese $\geq 30\,kg/m^2$), alcohol consumption (grams/day), and smoking status and intensity (never smoker, current 1–15 cigarettes/day, current 16–25 cigarettes/day, current >25 cigarettes/day, former quit at ≤10 years, former quit at 11–20 years, former quit at >20 years or other smokers including occasional smokers, smokers of cigar and/or pipe, and smokers with unknown status and/or unknown). In addition, we explored the independent effect of red meat, processed meat, and white meat by mutually adjusting for each other in an additional model. We evaluated the model assumptions with graphs and tests based on the scaled Schoenfeld residuals.

We analyzed the dietary intakes of meat as continuous variables rescaled to reflect approximately 1 SD (40 g/day for red meat, 30 g/day for processed meat, 50 g/day for total red meat, and 20 g/day for white meat) and as categorical variables using quartiles. For the HRs reported within quartiles, we used the lowest quartile as the reference category. To assess the linear trend across quartiles, we assigned a score ranging from 1 to 4 according to the quartile of intake and considered this score as a continuous variable in the Cox PH models. Furthermore, we checked the interaction by sex in the Cox models with the likelihood ratio test and performed separate analyses for men and women using sex-specific quartiles for the categorical meat intakes. The homogeneity of risk for cardia and non-cardia GC, as well as for intestinal and diffuse types of GC, was assessed using the Wald test.

Finally, we performed sensitivity analyses to confirm the consistency of our primary results. First, to minimize reverse causation, we conducted the analysis excluding cases diagnosed within the first 2 years of follow-up. Second, we studied the validity of the linearity assumption for the continuous intakes using restricted cubic splines models. Third, we assessed the effect of the assumption that diet remains constant since recruitment, conditioning the multivariable Cox model for different time periods from recruitment.

3 | Results

During a mean follow-up of 14.1 years, 876 gastric and 215 EACs were identified among the 450,112 individuals. The risk of GC was three-fold higher in men than in women, and higher in people aged 60 and over at recruitment. We accrued 233 CGCs, 329 NCGCs, and 314 overlapping or unknown tumor sites. According to the Lauren classification, 624 were GC of the intestinal type, 208 were GC of the diffuse type, and 44 could not be classified. Regarding EAC, the cases had a median age at recruitment of 58.6 years, and 78.6% of them were diagnosed among men.

Distribution of the participants, cancer incidence and meat intake according to the baseline characteristics of the population are displayed in Table 1. In summary, among consumers of both sexes, red meat was the most consumed meat in terms of quantity, with men having a 43% higher intake than women (54.3 g/day vs. 37.8 g/day, respectively). Likewise, processed meat consumption was higher in men, with an intake of 45.3 g/day compared to 28.4 g/day in women. Additional descriptive statistics of crude meat intake, such as quartiles, are displayed in Table S1. Ever smokers as well as moderate and heavy drinkers consumed more red meat than never smokers and nondrinkers or light drinkers, respectively. We also studied the correlations between the three types of meat (Table S2). The highest correlation observed was

TABLE 1 | Main characteristics, number of events, and meat intake (g/day) in the EPIC population.

	N (%)		GC (CGC/NCGC)		EAC	Mean (95% CI)[a]		
						Red meat	Processed meat	White meat
Sex								
Men	131,426	(29.2)	484	(154/157)	169	54.3 (54.1–54.5)	45.3 (45.2–45.5)	20.9 (20.8–21.0)
Women	318,686	(70.8)	392	(79/172)	46	37.8 (37.7–37.9)	28.4 (28.3–28.5)	18.1 (18.0–18.1)
Age at recruitment (years)								
< 40	51,328	(11.4)	23	(1/13)	2	28.7 (28.4–29.0)	27.2 (27.0–27.5)	14.3 (14.1–14.5)
40 to < 50	139,336	(31.0)	122	(32/49)	30	39.6 (39.5–39.8)	38.1 (38.0–38.3)	20.1 (19.9–20.2)
50 to < 60	175,649	(39.0)	382	(104/137)	83	48.7 (48.6–48.9)	32.9 (32.8–33.1)	19.7 (19.6–19.8)
≥ 60	83,799	(18.6)	349	(96/130)	100	43.4 (43.1–43.6)	29.8 (29.6–30.0)	18.0 (17.8–18.1)
Educational level								
None or primary school	126,615	(28.1)	419	(80/187)	86	44.4 (44.2–44.6)	36.8 (36.6–36.9)	22.2 (22.0–22.3)
Technical/professional	103,783	(23.1)	216	(74/69)	56	43.2 (43.0–43.4)	35.4 (35.2–35.5)	17.2 (17.1–17.3)
Secondary	93,910	(20.9)	91	(27/23)	16	44.4 (44.2–44.6)	32.0 (31.8–32.2)	18.4 (18.2–18.5)
Longer	108,931	(24.2)	115	(38/43)	39	39.6 (39.4–39.8)	30.0 (29.8–30.2)	16.9 (16.8–17.0)
Unknown	16,873	(3.7)	35	(14/7)	18	35.3 (34.8–35.8)	23.6 (23.1–24.0)	20.7 (20.4–21.0)
Smoking status								
Never	191,403	(42.5)	298	(56/138)	53	39.4 (39.2–39.5)	32.0 (31.9–32.2)	19.1 (19.0–19.2)
Former	122,680	(27.3)	254	(79/79)	94	41.5 (41.3–41.7)	32.6 (32.4–32.8)	18.6 (18.5–18.7)
Current	99,715	(22.2)	290	(91/99)	64	48.8 (48.6–49.0)	36.8 (36.6–37.0)	18.4 (18.3–18.5)
Pipe/cigar/occasional/other[b]	36,314	(8.1)	34	(7/13)	4	46.5 (46.2–46.9)	32.9 (32.6–33.2)	19.9 (19.7–20.1)
BMI (kg/m^2)								
Underweight	7128	(1.58)	8	(1/4)	1	37.3 (36.5–38.1)	27.4 (26.7–28.1)	14.0 (13.6–14.5)
Normal	232,565	(51.7)	327	(80/115)	61	40.7 (40.6–40.9)	31.0 (30.9–31.1)	17.0 (16.9–17.1)
Overweight	154,781	(34.4)	381	(121/143)	104	44.3 (44.1–44.5)	34.8 (34.7–35.0)	20.3 (20.2–20.4)
Obese	55,638	(12.4)	160	(31/67)	49	46.8 (46.5–47.0)	39.5 (39.2–39.7)	23.6 (23.4–23.7)
Alcohol consumption								
Non consumer	57,441	(12.8)	123	(18/52)	23	39.9 (39.6–40.2)	32.4 (32.2–32.7)	21.7 (21.6–21.9)
< 45.0 g/day	369,561	(82.1)	669	(192/249)	175	42.0 (41.9–42.1)	33.1 (33.0–33.2)	18.2 (18.2–18.3)
45.0–59.9 g/day	12,200	(2.7)	35	(13/12)	9	55.5 (54.8–56.1)	36.8 (36.3–37.4)	22.3 (22.0–22.7)
≥ 60.0 g/day	10,910	(2.4)	49	(10/16)	8	63.8 (63.1–64.4)	41.7 (41.1–42.2)	22.3 (21.9–22.6)
Energy intake (kcal/day, quartiles)								
Q1	112,528	(25.0)	180	(45/62)	34	28.2 (28.0–28.4)	23.7 (23.5–23.9)	14.1 (14.0–14.3)
Q2	112,528	(25.0)	199	(61/78)	34	37.9 (37.7–38.1)	29.0 (28.8–29.2)	17.4 (17.3–17.5)
Q3	112,528	(25.0)	213	(53/78)	71	45.8 (45.6–46.0)	33.9 (33.7–34.1)	19.8 (19.7–19.9)
Q4	112,528	(25.0)	284	(74/111)	76	58.7 (58.5–58.9)	46.6 (46.5–46.8)	24.2 (24.0–24.3)

(Continues)

TABLE 1 | (Continued)

	N (%)		GC (CGC/NCGC)		EAC	Mean (95% CI)[a]		
						Red meat	Processed meat	White meat
Country								
Denmark	55,014	(12.2)	162	(76/37)	53	72.6 (72.4–72.9)	27.4 (27.1–27.6)	20.9 (20.7–21.1)
France	67,403	(15.0)	11	(4/4)	0	52.7 (52.5–53.0)	34.9 (34.7–35.1)	20.6 (20.4–20.7)
Germany	48,557	(10.8)	106	(21/58)	11	28.2 (27.9–28.5)	59.0 (58.8–59.3)	12.1 (11.9–12.2)
Italy	44,545	(9.9)	123	(16/56)	4	49.0 (48.7–49.3)	24.2 (23.9–24.4)	25.7 (25.5–25.9)
Norway	33,975	(7.5)	33	(7/9)	2	26.0 (25.7–26.3)	42.8 (42.5–43.1)	13.2 (13.0–13.4)
Spain	39,989	(8.9)	119	(14/60)	12	41.3 (40.9–41.6)	35.7 (35.5–36.0)	35.4 (35.3–35.6)
Sweden	48,674	(10.8)	149	(32/58)	31	25.3 (25.1–25.6)	39.0 (38.8–39.2)	10.1 (10.0–10.3)
The Netherlands	36,539	(8.1)	59	(17/25)	20	62.7 (62.4–63.0)	31.5 (31.2–31.7)	13.0 (12.8–13.2)
United Kingdom	75,416	(16.8)	114	(46/22)	82	26.9 (26.7–27.1)	16.7 (16.5–16.9)	18.5 (18.4–18.7)

Abbreviations: CGC, cardia gastric cancer; EAC, esophageal adenocarcinoma; GC, gastric cancer; NCGC, non-cardia gastric cancer.
[a]Age and sex adjusted means (95% CIs) obtained from a linear regression model.
[b]Includes occasional smokers, exclusive smokers of cigar and/or pipe, and smokers with unknown status and/or unknown amount smoked.

between red meat and white meat, with a Pearson's coefficient slightly above 0.2, indicating a weak positive linear relationship.

Table 2 shows the association of meat intake and risk of GC and EAC. Processed meat intake was found positively associated with GC and EAC risk, with significant associations observed from the third quartile (GC: $HR_{Q3\ vs.\ Q1} = 1.38$, 95% CI: 1.11–1.71, $HR_{Q4\ vs.\ Q1} = 1.46$, 1.15–1.84; EAC: $HR_{Q3\ vs.\ Q1} = 1.70$, 1.07–2.69, $HR_{Q4\ vs.\ Q1} = 2.22$, 1.38–3.59) and with 30 g/day increase (GC: HR = 1.09, 1.02–1.17; EAC: HR = 1.13, 1.00–1.27). These associations remained significant even after adjusting for the consumption of the other types of meat (p-value < 0.001). We did not find an association between red meat or white meat intake and risk of all GC and EAC. Table 3 shows the mutually adjusted HRs for risk of GC by site and histological type. In this analysis, although the estimated association between processed meat intake and risk of NCGC was relatively high among the highest consumers, the wide CI, which included the null, indicates substantial uncertainty in the association ($HR_{Q4\ vs.\ Q1} = 1.43$, 95% CI: 0.97–2.12; $HR_{per\ 30\ g/day\ increase} = 1.06$, 0.95–1.18); in contrast, our data showed a positive association between white meat intake and risk of NCGC ($HR_{per\ 20\ g/day\ increase} = 1.12$, 1.02–1.24, p-value for homogeneity between NCGC and CGC = 0.003). Similarly, we observed a high HR of the association between processed meat intake and risk of CGC ($HR_{Q4\ vs.\ Q1} = 1.47$, 95% CI: 0.92–2.34; $HR_{per\ 30\ g/day\ increase} = 1.12$, 0.98–1.28); however, its wide CI included the null. On the other hand, neither red meat nor white meat intakes were found to be associated with risk of CGC. The subgroup analysis by the histological site of the gastric tumor showed that only processed meat was associated with the risk of both intestinal ($HR_{Q3\ vs.\ Q1} = 1.44$, 95% CI: 1.12–1.87, $HR_{Q4\ vs.\ Q1} = 1.41$, 1.06–1.87; $HR_{per\ 30\ g/day\ increase} = 1.11$, 1.02–1.20) and diffuse types ($HR_{Q4\ vs.\ Q1} = 1.84$, 1.12–3.04; $HR_{per\ 30\ g/day\ increase} = 1.07$, 0.94–1.22). Additional results can be found in Table S3, including results on overlapping GC.

The separate analyses for men and women revealed some differences between the sexes (Table 4); however, a significant interaction with sex was found only for white meat intake and GC risk (p-value = 0.007 without adjustment for other meat intakes and p-value = 0.008 after adjustment for other types of meat). Among men, only processed meat was associated with the risk of GC ($HR_{Q3\ vs.\ Q1} = 1.43$, 95% CI: 1.07–1.92, $HR_{Q4\ vs.\ Q1} = 1.56$, 1.13–2.15; $HR_{per\ 30\ g/day\ increase} = 1.10$, 1.01–1.19) whilst processed meat and white meat were both positively associated with the risk of GC among women ($HR_{Q4\ vs.\ Q1} = 1.50$, 1.07–2.11, $p_{trend} = 0.029$ for processed meat, $HR_{Q4\ vs.\ Q1} = 1.42$, 1.02–1.99, $p_{trend} = 0.033$ for white meat). The association with processed meat consumption persisted for risk of CGC, diffuse and intestinal subtypes in men, but only for the intestinal subtype in women. While the effect of white meat consumption among women remained only for risk of NCGC ($HR_{Q3\ vs.\ Q1} = 1.66$, 95% CI: 1.02–2.68, $HR_{Q4\ vs.\ Q1} = 1.69$, 1.02–2.80; $HR_{per\ 20\ g/day\ increase} = 1.20$, 1.05–1.38). Regarding EAC, all quartiles of processed meat intake were associated with an increased risk of EAC compared to low consumers in men ($p_{trend} = 0.005$), but no association was found in women, likely due to the small number of cases ($n = 46$).

We performed several sensitivity analyses, which revealed that our primary findings were consistent. The lag analysis, excluding the GC cases diagnosed within the first 2 years of follow-up, did not affect our results (Table S4). We could confirm the validity of the linearity assumption for the continuous meat intakes (data not shown) and the effect of the assumption that diet remains constant since recruitment (Table S5).

4 | Discussion

In this large European cohort study, we observed a 9% increase in GC risk and a 13% increase in EAC risk for every 30 g increase in processed meat consumption. This association between processed meat intake and risk of GC remained for intestinal and diffuse types of GC. In our data, no associations were observed for red meat. However, white meat intake was associated with

TABLE 2 | Adjusted hazard ratios (HRs) and 95% CIs for meat intake and gastric cancer and esophageal adenocarcinoma risk in the EPIC population.

	HR (95% CI)				HR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	*p*-trend	Continuous
GC (*N* = 876)					
Red meat	1.03 (0.83–1.28)	1.03 (0.82–1.29)	1.01 (0.79–1.30)	0.943	0.99 (0.91–1.08)
Processed meat	1.15 (0.92–1.43)	1.38 (1.11–1.71)	1.46 (1.15–1.84)	< 0.001	1.09 (1.02–1.17)
White meat	1.13 (0.92–1.39)	0.94 (0.76–1.16)	1.12 (0.91–1.39)	0.648	1.01 (0.95–1.08)
Mutually adjusted					
Red meat	0.98 (0.79–1.23)	0.98 (0.77–1.23)	0.94 (0.73–1.22)	0.651	0.98 (0.90–1.07)
Processed meat	1.15 (0.92–1.44)	1.39 (1.11–1.73)	1.47 (1.16–1.87)	< 0.001	1.09 (1.02–1.17)
White meat	1.11 (0.91–1.37)	0.92 (0.74–1.14)	1.11 (0.89–1.37)	0.732	1.01 (0.95–1.09)
EAC (*N* = 215)					
Red meat	1.20 (0.76–1.92)	1.15 (0.70–1.89)	1.11 (0.67–1.85)	0.846	1.00 (0.86–1.17)
Processed meat	1.23 (0.76–1.97)	1.70 (1.07–2.69)	2.22 (1.38–3.59)	< 0.001	1.13 (1.00–1.27)
White meat	1.32 (0.86–2.03)	1.15 (0.74–1.78)	1.15 (0.73–1.81)	0.808	1.06 (0.94–1.19)
Mutually adjusted					
Red meat	1.02 (0.63–1.66)	0.95 (0.56–1.60)	0.88 (0.51–1.51)	0.534	0.98 (0.83–1.15)
Processed meat	1.23 (0.75–2.01)	1.71 (1.05–2.76)	2.24 (1.36–3.70)	< 0.001	1.13 (1.00–1.27)
White meat	1.23 (0.79–1.91)	1.06 (0.67–1.67)	1.07 (0.67–1.71)	0.945	1.06 (0.94–1.19)

Note: Categorical variables: Reference categories are the lowest quartile. Continuous variables: HRs (95% CIs) correspond to an increase of 40 g/day for red meat, 30 g/day for processed meat and 20 g/day for white meat. Multivariable model [1]: stratified by age and center and adjusted for sex, energy intake, educational level, tobacco smoking, body mass index, and alcohol consumption. Mutually adjusted model: as in multivariable model [1], with red meat, processed meat and white meat mutually adjusted.
Abbreviations: EAC, esophageal adenocarcinoma; GC, gastric cancer.

an increased risk of non-cardia GC among women, with each 20 g increase in consumption corresponding to a 20% higher risk of NCGC.

Studies on the association between meat consumption and GC have yielded inconsistent results. A recent umbrella review of meta-analysis with prospective studies reported a significant association between processed meat and GC (number of studies = 8, Relative Risk 1.17 95% CI: 1.04, 1.31); however, the quality of the studies included was classified as weak based on AMSTAR (assessment of multiple systematic reviews) [2]. Additionally, a non-significant association was found between red meat and GC based on prospective studies, in contrast to the positive association observed in the sensitivity analysis that included prospective and non-prospective studies. Along the same lines, the World Cancer Research Fund (WCRF)/American Institute of Cancer Research (AICR) expert pannel [8] concluded that the evidence supporting processed meat as a risk factor for NCGC is limited and suggestive, and no specific recommendations were made concerning red meat or white meat due to lack of data. Our findings from this cohort study support that processed meat intake is a risk factor for GC, for both men and women; however, although the analysis by anatomic site showed high point effect estimators for NCGC and CGC in the highest quartiles of intake, the CIs were wide and included the null. We didn't find any association with red meat and GC overall nor by subtypes. Regarding white meat intake, we found a positive association with risk of GC among women (p-value = 0.0375), driven by an association with the NCGC site (p-value = 0.0074).

Concerning EAC, a recent meta-analysis [9] reported no associations between meat intake (red or processed) and risk of esophageal cancer, based on the results of 5 cohorts. Additionally, an updated umbrella review on diet and risk of EAC described suggestive evidence between processed meat and EAC [12]. In our analysis, processed meat consumption was associated with increased risk of EAC, similar to previous findings by Norat et al. in 2005 [20].

When comparing our analysis with the earlier EPIC report published in 2006 [13], the primary difference is the extended follow-up period, which translates into a higher number of GC cases. Additionally, we did not include data from Greece but incorporated data from Norway. We also excluded 14,964 participants who lacked lifestyle or dietary information and those with an extreme ratio of energy intake. This exclusion affected 2639 participants who were removed only for this reason. We observed an association between processed meat and the risk of GC and EAC; however, contrary to previous findings, not with NCGC. We attribute the loss of significance in our analysis mainly to the lower mean intakes, resulting from the exclusion of participants with the highest intakes. Furthermore, although we have a larger number of cases, dietary intake was

TABLE 3 | Adjusted hazard ratios (HRs) and 95% CIs for meat intake and gastric cancer risk by anatomic and histological subtypes in the EPIC population.

	HR (95% CI)				HR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	*p*-trend	Continuous
By anatomic site					
Cardia (233 cases)					
Red meat	1.12 (0.69–1.82)	1.22 (0.74–2.01)	1.15 (0.67–1.95)	0.657	0.96 (0.81–1.14)
Processed meat	1.22 (0.80–1.87)	1.10 (0.70–1.72)	1.47 (0.92–2.34)	0.165	1.12 (0.98–1.28)
White meat	1.05 (0.71–1.55)	0.77 (0.51–1.17)	0.78 (0.51–1.20)	0.105	0.84 (0.72–0.99)
Non-cardia (329 cases)					
Red meat	0.93 (0.66–1.31)	0.91 (0.64–1.31)	0.73 (0.48–1.11)	0.157	0.94 (0.80–1.10)
Processed meat	1.15 (0.80–1.66)	1.41 (0.98–2.03)	1.43 (0.97–2.12)	0.046	1.06 (0.95–1.18)
White meat	1.21 (0.86–1.69)	1.14 (0.79–1.64)	1.59 (1.11–2.28)	0.017	1.12 (1.02–1.24)
By histological type					
Intestinal (624 cases)					
Red meat	1.01 (0.77–1.31)	1.06 (0.81–1.40)	0.96 (0.71–1.30)	0.830	0.99 (0.89–1.10)
Processed meat	1.07 (0.82–1.39)	1.44 (1.12–1.87)	1.41 (1.06–1.87)	0.003	1.11 (1.02–1.20)
White meat	1.25 (0.97–1.60)	0.99 (0.76–1.28)	1.24 (0.96–1.61)	0.331	1.02 (0.94–1.10)
Diffuse (208 cases)					
Red meat	0.94 (0.61–1.45)	0.84 (0.53–1.33)	0.87 (0.52–1.45)	0.534	0.97 (0.80–1.18)
Processed meat	1.40 (0.87–2.23)	1.38 (0.85–2.25)	1.84 (1.12–3.04)	0.024	1.07 (0.94–1.22)
White meat	0.79 (0.53–1.18)	0.8 (0.52–1.22)	0.78 (0.50–1.21)	0.312	1.01 (0.88–1.18)

Note: Categorical variables: Reference categories are the lowest quartile. Continuous variables: HRs (95% CIs) correspond to an increase of 40 g/day for red meat, 30 g/day for processed meat and 20 g/day for white meat. HRs and 95% CIs from a multivariable model stratified by age and center, and adjusted for sex, energy intake, educational level, tobacco smoking, body mass index, alcohol consumption, with mutual adjustment for each type of meat.

assessed only at baseline, which may have diminished any potential effects over the extended follow-up period of the current study. We consider our approach of excluding participants with an extreme ratio of energy intake to estimated energy requirement to be more conservative, ensuring more plausible intakes.

The increase in case numbers enabled us to perform a stratified analysis by sex. Our interest in performing a subgroup analysis by sex is supported by significant differences in the overall incidence rates of GC and EAC, as well as in the distribution of anatomical and histological GC subtypes between men and women, according to historical trends [21, 22]. Lifestyle factors such as smoking and alcohol consumption, more prevalent in men, may contribute to the higher GC incidence in this group. Hormonal differences, along with variations in diet and tobacco use, may also play a role. Additionally, men have a higher risk of *Helicobacter pylori* infection, which could further explain sex differences in GC susceptibility [23].

Several plausible mechanisms have been proposed to explain the potential causal link between meat consumption and cancer risk. Specifically, in the context of GC and EAC, heme iron found in red and processed meats has been identified as a risk factor [24]. This type of iron acts as a nitrosating agent, promoting the endogenous formation of N-nitroso compounds (NOCs) [25], which are recognized carcinogens [26]. This process may elevate the production of carcinogenic nitrosamines, leading to DNA damage and oxidative stress, ultimately contributing to the formation of DNA adducts [27]. Such DNA adducts are regarded as risk factors for GC, particularly for NCGC [28]. Another well-established risk factor for the development of GC is the presence of *Helicobacter pylori*, which has been classified as a human carcinogen by the IARC since 1994 [29] and it accounts for 90% of distal adenocarcinomas [1]. Interestingly, a systematic review of published meta-analyses on modifiable factors and esophageal cancer found that *Helicobacter pylori* infection consistently showed a protective effect against EAC risk, while no significant association was observed with esophageal squamous cell carcinoma (ESCC) [30]. The mechanisms behind the protective link between *Helicobacter pylori* infection and EAC remain unclear, though some researchers suggest that reduced stomach acidity linked to gastric atrophy might play a role [31, 32].

Different cooking methods and individuals' doneness preferences of meat may also influence the risk of developing GC and EAC [33]. For example, polycyclic aromatic hydrocarbons and heterocyclic amines generated during high-temperature

TABLE 4 | Association between meat intake and risk of gastric cancer and esophageal adenocarcinoma by sex, in the EPIC population (models mutually adjusted; sex-specific quartiles).

	HR (95% CI)				HR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	*p*-trend	Continuous
GC					
Women (392 cases)					
Red meat	0.73 (0.53–1.01)	0.86 (0.62–1.19)	0.80 (0.55–1.15)	0.446	0.99 (0.84–1.17)
Processed meat	1.17 (0.87–1.58)	1.14 (0.83–1.57)	1.50 (1.07–2.11)	0.029	1.09 (0.96–1.25)
White meat	1.13 (0.82–1.55)	1.23 (0.88–1.71)	1.42 (1.02–1.99)	0.033	1.11 (1.01–1.23)
Men (484 cases)					
Red meat	1.11 (0.83–1.48)	1.21 (0.89–1.65)	1.05 (0.74–1.50)	0.725	1.00 (0.89–1.11)
Processed meat	1.38 (1.04–1.82)	1.43 (1.07–1.92)	1.56 (1.13–2.15)	0.011	1.10 (1.01–1.19)
White meat	1.10 (0.84–1.43)	0.77 (0.58–1.03)	0.99 (0.75–1.31)	0.503	0.95 (0.86–1.04)
Cardia GC					
Women (79 cases)					
Red meat	0.72 (0.33–1.59)	0.81 (0.37–1.78)	0.71 (0.31–1.63)	0.529	0.91 (0.64–1.30)
Processed meat	1.93 (0.98–3.79)	1.11 (0.51–2.40)	1.57 (0.70–3.51)	0.720	1.04 (0.75–1.43)
White meat	1.45 (0.71–2.96)	1.17 (0.55–2.50)	1.07 (0.48–2.39)	0.809	0.88 (0.66–1.18)
Men (154 cases)					
Red meat	0.98 (0.56–1.73)	1.6 (0.91–2.81)	1.07 (0.56–2.06)	0.583	1.02 (0.84–1.24)
Processed meat	1.04 (0.63–1.7)	1.39 (0.84–2.3)	1.83 (1.05–3.21)	0.020	1.15 (0.99–1.33)
White meat	0.86 (0.54–1.37)	0.67 (0.41–1.09)	0.76 (0.46–1.24)	0.186	0.82 (0.67–1.00)
Non-cardia GC					
Women (172 cases)					
Red meat	0.73 (0.46–1.17)	0.94 (0.58–1.52)	0.66 (0.37–1.17)	0.324	0.98 (0.77–1.26)
Processed meat	0.99 (0.62–1.58)	1.10 (0.68–1.77)	1.37 (0.83–2.26)	0.191	1.10 (0.92–1.31)
White meat	0.92 (0.56–1.51)	1.66 (1.02–2.68)	1.69 (1.02–2.80)	0.007	1.20 (1.05–1.38)
Men (157 cases)					
Red meat	0.87 (0.53–1.42)	0.90 (0.53–1.51)	0.73 (0.39–1.34)	0.369	0.92 (0.75–1.13)
Processed meat	1.68 (0.99–2.86)	1.70 (0.98–2.93)	1.54 (0.85–2.80)	0.242	1.05 (0.92–1.21)
White meat	1.45 (0.91–2.31)	0.84 (0.48–1.46)	1.50 (0.91–2.47)	0.289	1.05 (0.90–1.21)
Intestinal GC					
Women (252 cases)					
Red meat	0.76 (0.51–1.13)	0.91 (0.61–1.37)	0.77 (0.49–1.21)	0.447	0.96 (0.78–1.17)
Processed meat	1.19 (0.82–1.73)	1.11 (0.75–1.66)	1.69 (1.12–2.56)	0.024	1.16 (0.98–1.37)
White meat	1.20 (0.80–1.78)	1.27 (0.85–1.91)	1.46 (0.97–2.22)	0.074	1.10 (0.96–1.24)
Men (372 cases)					
Red meat	1.13 (0.80–1.58)	1.30 (0.91–1.86)	1.06 (0.70–1.59)	0.677	1.00 (0.88–1.14)
Processed meat	1.41 (1.03–1.92)	1.43 (1.03–1.99)	1.46 (1.01–2.12)	0.058	1.10 (1.00–1.21)
White meat	1.19 (0.87–1.62)	0.85 (0.61–1.19)	1.11 (0.8–1.53)	0.938	0.97 (0.87–1.08)

(Continues)

TABLE 4 | (Continued)

	HR (95% CI)				HR (95% CI)
	Quartile 2	Quartile 3	Quartile 4	*p*-trend	Continuous
Diffuse GC					
Women (117 cases)					
Red meat	0.65 (0.36–1.18)	0.8 (0.44–1.45)	0.93 (0.48–1.81)	0.901	1.13 (0.85–1.50)
Processed meat	1.00 (0.57–1.75)	1.11 (0.63–1.98)	1.11 (0.6–2.07)	0.666	0.97 (0.77–1.24)
White meat	0.85 (0.47–1.51)	1.21 (0.68–2.15)	1.11 (0.6–2.06)	0.439	1.13 (0.94–1.36)
Men (91 cases)					
Red meat	1.30 (0.69–2.48)	0.94 (0.46–1.94)	1.07 (0.48–2.34)	0.844	0.90 (0.68–1.18)
Processed meat	1.51 (0.71–3.20)	1.57 (0.74–3.37)	2.23 (1.02–4.88)	0.047	1.11 (0.95–1.31)
White meat	0.83 (0.47–1.45)	0.50 (0.25–0.97)	0.68 (0.36–1.28)	0.119	0.88 (0.70–1.11)
EAC					
Women (46 cases)					
Red meat	1.53 (0.43–5.50)	2.79 (0.82–9.48)	2.57 (0.71–9.26)	0.114	1.17 (0.82–1.65)
Processed meat	1.01 (0.39–2.59)	1.97 (0.79–4.91)	1.67 (0.58–4.80)	0.146	1.35 (0.99–1.85)
White meat	1.66 (0.54–5.15)	2.19 (0.73–6.55)	2.04 (0.65–6.41)	0.229	1.11 (0.84–1.48)
Men (196 cases)					
Red meat	0.92 (0.58–1.48)	0.53 (0.31–0.92)	0.70 (0.39–1.25)	0.125	0.92 (0.76–1.11)
Processed meat	1.72 (1.07–2.79)	1.89 (1.15–3.12)	2.24 (1.29–3.89)	0.005	1.09 (0.95–1.24)
White meat	1.18 (0.74–1.87)	0.87 (0.53–1.44)	0.96 (0.58–1.58)	0.559	1.03 (0.90–1.19)

Note: Continuous variables: HRs (95% CIs) correspond to an increase of 40 g/day for red meat, 30 g/day for processed meat and 20 g/day for white meat. Mutually adjusted model: model stratified by age and center and adjusted for energy intake, educational level, tobacco smoking, body mass index, and alcohol consumption, with red meat, processed meat and white meat mutually adjusted.
Abbreviations: EAC, esophageal adenocarcinoma; GC, gastric cancer.

cooking in red/processed and white meat pose additional concerns [34].

For processed meat, processing and storage methods are also important factors that can increase the risk of GC and EAC [10, 24]. In this context, processed meat consumption contributes to a higher intake of salt, which has been shown to irritate the gastric mucosa and trigger significant gastric damage and inflammation [35].

Concerning the intake of white meat and its association with the risk of GC, results remain controversial. Some studies have shown an inverse association between white meat consumption and this type of cancer [24]. This may be attributed to white meat's lower levels of heme iron compared to red meat, potentially suppressing the endogenous formation of N-nitroso compounds (NOCs) [25]. Additionally, white meat is a source of polyunsaturated fatty acids (PUFAs) and contains lower levels of cholesterol and saturated fats than red meat [36]. Some PUFAs may help limit chronic mucosal inflammation through apoptosis and their anti-inflammatory activity [37], potentially lowering the risk of GC [38]. However, other studies have shown a positive association between the consumption of this type of meat and the risk of GC; Boldo et al. [33] reported an increased risk of NCGA and intestinal tumors among consumers of well-done white or red meat. Furthermore, other cooking methods, such as stewing and baking, appeared to have the most pronounced effects on GC risk related to white meat [33]. The proposed mechanisms for this positive association include the formation of high levels of mutagens during high-temperature cooking or prolonged cooking of both red and white meat [39, 40]. However, an alternative hypothesis to explain the observed increase in risk with white meat could relate to the higher protein content and amino acids such as methionine found in white meat [34, 41–42]. These compounds, when metabolized, may lead to the production of reactive oxygen species (ROS) and nitrogen species, which have been implicated in DNA damage and cancer development. Additionally, white meat consumption may influence the gut microbiota, promoting the growth of bacteria that produce metabolites capable of damaging the gastrointestinal lining, potentially contributing to carcinogenesis. Emerging evidence suggests that a diet high in animal proteins, including those from white meat, can lead to shifts in the gut microbiota, increasing the abundance of pro-inflammatory bacteria, such as *Bacteroides* and *Firmicutes*, while decreasing beneficial bacteria, such as *Lactobacillus* [42]. These microbiota alterations are thought to create a more pro-inflammatory environment in the gut, which may increase the risk of gastrointestinal cancers [42]. Moreover, high-temperature cooking methods, which are

commonly used for preparing white meat, generate carcinogenic compounds such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) [34]. This could contribute to the observed association between white meat consumption and an increased risk of GC. Thus, while white meat is often considered healthier compared to red or processed meats, the potential for increased cancer risk due to protein metabolism, microbiota alterations, and cooking methods warrants further investigation.

This study offers several strengths, such as its prospective design, large sample size, extended follow-up and analysis by tumor subtypes, which addresses the association between meat consumption and GC subtypes—a topic rarely examined in prospective studies [2]. On the other hand, some limitations include imprecise estimates for food intake derived from FFQs [20], which may affect the accuracy of dietary assessments. Additionally, the potential impact of *Helicobacter pylori* infection on the study outcomes was not addressed, which could confound the results. Although our study lacks data on *Helicobacter pylori* infection status, this limitation may be mitigated by the fact that current serological tests do not always reflect past exposure, due to possible clearance or seroreversion over time [43]. Furthermore, previous large-scale studies have shown that adjusting for *Helicobacter pylori* infection does not materially alter the association between meat intake and GC risk, suggesting our findings remain robust despite this limitation [44]. Finally, the assumption that participants maintained a consistent diet from the beginning of the study may introduce bias, as dietary habits can change over time and may not accurately reflect their true dietary intake throughout the study period; however, sensitivity analyses were conducted to help mitigate these biases.

In conclusion, consumption of processed meat is associated with an increased risk of GC and EAC. Surprisingly, white meat intake was significantly associated with the risk of NCGC among women that requires further validation. Future studies should elucidate the underlying mechanisms and inform dietary guidelines to reduce cancer risk.

Author Contributions

Catalina Bonet: methodology, writing – review and editing, writing – original draft, formal analysis. **Lucía Rizzolo-Brime:** formal analysis. **Sara Montañés:** formal analysis. **Mariem Hajji:** writing – review and editing. **Chloé Marques:** writing – review and editing. **Gianluca Severi:** writing – review and editing. **Matthias B Schulze:** writing – review and editing. **Christina C. Dahm:** writing – review and editing. **Anne Tjønneland:** writing – review and editing. **Anja Olsen:** writing – review and editing. **Maria S. De Magistris:** writing – review and editing. **Valeria Pala:** writing – review and editing. **Alberto Catalano:** writing – review and editing. **Guri Skeie:** writing – review and editing. **Magritt Brustad:** writing – review and editing. **Torill Enget Jensen:** writing – review and editing. **Maria-José Sánchez:** writing – review and editing. **Marcela Guevara:** writing – review and editing. **Natalia Cabrera Castro:** writing – review and editing. **Keren Papier:** writing – review and editing. **Elisabete Weiderpass:** writing – review and editing. **Viktoria Knaze:** writing – review and editing. **Jin Young Park:** writing – review and editing. **Gwen Murphy:** writing – review and editing. **Antonio Agudo:** conceptualization, investigation, methodology. **Paula Jakszyn:** conceptualization, investigation, writing – review and editing, supervision, methodology.

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Disclosure

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Ethics Statement

This EPIC study was approved by the ethics committees of all participating centers and by the IARC ethics committee. All participants gave informed signed consent for study participation, including access to medical records.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The study is based on EPIC cohort data. Aggregated data and further information are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Meat consumption in EPIC (g/day). **Table S2:** Meat consumption in EPIC—Pearson Correlations. **Table S3:** Adjusted hazard ratios (HRs) and 95% CI for meat intake and gastric cancer by anatomic and histological subtypes in the EPIC population (models not mutually adjusted). **Table S4:** Adjusted hazard ratios (HRs) and 95% CI for meat intake and gastric cancer by anatomic and histological subtypes in the EPIC population, excluding gastric cancer cases diagnosed during the first 2 years of follow-up. **Table S5:** Adjusted hazard ratios (HRs) and 95% CIs for meat intake and gastric cancer and esophageal adenocarcinoma in the EPIC population according to follow-up time.