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Meat consumption and risk of esophageal and gastric cancer in a large prospective study

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Abstract

Background—Red and processed meats could increase cancer risk via several potential mechanisms involving iron, heterocyclic amines, polycyclic aromatic hydrocarbons and *N*-nitroso compounds. Although there have been multiple studies of meat and colorectal cancer, other gastrointestinal malignancies are understudied.

Methods—We estimated hazards ratios (HR) and 95% confidence intervals (CI) for the association between meat, meat components, and meat cooking by-products and risk of esophageal or gastric cancer in a large cohort study. During approximately 10 years of follow-up, we accrued 215 esophageal squamous cell carcinomas, 630 esophageal adenocarcinomas, 454 gastric cardia adenocarcinomas and 501 gastric non-cardia adenocarcinomas.

Results—Red meat intake was positively associated with esophageal squamous cell carcinoma (HR for the top versus bottom quintile = 1.79, 95% CI: 1.07–3.01, *P* for trend = 0.019). Individuals in the highest intake quintile of 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) had an increased risk for gastric cardia cancer (HR = 1.44, 95% CI: 1.01–2.07, *P* for trend = 0.104). Furthermore, those in the highest quintile of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) or heme iron intake had a suggestive increased risk for esophageal adenocarcinoma (HR = 1.35, 95% CI: 0.97–1.89, *P* for trend = 0.022; HR = 1.45, 95% CI: 0.99–2.12, *P* for trend = 0.463; HR = 1.47, 95% CI: 0.99-2.20, *P* for trend = 0.063, respectively). Benzo[a]pyrene, nitrate and nitrite were not associated with esophageal or gastric cancer.

Conclusions—We found positive associations between red meat intake and esophageal squamous cell carcinoma, and between DiMeIQx intake and gastric cardia cancer.

Keywords

meat; heterocyclic amines; iron; nitrate; nitrite; esophageal cancer; gastric cancer

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Competing Interest
None to declare.

Introduction

The positive association between both red and processed meat intake and colorectal cancer was deemed 'convincing' in a 2007 review of the large amount of epidemiologic data[1]; however, the prospective data for other gastrointestinal malignancies is limited. Based on data primarily from case-control studies, which can be subject to recall bias, the consensus for red and processed meat was that these foods were associated with a 'limited-suggestive increased risk' for esophageal cancer; although the same level of evidence was reported for the association between processed meat and gastric cancer, there was insufficient data for red meat intake and this malignancy[1]. There are multiple mechanisms through which meat could increase cancer risk. Meat cooked at high temperature results in the formation of the mutagens heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs)[2]. Furthermore, meat is a source of iron, and processed meat is also a source of nitrate, and nitrite; all of which have been associated with the formation of *N*-nitroso compounds (NOCs), which are known to cause cancer at a variety of anatomic sites in animals[2].

Esophageal cancer is the sixth leading cause of cancer mortality worldwide, and gastric cancer is the second[3]. Esophageal cancer is comprised of squamous cell carcinomas and adenocarcinomas, and although approximately 90% of gastric cancers are adenocarcinomas, these are typically subdivided according to anatomic location: cardia or non-cardia cancers. There are etiologic differences for both esophageal and gastric cancers by cell type or subsite[4, 5], although many previous dietary analyses have not addressed this.

Investigating a complex dietary exposure in relation to cancers that have important and under-studied subgroups requires a large prospective study with detailed data. Using the National Institutes of Health (NIH)-AARP Diet and Health study, a cohort of approximately half a million men and women who had completed a detailed meat intake questionnaire, we investigated meat and meat-related variables in relation to esophageal and gastric cancer.

Materials and Methods

Study population

The NIH-AARP Diet and Health study recruited men and women, aged 50–71 years, from six states throughout the U.S. (California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan); further study details have been reported previously[6]. This cohort study was designed to investigate a variety of hypotheses for the role of diet in cancer etiology. The study was approved by the institutional review board of the U.S. National Cancer Institute.

Dietary assessment

At baseline (1995–96), participants completed self-administered demographic and lifestyle questionnaires, including a 124-item food frequency questionnaire (FFQ). Approximately six months later, cancer-free participants were mailed a risk factor questionnaire, which elicited detailed information on meat intake and cooking preferences. The FFQ assessed the usual frequency of consumption and portion size information of foods and drinks over the previous twelve months. Portion sizes and daily nutrient intakes were calculated from the 1994–96 U.S. Department of Agriculture's Continuing Survey of Food Intakes by Individuals[6]. The FFQ compared favorably to other FFQs[6], and was calibrated within this study population against two nonconsecutive 24-hour dietary recalls.

All types of beef, pork, and lamb were considered red meat, including bacon, beef, cold cuts, ham, hamburger, hotdogs, liver, pork, sausage, and steak. White meat included chicken and turkey (poultry cold cuts, chicken mixtures, low-fat sausages and low-fat hotdogs made

from poultry), and fish. Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hotdogs and low-fat hotdogs made from poultry. Meats added to complex food mixtures, such as pizza, chili, lasagna, and stew, contributed to the relevant meat type. Total iron was the sum of dietary iron (from all sources including cereals, vegetables, and meat) plus supplementary iron. Heme iron levels in meat may vary according to cooking method[7–11]; therefore, we estimated heme iron intake using the detailed meat questionnaire in conjunction with a database of measured values from meats cooked by different methods and to varying degrees of doneness[12]. Furthermore, we estimated nitrate and nitrite intake from processed meats using a database of measured values from ten types of processed meats, which represent 90% of processed meats consumed in the U.S[12]; these meats were also measured for NOCs, but they were all below the detectable limit. Using the information collected on meat cooking methods (grilled/barbecued, pan-fried, microwaved, and broiled) and doneness levels (well-done and medium/rare) with the CHARRED database (http://charred.cancer.gov), we estimated intake of several HCAs, including 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), as well as benzo[a]pyrene (B[a]P) as a marker of PAH intake, and mutagenic activity (a measure of total mutagenic potential incorporating all meat-related mutagens)[12].

Cohort follow-up and case ascertainment

We ascertained vital status through annual linkage of the cohort to the U.S. Social Security Administration Death Master File, follow-up searches of the National Death Index Plus, cancer registry linkage, questionnaire responses, and responses to other mailings. Follow-up for these analyses began on the date the questionnaire was received until censoring at the end of 2006, or when the participant moved out of one of the state cancer registry areas (which included the eight original states plus two additional states where participants commonly move to: Texas and Arizona), had a cancer diagnosis, or died, whichever came first.

We identified cancer cases through probabilistic linkage with state cancer registries. Cancer cases were first primary cancers of the upper gastrointestinal tract. The cancer endpoints were defined by anatomic site and histologic code of the International Classification of Diseases for Oncology (ICD-O-3)[13]; esophageal cancer included topography codes: C15.0–C15.9, gastric cardia cancer included code: C16.0, and gastric non-cardia cancer included codes: C16.1–C16.7, as well as C16.8 (overlapping tumors) and C16.9 (not otherwise specified). Esophageal cancers were categorized as squamous cell carcinomas, which included histology codes: 8050–8076; and adenocarcinomas, which included: 8140, 8141, 8190–8231, 8260–8263, 8310, 8430, 8480–8490, 8560, 8570–8572. Gastric cancers were restricted to adenocarcinomas.

Statistical analysis

After excluding duplicates and participants who died or moved before the questionnaire was received or withdrew from the study, a total of 566,402 participants returned the baseline questionnaire and 337,074 of these also returned the risk factor questionnaire. For the analyses of baseline data, we excluded individuals whose questionnaire was filled in by someone else on their behalf (n = 15,760), who had prevalent cancer according to the cancer registry or self-report (n = 51,234), and those with extreme daily total energy intake (n = 4,417), defined as more than two inter-quartile ranges above the 75th or below the 25th percentile on the logarithmic scale. For the analyses of data from the risk factor questionnaire, we excluded individuals whose questionnaire was filled in by someone else on their behalf (n = 10,383), who had prevalent cancer (identified by cancer registry or self-

report) at the time they completed the risk factor questionnaire (n = 18,862), and those with extreme daily total energy intake (n = 2,503). After all exclusions, our baseline analytic cohort consisted of 494,979 persons (295,305 men and 199,674 women) and the risk factor questionnaire cohort consisted of 303,156 persons (176,842 men and 126,314 women).

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression with person years as the underlying time metric; analyses using age as the underlying time metric yielded almost identical HRs. The proportional hazards assumption was verified using a time interaction model. The models were constructed as addition models – where the model summed to total meat; for example, red and white meat were in the same model, as were processed and non-processed meat. A full range of potential confounders were investigated, the final multivariate models contained known and suspected confounders and included: age, sex, body mass index (BMI), education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, and intake of fruit, vegetables, saturated fat and calories. Inclusion of a comprehensive (31-level) smoking variable did not alter our findings.

Dietary variables were adjusted for energy by the multivariate nutrient density method[14]. Multivariate HRs are reported within quintiles, using the lowest quintile as the referent category. Tests for linear trend were calculated using the median value of each quintile. Interactions were evaluated by including cross product terms in multivariate models. Furthermore, we conducted a lag-analysis by excluding the first two years of follow up. All reported *P* values are two-sided and all statistical analyses were carried out using Statistical Analysis Systems (SAS) software (SAS Institute Inc, Cary, NC).

Results

During a median follow-up time of 10 years (interquartile range: 10.5 – 10.8 years), we accrued 215 esophageal squamous cell carcinomas, 630 esophageal adenocarcinomas, 454 gastric cardia cancers and 501 gastric non-cardia cancers with data from baseline. Within the subcohort of participants who completed the risk factor questionnaire, there were 128 incident esophageal squamous cell carcinomas, 377 esophageal adenocarcinomas, 255 gastric cardia cancers and 277 gastric non-cardia cancers.

Individuals in the highest, compared to the lowest, quintile of red meat intake were more likely to be male, a current smoker, Caucasian, in a physically demanding job, have a higher BMI, and to consume more calories and alcohol; furthermore, they tended to be younger, less educated and less likely to be physically active outside of work, and consumed fewer fruits and vegetables (Table 1). Although the intake of white meat was independent of red meat ($r = -0.049$), the majority of the baseline characteristics for those in the highest quintile of white meat were opposed to the highest quintile of red meat; for example, while red meat consumption was associated with a higher propensity to be a current smoker and less educated, those in the highest quintile of white meat were less likely to be current smoker and tended to be more educated.

Red meat intake was positively associated with esophageal squamous cell carcinoma (HR for the top versus bottom quintile = 1.79, 95% CI: 1.07–3.01, *P* for trend = 0.019; HR = 1.06, 95% CI: 1.00–1.13 for each 10g/1000kcal increase), but not with adenocarcinoma of the esophagus or gastric (cardia or non-cardia) cancer (Table 2). Neither white meat nor processed meat was associated with any of the malignancies investigated in this study. None of the meat-related variables we investigated proved to be statistically significantly associated with esophageal squamous cell carcinoma (Table 3). However, we found positive associations for HCA intake and the other malignancies investigated; specifically,

individuals in the highest quintile, compared to the lowest, of DiMeIQx intake had an elevated risk for gastric cardia cancer (HR = 1.44, 95% CI: 1.01–2.07); risks were elevated across quintiles two through five. Furthermore, we observed borderline statistically significant increased risks for adenocarcinoma of the esophagus for those in the highest intake quintile of MeIQx and PhIP (HR = 1.35, 95% CI: 0.97–1.89, *P* for trend = 0.022; HR = 1.45, 95% CI: 0.99–2.12, *P* for trend = 0.463, respectively). In addition to HCAs, we found a suggestive positive association for heme iron intake and esophageal adenocarcinoma (HR for the top versus bottom quintile = 1.47, 95% CI: 0.99–2.20, *P* for trend = 0.063), but no associations between other meat-related variables, including B[a]P, nitrate, or nitrite, and esophageal or gastric cancers. Examining the overall index of mutagenicity of the meats consumed did not reveal any further associations.

We conducted several sensitivity and stratified analyses, which revealed consistency in our findings. A lag analysis, excluding the first two years of follow-up did not affect our results. Upon stratification by gender, alcohol, smoking, BMI, and vitamin C, we did not find any consistent modification of our findings. For example, the association between red meat intake and esophageal squamous cell carcinoma was evident in never smokers (HR for the top versus bottom quintile = 1.50, 95% CI: 0.40–5.51) and in those who do not drink alcohol (HR for the top versus bottom quintile = 2.18, 95% CI: 0.77–6.13), although the risks were not statistically significant due to limited power within this subgroup.

Discussion

Individuals in the highest category of red meat intake had an elevated risk for esophageal squamous cell carcinoma and those in the highest category of DiMeIQx intake had an increased risk for gastric cardia cancer. Furthermore, we observed a suggestive increased risk for esophageal adenocarcinoma for those in the highest intake category of MeIQx, PhIP or heme iron.

The World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) consensus report concluded that the evidence to date for red meat and processed meat as risk factors for esophageal cancer was ‘limited suggestive increased risk’; although there was no consideration for histologic subtype, largely because of a lack of data[1]. There are very few cohort studies investigating meat intake and esophageal cancer; one Norwegian study with no data on histology and only 22 cases[15], one study of adenocarcinoma (n=65) from Europe[16], and one study of squamous cell cancer (n=1,958) from China that only gave risk estimates for total meat and not red and processed meat separately[17]. The European study reported a strong positive association for those in the highest tertile of processed meat intake and adenocarcinoma of the esophagus (HR=3.54, 95% CI: 1.57–7.99), but no association for red meat[16]. In addition, data from our cohort was presented as part of a multi-site cancer analysis with follow-up through 2003 that combined all esophageal cancer cases and used a standard set of covariates for all sites; this analysis reported elevated risks for those in the highest quintile of red meat (HR=1.51, 95%: 1.09–2.08), but no association for processed meat intake (HR=0.94, 95% CI: 0.70–1.25)[18]. Data from the present study, however, highlight the importance of analyzing squamous cell and adenocarcinoma of the esophagus separately. There are more case-control studies than cohort studies even though this is not an ideal study design for dietary analyses or for digestive tract cancers; in these studies, red meat intake has been positively associated with both adenocarcinoma[19, 20] and squamous cell cancer[20–23] of the esophagus.

Although there are many more studies of meat intake, particularly processed meat, and gastric cancer, the data remains inconsistent. The WCRF/AICR 2007 report concludes that there is ‘limited suggestive’ evidence for a positive association between processed meat

intake and gastric cancer[1], and insufficient data for red meat. The vast majority of studies conducted thus far have not differentiated between cardia and non-cardia gastric cancer. The cohort studies mainly reported data on processed meat, and while two studies reported statistically significant elevated risks[16, 24], which appeared to be confined to non-cardia in the one study with data by subsite[16], others found elevated risks that did not reach statistical significance[25, 26], and others were null[27, 28].

There are very few studies that have investigated components of meat or compounds formed during cooking or processing of meat in relation to esophageal or gastric cancer. Only one other study investigated HCA intake and esophageal cancer by subtype and this was a case-control study that reported an increased risk of squamous cell carcinoma for those in the highest quartile of MeIQx and DiMeIQx, but no association for adenocarcinoma of the esophagus[29]. Similarly, there are no cohort studies and very few case-control studies of HCAs in relation to gastric cancer; although a positive association was observed in one study[30], two other studies did not find statistically significant associations[29, 31], and a study that investigated well-done meat intake as a proxy for HCA exposure reported an increased risk[19]. We were not able to speculate about the potential mechanism relating red meat intake to esophageal squamous cell carcinoma since none of the meat-related variables we investigated proved to be statistically significantly associated with this cancer. Our observation that DiMeIQx was positively associated with gastric cardia cancer is supported by animal studies showing a diet high in HCAs results in increased stomach tumors[32]. Since HCAs are multisite carcinogens in animal models, their detrimental effects are possible at many anatomical subsites.

Meat is a source of iron and although high iron levels in toenails were indicative of an elevated risk of esophageal cancer in a case-control study[33], there was no association between iron levels in esophageal biopsy specimens in a prospective study of squamous cell carcinoma of the esophagus[34]. With regard to gastric cancer, a recent case-control study did not find an association for iron intake[35]. Heme iron specifically may contribute to carcinogenesis via increasing oxidative stress[36] or by catalyzing the endogenous formation of NOCs[37], which are known carcinogens. A large multi-center European cohort created an index for the propensity for endogenous NOC formation by estimating iron intake using standard food databases in relation to fecal NOC levels from published literature; individuals in the highest category of this index had an elevated risk for non-cardia gastric cancer[38]. Ours is the first study to estimate heme intake using a database of measured values from specific meats in relation to cancers of the esophagus and stomach; and we revealed a suggestive positive association between heme iron intake and esophageal adenocarcinoma, but not squamous cell carcinoma or gastric cancer.

In agreement with our data, two case-control studies reported null findings for high nitrite meat intake in relation to adenocarcinoma and squamous cell carcinoma of the esophagus[20, 39]. Furthermore, a case-control[31] and a cohort study[28] reported no association between nitrate or nitrite intake and gastric cancer; however, analyses by subsite found that a high nitrite diet[39] or meats high in nitrite[20] increased the risk of non-cardia gastric cancer, a finding not replicated in our study. There is very little data on NOC intake specifically; two cohort studies estimated intake of one NOC – *N*-nitrosodimethylamine (NDMA) using tables containing values for foods and beverages, one of the studies found an elevated risk for gastric cancer for those in the highest category of NDMA intake[24], but the other found no association for cardia or non-cardia gastric cancer[38].

There were many notable strengths of our study, several relating to the dietary questionnaire, which not only contained detailed questions pertaining to meat-cooking preferences and components of meat, but it was also completed prior to diagnoses, which limited recall bias

and reverse causation. This cohort was also very large, which enabled us to investigate esophageal and gastric cancer by their important subtypes, and produced a wide range of meat intake, increasing the ability to detect associations. However, some of the categories had a small number of cases in; power calculations revealed approximately 80% power to detect a risk of 1.4 for all subgroups, except for esophageal squamous cell carcinoma for which we had approximately 80% power to detect an association of 1.6. Other limitations of our study included the possibility of measurement error in general, and underestimation of both nitrate and heme iron, since we lacked data on nitrate intake from drinking water, and because the iron database was limited by the number of meats included. It is also possible that our risk estimates were confounded by other lifestyle factors and possibly by gastroesophageal reflux or *Helicobacter pylori*, for which we do not have information on in our cohort. Although there is no evidence that *H. pylori* is related to meat intake, they do both tend to be associated with socioeconomic status, which we attempted to control for in the form of years of education. A previous study, with limited statistical power, found stronger associations between meat intake and non-cardia gastric cancer in *H. pylori* antibody-positive individuals[16]; however, the findings from our study were limited to DiMeIQx intake from meat and cardia cancers. Lastly, adenocarcinoma of the esophagus and gastric cardia cancers both tend to arise near the esophageal-gastric junction[40], leading to difficulties in determining the subsite of origin; therefore, there may have been some misclassification in tumor site.

In conclusion, we found a positive association between red meat intake and squamous cell carcinoma of the esophagus, and between DiMeIQx intake and gastric cardia cancer. Processed meat intake was not associated with either esophageal or gastric cancer.

Study Highlights

What is current knowledge

- Red and processed meat are known sources of potential mutagens
- Red and processed meat are positively associated with colorectal cancer, but the effect on other gastrointestinal malignancies is unclear
- The majority of the literature on meat intake and the risk of esophageal and gastric cancers is from case-control studies, which are subject to biases, and do not differentiate between important subtypes of these cancers

What is new here

- We observed a positive association between red meat intake and squamous cell carcinoma of the esophagus, but no association for adenocarcinoma – suggesting differences in their etiology
- Heterocyclic amines formed in high temperature cooked meat were positively associated with gastric cardia cancer, and there was a suggestive positive association for esophageal adenocarcinoma
- Heme iron intake may be associated with esophageal adenocarcinoma risk

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Abbreviations

B[a]P	benzo[a]pyrene
BMI	body mass index
CI	confidence interval
DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline
FFQ	food frequency questionnaire
HR	hazard ratio
HCA	heterocyclic amine
MeIQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
NOC	*N*-nitroso compound
PAH	polycyclic aromatic hydrocarbon
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

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Table 1

Baseline characteristics of the cohort according to quintile of red meat and white meat intake (n=494,979)

	Red meat			White meat		
	Quintile 1	**Quintile 3**	**Quintile 5**	**Quintile 1**	**Quintile 3**	**Quintile 5**
Red meat, g/1000kcals‡	10.0 (5.7–13.4)	32.2 (29.6–34.9)	64.8 (57.6–76.9)	28.6 (15.9–45.0)	35.0 (22.3–50.0)	28.6 (15.8–45.1)
White meat, g/1000kcals‡	28.6 (14.0–51.2)	27.5 (17.2–42.9)	28.6 (17.9–43.0)	9.7 (6.6–12.3)	28.0 (25.6–30.7)	65.8 (56.4–82.6)
Male†	44,470 (15)	58,667 (20)	74,655 (25)	61,032 (21)	60,334 (20)	54,049 (18)
Age, years‡	63.0 (58.0–67.0)	62.8 (57.9–66.7)	61.7 (57.0–65.9)	63.2 (58.2–67.0)	62.7 (57.8–66.6)	61.8 (57.1–66.1)
BMI, kg/m^2‡	25.1 (22.8–27.9)	26.5 (24.1–29.4)	27.5 (25.0–30.7)	26.0 (23.6–29.2)	26.5 (24.0–29.6)	26.6 (24.1–29.7)
Calories, kcal/day‡	1,542 (1,180–2,009)	1,654 (1,260–2,159)	1,789 (1,347–2,348)	1,725 (1,286–2,297)	1,660 (1,261–2,168)	1,571 (1,205–2,044)
Vegetable, servings/1000kcals‡	2.4 (1.6–3.4)	2.0 (1.5–2.7)	1.9 (1.4–2.5)	1.7 (1.2–2.5)	2.0 (1.5–2.7)	2.4 (1.7–3.1)
Fruit, servings/1000kcals‡	2.2 (1.4–3.2)	1.5 (0.9–2.2)	1.0 (0.6–1.5)	1.4 (0.8–2.4)	1.5 (0.9–2.3)	1.5 (1.0–2.3)
Education, completed graduate school§	24,517 (26)	18,818 (20)	16,467 (17)	15,109 (16)	19,989 (21)	23,147 (24)
Current smoker, >1 pack/day§	1,877 (2)	4,402 (5)	8,485 (9)	7,007 (7)	4,597 (5)	3,081 (3)
Ethnicity						
Non-Hispanic white§	85,863 (88)	91,215 (93)	92,497 (95)	90,121 (93)	90,900 (93)	88,979 (91)
Non-Hispanic black§	6,200 (6)	3,465 (4)	2,324 (2)	2,986 (3)	3,666 (4)	5,052 (5)
Hispanic§	2,427 (3)	1,733 (2)	1,824 (2)	2,263 (2)	1,631 (2)	1,982 (2)
Other§	2,707 (3)	1,429 (1)	1,120 (1)	1,918 (2)	1,602 (2)	1,663 (2)
Physical activity at work, heavy work/carry loads§	2,251 (2)	2,744 (3)	3,619 (4)	3,972 (4)	2,736 (3)	1,990 (2)
Vigorous physical activity, ≥5 times/week§	26,119 (27)	17,753 (18)	14,821 (15)	18,966 (19)	18,570 (19)	20,422 (21)
Alcoholic drinks, >3/day§	3,185 (3)	6,954 (7)	12,503 (13)	7,643 (8)	7,582 (8)	6,767 (7)

†Number, percent among the row

‡Median, inter-quartile range

§Number, percent among the category

Table 2

Meat intake in relation to esophageal and gastric cancer using baseline data (n=494,979)[†]

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous scale (per 10g/1000kcal)
Red meat							
Quintile median (g/1000kcals)	10.0	21.9	32.2	44.1	64.8		
ESCC[‡]							
Cases	28	35	42	41	69		
HR (95%CI)	1.00	1.18 (0.71–1.96)	1.34 (0.80–2.22)	1.19 (0.70–2.01)	1.79 (1.07–3.01)	0.019	1.06 (1.00–1.13)
EADC[‡]							
Cases	74	112	113	154	177		
HR (95%CI)	1.00	1.18 (0.87–1.59)	1.00 (0.74–1.37)	1.17 (0.87–1.59)	1.15 (0.84–1.57)	0.492	1.01 (0.98–1.06)
Gastric Cardia							
Cases	57	90	90	104	113		
HR (95%CI)	1.00	1.29 (0.92–1.81)	1.12 (0.79–1.59)	1.13 (0.79–1.61)	1.04 (0.72–1.51)	0.589	1.00 (0.95–1.04)
Gastric Noncardia							
Cases	110	95	88	105	103		
HR (95%CI)	1.00	0.81 (0.61–1.08)	0.72 (0.53–0.97)	0.83 (0.61–1.11)	0.77 (0.56–1.06)	0.261	0.99 (0.94–1.04)
White meat							
Quintile median (g/1000kcals)	9.7	18.9	28.0	40.3	65.8		
ESCC[‡]							
Cases	55	44	47	36	33		
HR (95%CI)	1.00	0.84 (0.56–1.25)	0.92 (0.62–1.37)	0.73 (0.47–1.12)	0.69 (0.44–1.08)	0.089	0.96 (0.90–1.02)
EADC[‡]							
Cases	151	138	118	120	103		
HR (95%CI)	1.00	0.92 (0.73–1.16)	0.82 (0.64–1.05)	0.88 (0.69–1.13)	0.84 (0.65–1.09)	0.239	0.98 (0.95–1.02)
Gastric Cardia							
Cases	94	92	85	97	86		
HR (95%CI)	1.00	1.02 (0.76–1.36)	1.00 (0.74–1.35)	1.22 (0.91–1.63)	1.18 (0.87–1.60)	0.154	1.03 (1.00–1.07)
Gastric Noncardia							
Cases	113	101	103	102	82		
HR (95%CI)	1.00	0.98 (0.75–1.29)	1.05 (0.80–1.38)	1.09 (0.83–1.44)	0.90 (0.67–1.20)	0.578	0.99 (0.95–1.03)

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous scale (per 10g/1000kcal)
Processed meat							
Quintile median (g/1000kcals)	1.7	4.5	7.8	12.6	23.2		
ESCC[‡]							
Cases	34	38	34	49	60		
HR (95%CI)	1.00	1.03 (0.64–1.66)	0.86 (0.52–1.42)	1.15 (0.72–1.86)	1.32 (0.83–2.10)	0.085	1.08 (0.96–1.21)
EADC[‡]							
Cases	83	101	128	137	181		
HR (95%CI)	1.00	0.92 (0.68–1.24)	0.98 (0.74–1.32)	0.91 (0.68–1.22)	1.08 (0.81–1.43)	0.262	1.03 (0.96–1.11)
Gastric Cardia							
Cases	68	78	93	108	107		
HR (95%CI)	1.00	0.89 (0.64–1.24)	0.91 (0.66–1.26)	0.92 (0.67–1.28)	0.82 (0.59–1.14)	0.285	1.00 (0.92–1.09)
Gastric Noncardia							
Cases	93	81	105	105	117		
HR (95%CI)	1.00	0.87 (0.64–1.18)	1.10 (0.82–1.47)	1.04 (0.77–1.41)	1.09 (0.81–1.48)	0.329	1.02 (0.94–1.11)

[†] age (continuous), sex, BMI (<18.5, ≥ 18.5 to <25, ≥ 25 to <30, ≥ 30 to <35, 35 kg/m^2, unknown), education (≤ 11years school, 12 years or completed high school, post-high school/some college, college graduate, postgraduate, unknown), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other, unknown), tobacco smoking (never, quit smoking ≥20 cigarettes/day, quit smoking >20 cigarettes/day, current smoker of ≥20 cigarettes/day, current smoker of >20 cigarettes/day, unknown), alcohol drinking (none, >0 to 1, >1 to 3, >3 drinks per day, unknown), usual physical activity at work (all day sitting, mostly sitting, walking around a lot, lifting/carrying light loads/climbing stairs or hills often, heavy work/carrying heavy loads, unknown), vigorous physical activity (never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, unknown), and the daily intake of fruit (continuous/1000kcals), vegetables (continuous/1000kcals), saturated fat (continuous/1000kcals), and calories (kcals/day)

[‡] ESCC = Esophageal squamous cell carcinoma, EADC = Esophageal adenocarcinoma

[§] P values for trend were calculated by representing intake as an ordinal variable for each category in the adjusted models described above.

Table 3

Components of meat in relation to esophageal and gastric cancer using data from the risk factor questionnaire (n=303,156)

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous data
DiMeIQx							per 0.5 ng increase
Quintile median (ng/1000kcals)	0.0	0.1	0.4	0.8	2.1		
ESCC[‡]							
Cases	44	23	24	18	19		
HR (95%CI)	1.00	1.21 (0.73–2.02)	1.31 (0.79–2.16)	0.97 (0.56–1.69)	1.00 (0.58–1.73)	0.747	1.02 (1.00–1.03)
EADC[‡]							
Cases	130	49	47	77	74		
HR (95%CI)	1.00	0.93 (0.67–1.30)	0.81 (0.58–1.13)	1.20 (0.90–1.59)	1.11 (0.83–1.48)	0.237	1.01 (1.00–1.02)
Gastric Cardia							
Cases	72	37	48	46	52		
HR (95%CI)	1.00	1.24 (0.83–1.85)	1.49 (1.04–2.16)	1.34 (0.92–1.94)	1.44 (1.01–2.07)	0.104	1.01 (1.00–1.02)
Gastric Noncardia							
Cases	95	45	42	49	46		
HR (95%CI)	1.00	1.01 (0.71–1.45)	0.93 (0.64–1.33)	1.07 (0.75–1.51)	0.97 (0.68–1.39)	0.934	1.00 (0.97–1.03)
MeIQx							per 5 ng increase
Quintile median (ng/1000kcals)	0.5	2.5	5.5	10.6	25.0		
ESCC[‡]							
Cases	22	28	28	25	25		
HR (95%CI)	1.00	1.21 (0.69–2.13)	1.18 (0.67–2.09)	1.03 (0.57–1.86)	0.96 (0.53–1.75)	0.527	1.02 (1.00–1.05)
EADC[‡]							
Cases	56	72	65	69	115		
HR (95%CI)	1.00	1.13 (0.79–1.60)	0.91 (0.64–1.31)	0.89 (0.62–1.27)	1.35 (0.97–1.89)	0.022	1.01 (0.99–1.03)
Gastric Cardia							
Cases	41	38	55	55	66		
HR (95%CI)	1.00	0.85 (0.55–1.32)	1.14 (0.75–1.71)	1.06 (0.70–1.60)	1.16 (0.77–1.75)	0.295	1.01 (0.99–1.03)
Gastric Noncardia							
Cases	58	49	48	62	60		
HR (95%CI)	1.00	0.82 (0.56–1.21)	0.76 (0.52–1.12)	0.93 (0.65–1.35)	0.83 (0.57–1.22)	0.739	0.98 (0.94–1.02)

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous data
PhIP							per 25 ng increase
Quintile median (ng/1000kcals)	2.1	11.2	25.4	51.0	127.3		
ESCC[‡]							
Cases	21	32	25	24	26		
HR (95%CI)	1.00	1.44 (0.83–2.52)	1.08 (0.59–1.95)	1.00 (0.54–1.82)	1.09 (0.60–1.97)	0.702	1.00 (0.95–1.05)
EADC[‡]							
Cases	39	76	91	78	93		
HR (95%CI)	1.00	1.45 (0.98–2.14)	1.50 (1.02–2.19)	1.20 (0.81–1.78)	1.45 (0.99–2.12)	0.463	1.01 (0.98–1.03)
Gastric Cardia							
Cases	42	35	65	53	60		
HR (95%CI)	1.00	0.67 (0.43–1.06)	1.11 (0.75–1.66)	0.87 (0.57–1.31)	0.97 (0.64–1.46)	0.695	1.01 (0.98–1.04)
Gastric Noncardia							
Cases	45	60	58	54	60		
HR (95%CI)	1.00	1.25 (0.84–1.84)	1.17 (0.79–1.74)	1.09 (0.73–1.64)	1.22 (0.82–1.83)	0.620	1.01 (0.98–1.04)
B[a]P							per 10 ng increase
Quintile median (ng/1000kcals)	0.2	1.5	6.3	17.3	45.8		
ESCC[‡]							
Cases	27	28	23	30	20		
HR (95%CI)	1.00	1.06 (0.62–1.80)	0.98 (0.56–1.72)	1.23 (0.72–2.08)	0.70 (0.39–1.26)	0.179	0.99 (0.93–1.05)
EADC[‡]							
Cases	59	80	75	84	79		
HR (95%CI)	1.00	1.19 (0.85–1.67)	1.18 (0.84–1.66)	1.11 (0.79–1.55)	0.86 (0.61–1.22)	0.062	0.99 (0.96–1.02)
Gastric Cardia							
Cases	44	42	52	53	64		
HR (95%CI)	1.00	0.88 (0.58–1.34)	1.14 (0.76–1.71)	1.04 (0.70–1.56)	1.09 (0.73–1.61)	0.547	1.00 (0.97–1.04)
Gastric Noncardia							
Cases	55	56	54	58	54		
HR (95%CI)	1.00	0.95 (0.65–1.38)	1.01 (0.69–1.48)	1.08 (0.74–1.56)	0.99 (0.67–1.46)	0.925	0.99 (0.94–1.03)
Mutagenic activity							per 1000 revertant colonies increase
Quintile median (revertant colonies/1000kcals)	168	617	1186	2097	4468		

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous data
ESCC[‡]							
Cases	25	29	27	21	26		
HR (95%CI)	1.00	1.08 (0.62–1.85)	0.98 (0.56–1.72)	0.74 (0.41–1.36)	0.93 (0.53–1.66)	0.609	1.01 (1.00–1.02)
EADC[‡]							
Cases	41	66	94	83	93		
HR (95%CI)	1.00	1.20 (0.81–1.78)	1.51 (1.04–2.20)	1.26 (0.86–1.85)	1.37 (0.94–2.01)	0.347	1.00 (0.99–1.02)
Gastric Cardia							
Cases	38	51	49	60	57		
HR (95%CI)	1.00	1.08 (0.70–1.65)	0.94 (0.61–1.45)	1.09 (0.72–1.67)	1.00 (0.65–1.54)	0.955	1.00 (0.99–1.02)
Gastric Noncardia							
Cases	53	54	60	51	59		
HR (95%CI)	1.00	0.91 (0.62–1.34)	0.97 (0.67–1.43)	0.82 (0.55–1.22)	0.94 (0.64–1.39)	0.807	0.99 (0.95–1.03)
Heme Iron							per 100 μg increase
Quintile median (μg/1000kcals)	48.8	102.9	154.2	218.7	347.7		
ESCC[‡]							
Cases	17	25	31	27	28		
HR (95%CI)	1.00	1.38 (0.74–2.58)	1.60 (0.87–2.96)	1.33 (0.70–2.53)	1.25 (0.64–2.42)	0.944	1.02 (0.89–1.17)
EADC[‡]							
Cases	39	55	81	88	114		
HR (95%CI)	1.00	1.12 (0.74–1.70)	1.40 (0.94–2.07)	1.32 (0.89–1.97)	1.47 (0.99–2.20)	0.063	1.04 (0.96–1.12)
Gastric Cardia							
Cases	38	45	58	56	58		
HR (95%CI)	1.00	0.98 (0.63–1.52)	1.10 (0.72–1.68)	0.94 (0.60–1.45)	0.83 (0.53–1.30)	0.256	0.95 (0.86–1.05)
Gastric Noncardia							
Cases	63	49	39	69	57		
HR (95%CI)	1.00	0.71 (0.49–1.04)	0.54 (0.36–0.82)	0.92 (0.64–1.33)	0.72 (0.48–1.08)	0.531	0.96 (0.87–1.06)
Nitrate							per 100 μg increase
Quintile median (μg/1000kcals)	24.2	66.9	112.7	174.5	298.0		
ESCC[‡]							

	Q1	Q2	Q3	Q4	Q5	*P* for trend[§]	Continuous data
Cases	22	25	15	25	41		
HR (95%CI)	1.00	1.06 (0.59–1.91)	0.60 (0.30–1.18)	0.90 (0.49–1.67)	1.30 (0.72–2.35)	0.153	1.08 (0.96–1.23)
EADC[‡]							
Cases	47	61	68	89	112		
HR (95%CI)	1.00	0.97 (0.66–1.43)	0.91 (0.62–1.35)	1.01 (0.70–1.47)	1.10 (0.75–1.60)	0.350	1.04 (0.96–1.12)
Gastric Cardia							
Cases	39	57	36	61	62		
HR (95%CI)	1.00	1.17 (0.77–1.77)	0.64 (0.40–1.02)	0.94 (0.61–1.45)	0.81 (0.52–1.25)	0.259	0.99 (0.90–1.09)
Gastric Noncardia							
Cases	50	48	50	56	73		
HR (95%CI)	1.00	0.90 (0.60–1.35)	0.89 (0.59–1.33)	0.91 (0.61–1.37)	1.04 (0.69–1.55)	0.578	1.01 (0.92–1.10)
Nitrite							per 100 μg increase
Quintile median (μg/1000kcals)	12.1	34.6	61.4	102.9	199.2		
ESCC[‡]							
Cases	20	30	19	28	31		
HR (95%CI)	1.00	1.36 (0.76–2.43)	0.82 (0.43–1.57)	1.15 (0.63–2.11)	1.21 (0.67–2.20)	0.651	1.00 (0.83–1.21)
EADC[‡]							
Cases	50	60	66	81	120		
HR (95%CI)	1.00	0.89 (0.61–1.30)	0.82 (0.56–1.20)	0.88 (0.61–1.27)	1.19 (0.84–1.68)	0.029	1.05 (0.95–1.15)
Gastric Cardia							
Cases	44	40	55	61	55		
HR (95%CI)	1.00	0.72 (0.47–1.11)	0.88 (0.58–1.32)	0.87 (0.58–1.31)	0.71 (0.47–1.08)	0.250	0.89 (0.77–1.03)
Gastric Noncardia							
Cases	54	44	48	67	64		
HR (95%CI)	1.00	0.77 (0.51–1.15)	0.79 (0.53–1.18)	1.04 (0.71–1.52)	0.93 (0.63–1.37)	0.615	1.02 (0.91–1.15)

[†] age (continuous), sex, BMI (<18.5, ≥ 18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35 kg/m^2, unknown), education (≤11years school, 12 years or completed high school, post-high school/some college, college graduate, postgraduate, unknown), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other, unknown), tobacco smoking (never, quit smoking ≤ 20 cigarettes/day, quit smoking >20 cigarettes/day, current smoker of ≤ 20 cigarettes/day, current smoker of >20 cigarettes/day, unknown), alcohol drinking (none, >0 to 1, >1 to 3, >3 drinks per day, unknown), usual physical activity at work (all day sitting, mostly sitting, walking around a lot, lifting/carrying light loads/climbing stairs or hills often, heavy work/carrying heavy loads, unknown), vigorous physical activity (never, rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, ≥5 times/week, unknown), and the daily intake of fruit (continuous/1000kcals), vegetables (continuous/1000kcals), saturated fat (continuous/1000kcals), and calories (kcals/day)

‡ESCC = Esophageal squamous cell carcinoma, EADC = Esophageal adenocarcinoma

§P values for trend were calculated by representing intake as an ordinal variable for each category in the adjusted models described above.