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Meat intake and risk of gastric cancer in the Stomach cancer Pooling (StoP) Project

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Abstract

The consumption of processed meat has been associated with non-cardia gastric cancer, but evidence regarding a possible role of red meat is more limited. This study aims to quantify the association between meat consumption, namely white, red and processed meat, and the risk of gastric cancer, through individual participant data meta-analysis of studies participating in the 'Stomach cancer Pooling (StoP) Project'.

Data from 22 studies, including 11,443 cases and 28,029 controls, were used. Study-specific odds ratios (ORs) were pooled through a two-stage approach based on random-effects models. An exposure-response relationship was modelled, using one and two-order fractional polynomials, to evaluate the possible non-linear association between meat intake and gastric cancer.

An increased risk of gastric cancer was observed for the consumption of all types of meat (highest vs. lowest tertile), which was statistically significant for red (OR: 1.24; 95%CI: 1.00–1.53), processed (OR: 1.23; 95%CI: 1.06–1.43) and total meat (OR: 1.30; 95%CI: 1.09–1.55). Exposure-response analyses showed an increasing risk of gastric cancer with increasing consumption of both processed and red meat, with the highest OR being observed for an intake of 150 g/day of red meat (OR: 1.85; 95%CI: 1.56–2.20).

This work provides robust evidence on the relation between the consumption of different types of meat and gastric cancer. Adherence to dietary recommendations to reduce meat consumption may contribute to a reduction in the burden of gastric cancer.

Introduction

Gastric cancer incidence has long been falling and is expected to decline in the next years.[1] Nevertheless, mortality rates remain high, placing gastric cancer as the third cause of oncological death worldwide.[2]

Dietary patterns have been associated with the risk of gastric cancer,[3] but the role of specific food groups is generally less clear.[4] Meat can be an important part of a balanced diet since it provides essential nutrients, such as proteins, amino acids, vitamins and other micronutrients.[5, 6] However, it can also represent a source of compounds, such as heterocyclic amines, polycyclic aromatic hydrocarbons, N-nitroso compounds and heme iron, which have the potential to increase the risk of cancer.[7, 8] In 2015, the International Agency for Research on Cancer classified processed meat (smoked and salted goods) as "carcinogenic to humans" and the "consumption of red meat" as "probably carcinogenic to humans" based essentially on data for colorectal cancer.[9] More recently, the World Cancer Research Fund (WCRF) revised its Report on Diet, Nutrition, Physical Activity and Stomach Cancer, and concluded that there was suggestive evidence supporting a probable causal link between processed meat and non-cardia cancers,[10] but for red meat no pooled analyses were available in that revision.[10]

The aim of this study is to quantify the association between meat consumption, namely white, red and processed meat, and the risk of gastric cancer, through individual participant data meta-analysis of studies participating in the 'Stomach cancer Pooling (StoP) Project'.

Material and Methods

Study population

This study is based on the second release of the StoP Project dataset, which included 30 case-control studies, or case-control analyses nested within cohort studies, for a total of 14,016 cases of gastric cancer (9,247 men, 4,769 women) and 33,704 controls (20,352 men and 13,352 women). The StoP Project aims at examining the role of several lifestyles and genetic determinants in the etiology of gastric cancer through pooled analyses of individual-level data, after central collection and validation of the original data sets. For each study, a completion of a study description form providing information on the study characteristics was asked. Investigators who agreed to participate provided a signed DTA and, thereafter, the complete original data set; investigators not wishing to share the complete data set were invited to provide a set of core variables including, among others, age, sex, education/ social class, smoking habits, family history of gastric cancer, selected variables, as well as markers of *H. pylori* infection, whenever available. In addition to the data sets, the original questionnaires and any useful information to help with data handling (codebooks, labels, etc.) was collected from the participating studies, to optimize data harmonization. All data were harmonized at the pooling center, according to a pre-specified format; the whole body of information was divided into several sections (e.g. sociodemographic characteristics, smoking habits, lifetime alcohol use, physical activity, etc.), and, for each topic, a project codebook was created reporting which variables were present in each study, their names and codes. The data for the core variables were standardized among studies, as well as for the variables for selected topics of interest. The StoP Project received ethical approval from the University of Milan Review Board (reference 19/15 on 01/04/2015), and detailed information on the overall aims and methods has been given elsewhere.[11]

For the present analyses, individual-level data from 22 studies with information on meat intake was used, including 11,443 cases and 28,029 controls, from Brazil (two studies),[12, 13] Canada,[14] China (two studies),[15, 16] Greece,[17] Iran,[18] Italy (four studies),[19–22] Japan (three studies),[23–25] Mexico (three studies),[26–28] Portugal,[29] Russia,[30] Spain (two studies),[31, 32] and the USA.[33]

Variables defining the exposure

All studies assessed the participants' dietary habits through food frequency questionnaires (FFQ) focusing on diet in periods of one, two, three or five years before diagnosis (for cases), onset of disease or hospital admission (for hospital-based controls) or recruitment (for population-based controls). Twelve of the included studies reported that the questionnaire used was previously validated by comparison with multiple 24-hour recall interviews and/or diet records (Supplementary Table 1).These FFQs included between 15 and 147 individual food and beverage items frequently consumed in each country (Supplementary Table 1).

Food items identified as "chicken", "turkey" and "rabbit" were classified as white meat. Those identified as "beef", "pork", other non-poultry meat (e.g. "lamb"), as well as mammalian offals (such as "liver") were considered red meat. All meat items that had undergone some form of transformation (salting, curing, smoking, fermentation or other processes to enhance flavor or improve preservation) including those identified as “sausages”, “bacon”, “ham”, “cold cuts”, “croquettes” and “hot dogs” were classified as processed meat, regardless of including white or red meat.[34]

Statistical analysis

Study-specific frequency of consumption of each food item or group was converted into g/day, according to the information available in each questionnaire or country specific dietary standards (Brazilian[35] studies), and categorized into tertiles on the basis of the study-specific distribution in the controls.

To quantify the associations between gastric cancer and white, red, processed, and total meat intake, both two- and one-stage modeling approaches were used.[36]

For the two-stage analysis, the association between meat intake and gastric cancer was first assessed by estimating the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for each study, using multivariable unconditional logistic regression models. Considering that the proportion of missing data was low, a complete case approach was adopted. Models included, when available and applicable, terms for sex, age (5-year age groups: <40;40–44; …; 70–74; ≥75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11 to 20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: >12 to 47 g of ethanol/day, high: >47 g of ethanol/day), fruits and vegetables consumption (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies), race/ethnicity (“White”, “Black/African American”, “Asian”, “Hispanic/Latino”, “Other”), body mass index (BMI) categories (<18.5, 18.5–25, 25–30, >30 kg/m^2) and family history of gastric cancer (Supplementary Table 2). Then, summary (pooled) effects estimates were computed as weighted averages of each study’s ORs, using random-effects models.[37] This was performed for the comparison between the second and third study-specific tertile, with the first as the reference category.

Heterogeneity between studies was tested using the Q test statistics and quantified using I^2, i.e. the percentage of the total variation across studies that is due to heterogeneity rather than chance.[38]

Stratified analyses were carried out to investigate the effect of high consumption of each type of meat across strata of selected covariates, including sex, age, geographic area of the studies, socioeconomic status, smoking status, alcohol drinking, BMI categories, family history of gastric cancer, but also according to and type of controls (hospital-based, population-based), cancer anatomical location (cardia, non-cardia) and histological type (intestinal, diffuse and undifferentiated, as defined by the Lauren classification). For the analyses according to cancer subsite and histological type we used multinomial logistic regression models to estimate the ORs for each type of cancer separately (i.e., cardia and non-cardia or intestinal and diffuse). The difference between groups was assessed through the Q test for heterogeneity.[38] Sensitivity analyses were performed by excluding one study at a time, and by defining the same categories of exposure for all studies: initially using tertiles of the distribution of meat consumption in all controls as cut-offs to define the categories; then, since the maximum amounts of intake recommended by the WCRF are 300 g/week for red meat and 50 g/week for processed meat, using cut-offs that describe intakes of less than half of the recommended intake, between half and the recommended amount, or more than the recommended amount, resulting in three categories of exposure. Additionally, adjusted and unadjusted estimates for total energy intake, as well as for *H. pylori* infection status were compared, among studies with information on these variables.

A one-stage strategy of analysis was used to assess the significance of a linear trend, by considering the variables defining meat intake as continuous,[39] and to model the functional form of the relation between the daily amount (g) of meat consumed (continuous) and gastric cancer risk. The latter was accomplished through first- and second-order fractional polynomial models, including study center and the core variables used in the main analysis as covariates; this family of models includes the predefined set of power terms P={−2;−1;−0.5;0;1;0.5;2;3}, where P=0 means Log(X) and the linear model has P=1. The best-nonlinear fitting model, i.e., the one minimizing the model difference with respect to the linear model, was selected.[40]

Data availability

The data that support the findings of this study are available from the Stomach cancer Pooling (StoP) Project but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Steering Committee of the StoP Project.

Results

Tables 1 and 2 describe the main characteristics of the 11,443 cases and 28,029 controls considered for the present analysis. The median meat intake among controls ranged between 0.3 and 38.7 g/day for white meat, between 21.4 and 99.5 g/day for red meat and between 0.0 and 26.9 g/day for processed meat; gastric cancer cases generally presented higher levels of consumption, particularly for red meat and among studies from the Americas (median intake: 61.3 g/day) (Table 1). Compared to controls, cases had higher proportions of men (65.1 vs 59.4%) and individuals who were older (45.6 vs 39.8% over 65 years of age), with low socioeconomic status (50.4 vs 36.8%), current smokers (29.9 vs 25.9%) or alcohol drinkers (59.2 vs 51.9%) (Table 2).

Pooled ORs and corresponding 95%CIs for the association between meat consumption and gastric cancer are presented in Table 3 and Figure 1. The odds were significantly higher for the highest versus the lowest tertile of red (OR: 1.24; 95%CI: 1.00–1.53), processed (OR: 1.23; 95%CI: 1.06–1.43) and total meat intake (OR: 1.30; 95%CI: 1.09–1.55).

Table 4 presents the results from the stratified analyses. For most of the strata considered, there was an increased risk of gastric cancer with a high intake of all types of meat analyzed. The only significant difference across strata was observed for processed meat, regarding the geographic area of the studies; the strongest associations were observed among the American (OR: 1.45; 95% CI: 1.15–1.84) and the European studies (OR: 1.28; 95% CI: 1.02–1.60), whereas in Asian studies there was no significant association (OR: 0.98; 95% CI: 0.80–1.20).

When considering results adjusted for total energy intake, heterogeneity tended to be lower and the association remained significant for processed (OR: 1.16; 95% CI: 1.00–1.35) and total meat intake (OR: 1.22; 95% CI: 1.06–1.41). Regarding adjustment for *H. pylori* infection, it also contributed to lower heterogeneity, though no significant associations were observed. (Table 4). The main findings remained unchanged after further sensitivity analyses (Supplementary Tables 3 and 4 and Supplementary Figure 1), though heterogeneity decreased slightly when defining the same categories of exposure for all studies, either using the overall distribution in all controls (Supplementary Table 3) or the amounts recommended by the WCRF (Supplementary Table 4).

The dose-response relationships between the intake of red and processed and gastric cancer are depicted in Figure 2A and 2B, respectively. There is a trend towards increased gastric cancer risk with a higher consumption of red and processed meat, with an OR of 1.85 (95% CI: 1.56–2.20) for the consumption of 150 g/day of red meat, and an OR of 1.38 (95% CI: 1.28–1.49) for the consumption of 50 g/day of processed meat.

Discussion

This study was based on an individual participant data approach, which constitutes the gold standard in evidence synthesis, allowing us to better quantify than previously available reports an increased risk of gastric cancer with high intakes of meat, particularly red and processed meat. This was further confirmed through the computation and graphical depiction of the exposure-response association.

Previous studies have shown positive and significant associations between high intakes of red and processed meat and gastric cancer. Compared to meta-analyses of cohort studies, our estimates are higher (Zhu *et al*.,[41]relative risk [RR] for the highest vs lowest intake of red meat 1.05 [95% CI: 0.87–1.27]; Song *et al.,*[42] RR for the highest vs lowest intake of red meat 1.00 [95% CI: 0.82–1.20]; Zhao *et al*.,[43] RR for the highest vs lowest intake of red meat 1.14 [95% CI: 0.97–1.34] and RR for the highest vs lowest intake of processed meat 1.23 [95% CI: 0.98–1.55]; Kim *et al*,[44] RR for the highest vs lowest intake of red meat 1.03 [95%CI: 0.83–1.28] and RR for the highest vs lowest intake of processed meat 1.24 [95%CI: 1.04–1.47]). Nevertheless, the estimates obtained in this study are of lower magnitude than those from the previous meta-analyses of case-control studies: Zhu *et al*[41] found RR estimates of 1.63 (95% CI: 1.33–1.99) for red meat and 1.64 (95% CI: 1.47–1.83) for processed meat from a total of 13 and 18 case-control studies, respectively; Song *et al*[42] had a relative risk estimate of 1.59 (95% CI:1.34–1.89) for red meat with 18 studies; Zhao *et al*[43], with 20 case-control studies for red meat and 25 for processed meat, obtained even higher estimates (red meat: 1.67 [95% CI: 1.36–2.05]; processed meat: 1.76 [95% CI: 1.51–2.05] and, most recently, Kim *et al*,[44] with 20 case-control studies for red meat and 23 for processed meat obtained estimates similar to those from Zhao *et al* (red meat: 1.57 [95%CI:

1.30–1.89]; processed meat: 1.79 [95%CI: 1.51–2.12]). We have previously observed that, both smoking and alcohol drinking, the estimates obtained from the StoP Project were lower than the ones found in previous meta-analyses of case-control studies,[45, 46] which is likely a reflection of the methodological strengths of individual participant data pooled analyses in terms of a more uniform strategy of analysis across studies, including control of confounding and reduction of publication bias.

The higher concentration of carcinogenic compounds such as heme iron[47] and N-nitroso compounds[8] present in red and processed meat contributes to explain the higher OR estimates obtained for these food groups compared with those for white meat. Furthermore, the type of processing determines the degree of carcinogenicity,[48] with smoking and grilling of meats resulting in the formation of more polycyclic aromatic hydrocarbons, heterocyclic amines and other carcinogens.[49] An additional hypothesis was bacterial plasmids (DNA) from meat, namely from dairy cattle, which may contribute to chronic inflammation and, in the long term, promote carcinogenesis.[50]

Regional differences, in particular higher estimates for American and European countries, were observed. Though previous meta-analyses have shown an increased risk of gastric cancer for higher consumptions of meat regardless of the geographic region, Asian studies tend to present the lowest estimates.[41, 42, 44] The different dietary patterns between geographical regions, which determine the exposure to different amounts and types of meat, can help explain the geographic differences; as well as methodological issues of the studies included in previous meta-analyses, namely regarding control of confounding. In our study, Asian studies are those that present, for all types of meat considered, lower median values of consumption, which may contribute to the lower estimate obtained compared with the other studies where consumption is higher. Also, the variability in the detail, definition and assessment of dietary exposures across countries also contributes to the regional differences and to the high heterogeneity observed for all estimates in the present study, as well as in other investigations on dietary factors.[51] Although most studies within the StoP Project used validated FFQs, and the methods used to obtain dietary information and some of the dietary items included in the questionnaires were similar among studies, there are considerable differences concerning the dietary patterns within each study. Nevertheless, stratified and sensitivity analyses did not result in significant changes in cancer risk estimates for all types of meat considered. However, we observed slight lower heterogeneity particularly when adjusting for total energy intake and when considering the same cut-offs for all studies.

This work adds to previous evidence by providing pooled OR estimates for different types of meat, including the characterization of the exposure-response relationships. Our results provide additional evidence that adherence to the dietary recommendations to reduce meat consumption, as those from the WCRF, is likely to contribute to a reduction in the burden of gastric cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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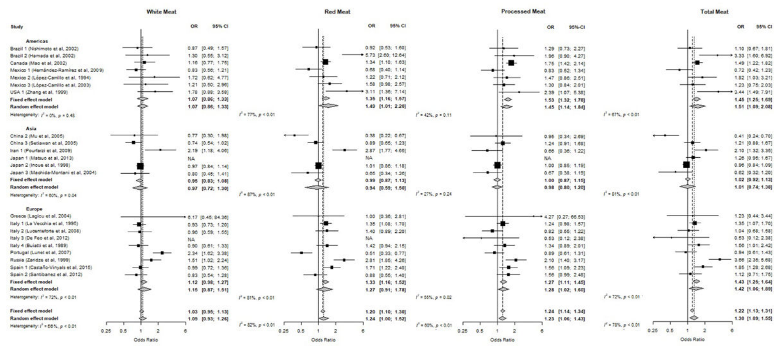
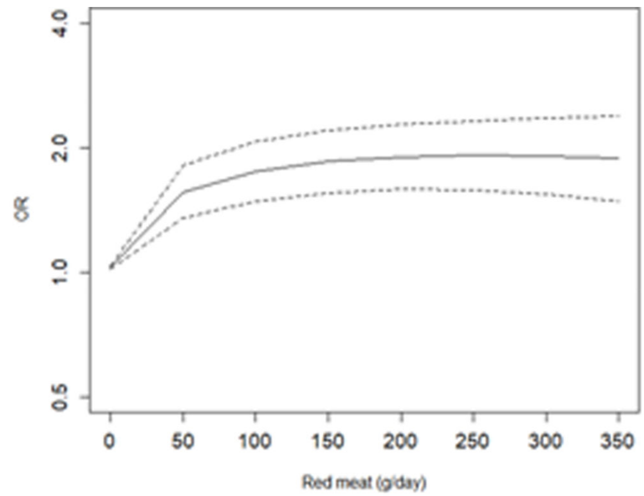


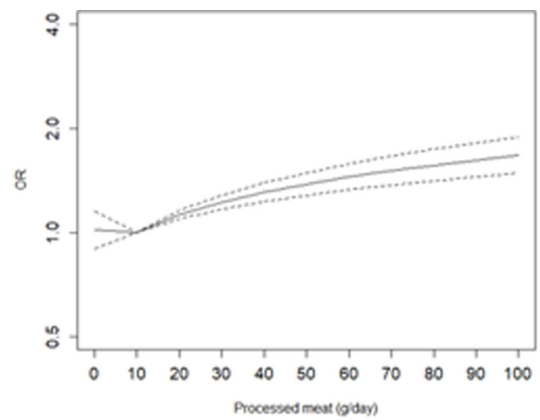
Figure 1.

Study-specific and pooled odds ratio (ORs) and corresponding 95% confidence intervals (CI) of gastric cancer risk for the highest tertile of meat (white, red, processed and total meat) consumption compared to the lowest tertile.

NA – not available; OR – Odds ratio; 95%CI – 95% confidence interval; USA – United States of America



$$\ln(OR) = 0.814\left(\frac{g\ of\ red\ meat/day + 0.1}{100}\right)^{0.5} - 0.254\left(\frac{(g\ of\ red\ meat/day) + 0.1}{100}\right)$$



$$\ln(OR) = 0.147\ln\left(\frac{g\ of\ processed\ meat\ /day + 0.1}{10}\right) + 0.033\left(\ln\left(\frac{g\ of\ processed\ meat/day + 0.1}{10}\right)\right)^2$$

Figure 2.

Relation between red (A) and processed (B) meat (g/day) and risk of gastric cancer fitted by a fractional polynomial.

OR – odds ratio

Table 1.

Median and interquartile range (grams per [g/] day) of white, red and processed meat intake, by case-control status and study.

	Cases (n=*11,443*)					Controls (n=*28,029*)				
	N	%	Median (P25-P75) g/day			N	%	Median (P25-P75) g/day		
			White	Red	Processed			White	Red	Processed
Study center										
America	*2,324*	*20.3*	*20.0 (9.0–48.6)*	*61.3 (32.4–100.0)*	*13.9 (4.0–27.6)*	*7,261*	*25.9*	*16.2 (9.7–48.6)*	*56.2 (31.4–88.6)*	*11.9 (3.2–24.8)*
Brazil 1[13]	226	2.0	20.0 (20.0–50.0)	78.0 (48.0–100.0)	0.0 (0.0–26.5)	226	0.8	20.0 (20.0–50.0)	99.5 (50.0–100.0)	0.0 (0.0–26.5)
Brazil 2[12]	93	0.8	50.0 (20.0–50.0)	85.0 (50.0–100.0)	0.0 (0.0–26.5)	186	0.7	20.0 (20.0–50.0)	50.0 (20.0–100.0)	0.0 (0.0–26.5)
Canada [14]	1,171	10.2	16.2 (16.2–48.6)	71.4 (40.0–104.8)	19.1 (8.9–33.7)	5,019	17.9	16.2 (16.2–48.6)	63.8 (39.0–97.2)	14.7 (4.7–26.6)
Mexico 1[26]	248	2.2	26.9 (9.0–26.9)	38.6 (21.8–64.7)	7.6 (2.8–15.1)	478	1.7	26.9 (9.0–26.9))	30.3 (14.5–54.9)	6.6 (2.3–12.7)
Mexico 2[28]	220	1.9	29.1 (29.1–29.1)	48.6 (32.2–81.4)	14.9 (6.9–28.2)	752	2.7	29.1 (9.7–29.1))	43.4 (26.5–71.2)	12.4 (4.1–24.4)
Mexico 3[27]	234	2.0	8.9 (4.5–26.8)	42.4 (16.8–77.5)	6.4 (2.3–12.9)	468	1.7	8.9 (4.5–26.8)	36.7 (12.1–71.3)	5.8 (2.1–10.0)
USA 1[33]	132	1.2	1.4 (0.0–6.7)	42.2 (21.2–83.9)	15.7 (4.5–31.9)	132	0.5	0.3 (0.0–3.3)	25.8 (7.1–50.3)	6.1 (1.3–18.3)
Asia	*5,054*	*44.2*	*10.5 (3.5–10.5)*	*26.6 (12.6–38.9)*	*1.8 (0.0–5.3)*	*10,826*	*38.6*	*10.5 (3.5–10.5)*	*26.6 (12.6–37.8)*	*1.7 (0.0–5.3)*
China 2[15]	182	1.6	0.4 (0.0–3.3)	25 (10.4–42.9)	0.8 (0.0–12.5)	403	1.4	2.5 (0.3–6.9)	36.9 (14.6–68.8)	0.4 (0.0–14.3)
China 3[16]	692	6.1	5.0 (2.2–10.0)	31.9 (15.9–59.5)	5.0 (1.4–10.0)	686	2.5	6.7 (3.3–13.3)	40.0 (19.3–66.2)	3.6 (1.1–10.0)
Iran 1[18]	216	1.9	21.0 (21.0–50.0)	50 (21.0–250.0)	0.0 (0.0–0.0)	393	1.4	21.0 (21.0–50.0)	35.5 (21.0–50.0)	0.0 (0.0–0.0)
Japan 1[24] [*1*]	1,260	11.1		27.0 (18.5–42.5)		3,914	14,0		27.0 (17.5–42.5)	
Japan 2[23]	2,551	22.3	10.5 (3.5–10.5)	26.6 (12.6–37.8)	1.8 (0.0–5.3)	5,127	18.4	10.5 (3.5–10.5)	26.6 (12.6–37.8)	1.8 (0.0–5.3)1
Japan 3[25]	153	1.3	6.7 (2.3–14.7)	41.7 (28.3–61.2)	4.3 (1.5–10.3)	303	1.1	7 (2.3–15.0)	45.8 (25.8–71.4)	5.2 (2.0–11.2)
Europe	*4,065*	*35.5*	*25.7 (14.3–42.9)*	*49.1 (28.1–66.8)*	*21.4 (10.7–38.3)*	*9,942*	*35.5*	*21.6 (14.3–35.2)*	*38.1 (21.4–58.7)*	*21.4 (10.7–34.6)*

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	Cases (n=*11,443*)					Controls (n=*28,029*)				
	N	%	Median (P25-P75) g/day			N	%	Median (P25-P75) g/day		
			White	Red	Processed			White	Red	Processed
Greece[17]	110	1.0	14.3 (14.3–28.6)	44.5 (28.6–71.4)	0.0 (0.0–1.7)	100	0.4	14.3 (8.8–28.6)	42.9 (28.6–57.1)	0.0 (0.0–1.7)
Italy 1[19]	769	6.7	28.6 (14.3–28.6)	46.4 (32.1–71.4)	28.6 (17.9–39.3)	2,081	7.4	28.6 (14.3–28.6)	46.4 (28.6–60.7)	25.0 (14.3–35.7)
Italy 2[20]	230	1.2	14.3 (7.1–14.3)	25 (17.9–32.1)	14.3 (10.7–17.9)	547	2.0	14.3 (7.1–14.3)	21.4 (14.3–28.6)	14.3 (10.7–17.9)
Italy 3[21]	133	1.2	NA	NA	23.8 (12.2–41.6)	400	1.4	NA	NA	21.4 (21.4–57.1)
Italy 4[22]	1,016	8.9	27.1 (14.5–40)	55.4 (36.0–77.4)	28.3 (15.0–48.6)	1,159	4.1	28.6 (14.6–38.6)	48.7 (33.1–69.3)	23.8 (12.2–41.6)
Portugal[29]	633	5.5	42.8 (25.1–59.4)	51.4 (25.7–59.4)	8.6 (1.4–18.6)	1,600	5.7	33.7 (17.1–59.4)	51.4 (25.7–77.1)	8.7 (3.1–18.6)
Russia[30]	446	3.9	21.4 (13.4–42.9)	48.3 (28.1–77.7)	23.2 (10.7–39.7)	607	2.2	21.4 (6.7–42.9)	40.3 (20.1–64.3)	17.1 (7.4–35.4)
Spain 1[31]	330	2.9	20.7 (14.5–30.5)	32.0 (20.5–50.6)	32.6 (20.5–55.6)	2,993	10.7	18.9 (12.7–26.6)	26.5 (15.5–42.9)	26.9 (15.5–42.1)
Spain 2[32]	398	3.5	37.6 (25.4–44.3)	53.8 (24.6–60.5)	24.8 (15.8–31.8)	455	1.6	38.7 (32.2–44.3)	53.8 (24.2–60.5)	24.8 (14.3–30.1)

NA – not available; P25-P75 – percentile 25- percentile 75; USA – United States of America

*[1]*Only total meat available.

Table 2.

Distribution of gastric cancer cases and controls according to sex, age and other selected covariates.

	Cases		Controls	
	N	**%**	**N**	**%**
Sex				
Male	7,448	65.1	16,650	59.4
Female	3,995	34.9	11,379	40.6
Age				
<40	496	4.3	2,113	7.5
40–45	479	4.2	1,679	6.0
45–50	781	6.8	2,254	8.0
50–54	1,128	9.9	2,969	10.6
55–59	1,538	13.4	3,552	12.7
60–64	1,803	15.8	4,289	15.3
65–69	2,028	17.7	4,525	16.1
70–74	1,824	15.9	3,779	13.5
≥75	1,366	12.0	2,869	10.2
Socioeconomic status [1]				
Low	4,486	50.4	8,433	36.8
Intermediate	2,416	27.2	6,955	30.4
High	1,156	13.0	5,099	22.3
Missing	*834*	*9.4*	*2,415*	*10.5*
History of stomach cancer in first degree relatives [2]				
No	6,495	73.2	16,330	79.2
Yes	1,376	15.5	1,982	9.6
Missing	*1,007*	*11.3*	*2,314*	*11.2*
Vegetables and fruit intake [3]				
Low	3,840	33.6	8,515	30.4
Intermediate	3,938	34.4	9,737	34.7
High	3,647	31.8	9,484	33.8
Missing	*18*	*0.2*	*293*	*1.1*
Total energy intake [4]				
1st quintile	1,120	17.2	3,123	19.8
2nd quintile	1,172	18.4	3,133	19.9
3rd quintile	1,228	18.8	3,135	19.9
4th quintile	1,268	19.5	3,136	19.9
5th quintile	1,501	23.1	3,137	19.9
Missing	*198*	*3.1*	*72*	*0.5*
Body Mass Index (kg/m^2) [5]				
<18.5	533	4.9	826	3.1

	Cases		Controls	
	N	%	N	%
18.5–25	5,605	51.3	13,360	49.4
25–30	2,707	24.8	7,693	28.5
>30	1,446	13.2	3,197	11.8
Missing	*639*	*5.9*	*1,953*	*7.2*
Cigarette smoking				
Never	4,670	40.9	12,787	45.7
Former	3,063	26.8	7,626	27.2
Current (cigarettes/day)				
≤10	775	6.8	2,208	7.9
11–20	1,607	14.1	3,164	11.3
>20	1,026	9.0	1,867	6.7
Missing	*281*	*2.5*	*343*	*1.2*
Alcohol intake				
Never	3,810	37.8	10,803	43.5
Low (≤12 g of ethanol/day)	2,423	24.1	5,283	21.3
Intermediate (>12–47 g of ethanol/day)	2,497	24.8	5,582	22.4
High (>47 g of ethanol/day)	1,036	10.3	2,035	8.2
Missing	*302*	*3.0*	*1,145*	*4.6*

[1] No information for the study Japan 2.[23] As defined in each original study based on education, income or occupation.

[2] No information for the studies Canada,[14] China 3,[16] Mexico 1,[26] Mexico 2[28] and Mexico 3.[27]

[3] Defined according to study-specific tertiles.

[4] No information for the studies Canada,[14] China 2,[15] Russia,[30] Iran 1,[18] Japan 2,[23] Brazil 1[13] and Brazil 2.[12]

[5] No information for the studies Mexico 2, Mexico 3, Brazil 1[13] and Brazil 2.[12]

Table 3.

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to tertiles of meat consumption (grams per [g/] day).

	Cases			Controls			OR (95% CI) [1]	I^2 (%)
	N	%	g/day Median (P25-P75)	N	%	g/day Median (P25-P75)		
White meat [2]								
1st tertile	4,074	40.5	7.1 (3.3–15.4)	9,771	41.2	7.6 (3.5–16.2)	1	
2nd tertile	3,697	36.8	20.9 (10.5–29.1)	9,070	38.3	22.7 (10.5–44.3)	1.01 (0.92–1.11)	28.2
3rd tertile	2,093	20.8	42.9 (25.0–59.4)	4,578	19.3	40.9 (25.0–57.1)	1.09 (0.93–1.26)	56.4
Missing	*186*	*1.9*		*296*	*1.3*			
P value for trend							0.473	
Red meat [2]								
1st tertile	3,158	31.4	13.4 (7.1–24.2)	8,146	34.4	14.3 (7.1–23.8)	1	
2nd tertile	3,922	39.0	37.8 (29.9–51.4)	9,107	38.4	39.1 (28.8–51.4)	1.16 (1.02–1.32)	59.8
3rd tertile	2,961	29.5	88.6 (64.6–113.4)	6,446	27.2	88.6 (61.0–113.4)	1.24 (1.00–1.53)	82.3
Missing	*9*	*0.1*		*16*	*0.1*			
P value for trend							<0.001	
Processed meat [3]								
1st tertile	4,060	39.7	1.8 (0.0–3.4)	9,997	41.5	1.8 (0.0–7.1)	1	
2nd tertile	2,879	28.3	13.2 (5.3–21.5)	7,315	30.3	14.3 (5.3–22.1)	1.09 (0.94–1.26)	63.6
3rd tertile	2,987	29.3	37.5 (22.8–57.1)	6,353	26.3	36.1 (23.7–52.4)	1.23 (1.06–1.43)	60.2
Missing	*257*	*2.5*		*450*	*1.9*			
P value for trend							<0.001	
Total meat								
1st tertile	3,468	30.3	25.6 (16.0–57.1)	9,524	34.0	31.9 (16.1–59.3)	1	
2nd tertile	3,795	33.2	65.4 (38.9–101.4)	9,315	33.2	75.3 (39.4–101.6)	1.14 (1.03–1.27)	41.2
3rd tertile	4,180	36.5	132.2 (75.3–170.0)	9,190	32.8	126.7 (71.0–164.3)	1.30 (1.09–1.55)	77.9
P value for trend							<0.001	

[1] Pooled ORs were computed using random-effects models which included, when available and applicable, terms for sex, age (5-year age groups: <40;40–44; …; 70–74; ≥75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11 to 20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12g of ethanol/day, intermediate: >12 to 47g of ethanol/day, high: >47g of ethanol/day), fruits and vegetables consumption (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies), and race/ethnicity ("White", "Black/ African American", "Asian", "Hispanic/Latino", "Other"), family history of gastric cancer and body mass categories (<18.5; 18.5–25; 25–30; >30 kg/m^2).

[2] No information for the studies Italy 3[21] and Japan 1.[24]

[3] No information for the study Japan 1.[24]

Table 4.

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of gastric cancer for the highest compared to the lowest study-specific tertile of different sources of meat in strata of selected variables.

	White Meat		Red Meat		Processed Meat		Total Meat	
	OR (95% CI) [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**
Overall	1.09 (0.93–1.26)	56.4	1.24 (1.00–1.53)	82.3	1.23 (1.06–1.43)	60.2	1.30 (1.09–1.55)	77.9
Sex								
Men	1.00 (0.89–1.13)	5.4	1.19 (0.97–1.46)	65.6	1.21 (1.05–1.38)	26.4	1.23 (1.05–1.45)	52.3
Women	1.27 (0.94–1.70)	67.4	1.28 (0.96–1.69)	69.0	1.29 (0.99–1.68)	64.0	1.41 (1.06–1.86)	72.4
P for interaction	0.146		0.690		0.656		0.421	
Age (years)								
≤55	1.04 (0.86–1.27)	14.5	1.05 (0.78–1.42)	62.6	1.39 (1.18–1.63)	2.1	1.10 (0.90–1.35)	35.0
>55 to ≤65	1.19 (0.93–1.54)	42.2	1.26 (0.95–1.66)	60.6	1.19 (0.93–1.53)	46.0	1.44 (1.10–1.88)	61.0
>65	0.97 (0.83–1.14)	12.4	1.38 (1.09–1.75)	59.9	1.13 (0.92–1.39)	45.2	1.33 (1.07–1.67)	58.2
P for interaction	0.389		0.364		0.265		0.238	
Area								
Europe	1.15 (0.88–1.52)	72.2	1.27 (0.91–1.78)	81.4	1.28 (1.02–1.60)	55.3	1.42 (1.06–1.89)	72.1
Asia	0.97 (0.72–1.30)	60.0	0.94 (0.59–1.51)	87.3	0.98 (0.80–1.20)	27.3	1.01 (0.74–1.38)	81.1
Americas	1.07 (0.86–1.33)	0.0	1.49 (1.01–2.20)	76.7	1.45 (1.14–1.84)	42.4	1.51 (1.09–2.08)	66.6
P for interaction	0.700		0.330		0.038		0.159	
Socioeconomic status [2]								
Low	1.19 (0.91–1.57)	61.1	1.33 (1.04–1.70)	61.5	1.25 (1.00–1.55)	47.4	1.33 (1.09–1.63)	47.6
Intermediate	0.91 (0.73–1.13)	14.1	1.13 (0.81–1.58)	66.4	1.25 (0.95–1.63)	49.9	1.28 (0.95–1.74)	62.5
High	1.10 (0.79–1.53)	0.0	0.99 (0.57–1.71)	62.4	1.34 (0.96–1.86)	15.8	1.20 (0.80–1.82)	51.6
P for interaction	0.280		0.540		0.934		0.903	
Smoking status								
Never	1.24 (0.97–1.59)	63.2	1.29 (0.99–1.69)	72.4	1.18 (0.93–1.49)	60.1	1.33 (1.04–1.69)	70.5
Former	1.01 (0.85–1.19)	0.0	1.28 (1.08–1.52)	4.3	1.31 (1.06–1.62)	24.1	1.32 (1.14–1.53)	0.7
Current	0.89 (0.72–1.11)	14.3	1.04 (0.76–1.41)	55.3	1.10 (0.93–1.30)	0.0	1.08 (0.88–1.32)	26.5
P for interaction	0.138		0.458		0.446		0.238	

	White Meat		Red Meat		Processed Meat		Total Meat	
	OR (95% CI) [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**
Alcohol drinking								
Non-drinker	1.17 (0.97–1.46)	33.4	1.31 (0.97–1.75)	72.2	1.24 (1.02–1.50)	32.3	1.34 (1.05–1.73)	66.6
Drinker								
Low (≤12 g/day)	1.19 (0.88–1.59)	50.2	1.10 (0.79–1.53)	67.7	1.32 (0.97–1.81)	60.5	1.26 (0.92–1.72)	68.1
Intermediate (>12–47 g/day)	0.90 (0.70–1.15)	15.3	1.23 (0.98–1.53)	13.4	0.98 (0.75–1.28)	32.0	1.20 (1.02–1.39)	0.0
High (>47 g/day)	0.96 (0.57–1.61)	36.5	1.03 (0.65–1.63)	31.7	1.54 (1.12–2.12)	0.0	1.42 (1.06–1.91)	0.0
P for interaction	0.312		0.792		0.175		0.642	
Controls								
Hospital-based[3]	1.05 (0.87–1.26)	17.3	1.51 (1.09–2.11)	76.4	1.31 (1.03–1.66)	54.0	1.42 (1.08–1.86)	72.6
Population-based[4]	1.10 (0.89–1.40)	72.5	1.05 (0.80–1.38)	84.8	1.17 (0.96–1.44)	68.1	1.20 (0.94–1.53)	81.8
P for interaction	0.687		0.096		0.505		0.372	
Site [5]								
Cardia	1.30 (0.96–1.75)	15.8	1.61 (0.99–2.63)	69.0	1.34 (0.97–1.84)	29.3	1.76 (1.15–2.70)	59.5
Non-cardia	1.11 (0.95–1.30)	53.8	1.28 (1.03–1.59)	78.7	1.24 (1.03–1.49)	68.3	1.34 (1.11–1.62)	74.9
P for interaction	0.370		0.406		0.676		0.255	
Histological type [6]								
Intestinal	1.19 (0.91–1.55)	48.9	1.67 (1.04–2.66)	81.9	1.17 (0.84–1.65)	66.2	1.50 (1.06–2.13)	73.8
Diffuse	1.28 (1.03–1.58)	11.0	1.34 (0.91–1.98)	63.4	1.44 (1.16–1.80)	12.4	1.46 (1.12–1.90)	46.1
Undifferentiated	1.33 (0.84–2.09)	55.3	1.56 (0.85–2.87)	69.6	1.23 (0.87–1.74)	50.7	1.57 (0.98–2.53)	61.7
P for interaction	0.883		0.770		0.532		0.964	
Vegetables and fruits intake								
Low	1.04 (0.83–1.30)	17.4	1.02 (0.79–1.33)	49.9	1.33 (1.04–1.71)	43.6	1.12 (0.90–1.38)	39.1
Intermediate	0.97 (0.83–1.12)	0.0	1.29 (1.02–1.62)	44.3	1.23 (1.00–1.52)	34.9	1.32 (1.07–1.63)	44.5
High	1.23 (0.99–1.53)	40.3	1.23 (0.89–1.71)	75.8	1.16 (0.92–1.45)	50.5	1.38 (1.02–1.88)	75.0
P for interaction	0.188		0.413		0.711		0.418	
Family history of GC [7]								
No	1.12 (0.91–1.37)	62.0	1.36 (1.01–1.85)	85.2	1.11 (0.90–1.36)	60.7	1.31 (1.04–1.67)	79.2

	White Meat		Red Meat		Processed Meat		Total Meat	
	OR (95% CI) [1]	**I^2 (%)**	**OR (95% CI) [1]**	**I^2 (%)**	**OR (95% CI) [1]**	**I^2 (%)**	**OR (95% CI) [1]**	**I^2 (%)**
Yes	1.16 (0.91–1.48)	0.0	1.19 (0.68–2.07)	77.9	1.30 (0.84–1.99)	37.2	1.56 (0.83–2.93)	68.9
P for interaction	0.824		0.671		0.518		0.626	
Body Mass Index (BMI) (kg/m^2)								
<18.5	0.56 (0.14–2.27)	60.9	1.76 (0.66–4.73)	43.7	0.94 (0.25–3.56)	55.2	0.97 (0.62–1.53)	0.7
18.5–25	1.00 (0.86–1.15)	5.7	1.24 (1.01–1.52)	43.0	1.15 (0.89–1.50)	64.1	1.29 (1.01–1.66)	70.2
25–30	1.03 (0.75–1.42)	59.0	1.15 (0.84–1.58)	61.7	1.46 (1.18–1.81)	22.8	1.28 (1.01–1.63)	42.3
>30	1.50 (0.83–2.69)	65.8	1.37 (0.73–2.59)	58.9	1.37 (0.98–1.91)	0.0	1.51 (1.02–2.22)	36.0
P for interaction	0.485		0.852		0.530		0.553	
Studies with information on total energy intake [7]								
Adjusting for energy	1.02 (0.82–1.26)	63.0	1.06 (0.84–1.33)	68.9	1.16 (1.00–1.35)	35.9	1.22 (1.06–1.41)	35.7
Not-adjusting for energy	1.06 (0.86–1.31)	64.4	1.22 (0.95–1.56)	77.8	1.31 (1.10–1.56)	54.9	1.36 (1.13–1.63)	64.3
Studies with information on *H. pylori* (HP) infection [8]								
Adjusting for HP	1.22 (0.92–1.62)	60.3	1.29 (0.77–2.17)	89.7	1.15 (0.91–1.46)	44.6	1.35 (0.93–1.96)	82.6
Not-adjusting for HP	1.21 (0.91–1.60)	66.0	1.25 (0.76–2.04)	89.9	1.15 (0.88–1.49)	61.3	1.28 (0.89–1.82)	84.5

[1] Pooled ORs were computed using random-effects models, which included, when available and applicable, terms for sex, age (5-year age groups: <40;40–44; …; 70–74; ≥75), socioeconomic status (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11 to 20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: >12 to 47 g of ethanol/day, high: >47 g of ethanol/day), fruits and vegetables consumption (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies), and race/ethnicity ("White", "Black/African American", "Asian", "Hispanic/Latino", "Other", family history of gastric cancer and body mass categories (<18.5; 18.5–25; 25–30; >30 kg/m^2).

[2] No information for the study Japan 2.[23] As defined in each original study based on education, income or occupation.

[3] Includes studies Brazil 1,[13] Brazil 2,[12] Greece,[17] Italy 1,[19] Italy 2,[20] Italy 3,[21] Japan 1,[24] Japan 2,[25] Japan 3,[23] Mexico 3,[27] Russia[30] and Spain 2.[32]

[4] Includes studies Canada,[14] China 2,[15] China 3,[16] Iran 1,[18] Italy 4,[22] Mexico 1,[26] Mexico 2,[28] Portugal[29] and Spain 1.[31]

[5] Excluding studies China 2,[15] China 3[16] and Mexico 3.[27]

[6] Excluding studies China 2,[15] Greece,[17] Italy 1,[19] Japan 2,[25] Japan 3[23] and Mexico 2.[28]

[7] No information for studies Canada,[14] Russia,[30] Iran 1,[18] Japan 2,[23] Brazil 1[13] and Brazil 2.[12]

[8] *H. pylori* infection was defined using the same criteria of the original studies, according to the following serological tests: enzyme-linked immunosorbent assay (ELISA) tests (9 studies)[12, 13, 18, 23, 24, 26, 27, 29, 30] to determine immunoglobulin G (IgG) antibody titers in serum, and in one study through multiplex serology.[31] When anti-*H. pylori* serum IgG titers were assessed using an ELISA-based method, participants with borderline results were classified as testing positive for *H. pylori* infection.