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Meat and heme iron intake and esophageal adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition study

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Although recent studies suggest that high intakes of meat and heme iron are risk factors for several types of cancer, studies in relation to esophageal adenocarcinoma (EAC) are scarce. Previous results in the European Prospective Investigation into Cancer and Nutrition (EPIC) based on a relatively small number of cases suggested a positive association between processed meat and EAC. In this study, we investigate the association between intake of different types of meats and heme iron intake and EAC risk in a larger number of cases from EPIC. The study included 481,419 individuals and 137 incident cases of EAC that occurred during an average of 11 years of follow-up. Dietary intake of meat (unprocessed/processed red and white meat) was assessed by validated center-specific questionnaires. Heme iron was calculated as a type-specific percentage of the total iron content in meat. After adjusting for relevant confounders, we observed a statistically significant positive association of EAC risk with heme iron and processed meat intake, with HR: 1.67, 95% CI: 1.05–2.68 and HR: 2.27, 95% CI:1.33–3.89, respectively, for comparison of the highest *vs.* lowest tertile of intake. Our results suggest a potential association between higher intakes of processed meat and heme iron and risk of EAC.

What's new?
Previous results have shown that eating red meat can increase one's risk of developing certain cancers, including esophageal adenocarcinoma (EAC). That work included few cases of EAC, however. This study expands on those findings by investigating the effect of eating different kinds of meats and includes a larger number of esophageal cancer cases. Using a questionnaire, they assessed the amount of processed and unprocessed red or white meat consumed by individuals, including 137 EAC patients. They also estimated the amount of heme iron consumed based on the amount and types of meat eaten by the study subject. The analysis shows that consumption of processed meat and heme iron appear to be associated with higher risk of esophageal adenocarcinoma.

Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are the two major types of esophageal cancer (EC). The incidence of adenocarcinomas of the esophagus and gastric cardia has risen in most European countries, with the strongest increase in the United Kingdom and Ireland.[1] EAC is associated with gastresophageal reflux disease, Barrett's esophagus, smoking and obesity.[2] Furthermore, there is evidence that mate and other high-temperature drinks and dietary intake of red and processed meat may increase the risk of developing EAC.[3] A review conducted by our group showed that high intake of nitrosamines, red and processed meat tends to increase the risk of EC.[4] Furthermore, the World Cancer Research Fund report [3] considered the evidence regarding meat intake in relation to increased risk of EC as "limited suggestive." The same report concluded that evidence for poultry intake and cancer risk was "too limited in amount, consistency and quality to draw any conclusions." Furthermore, heme iron (mainly provided by red meat intake) may specifically contribute to carcinogenesis by increasing oxidative stress[5] or by catalyzing endogenous formation of nitrosocompounds.[6]

Previous results from the Eurogast-Epic [7] based on 65 EAC cases showed a nonsignificant positive association between processed meat and EAC and an unexpected significant positive association with poultry. Overall, the evidence from epidemiological studies on the association between meat intake and heme iron and EC is limited. Therefore, we reinvestigate the association between meat intake and EAC risk in a larger number of cases from EPIC study. Furthermore, we also analyzed the effect of heme iron intake on EAC risk.

Material and Methods

The methodological details and rationale behind the EPIC study have been described previously.[8,9] In brief, EPIC is a prospective cohort study involving 23 centers from 10 European countries. A total of 521,457 subjects (153,447 men), aged mostly 35–70 years, were recruited between 1992 and 1998. This study was approved by ethical committees from all local participating centers and by the International Agency for Research on Cancer.

Case identification during follow-up was mostly based on population cancer registries except in France, Germany Greece and Naples, where a combination of methods including health insurance records, cancer and pathology hospital registries and active follow-up were used. EAC was classified using topographical and morphology codes according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Since Greece

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and Norway did not contribute with any cases, these countries were not included in the final model. After a mean of 11 years of follow-up, 142 EAC incident cases were identified. A total of 28,292 participants were excluded due to a prevalent cancer or were lost of follow-up. A total of 15,853 (9 EAC) individuals without dietary information or who were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement were also excluded from the analysis. Afterward, subjects with a density of total meat >222.5 g/2,000kcal/d (99th percentile) were considered as outliers and were excluded from the final sample (3,493 subjects). Thus, the final sample for analyses consisted of 472,538 participants, 137 of which were incident EAC.

Dietary data were collected using validated country-specific questionnaires (quantitative or semiquantitative) recording the usual diet over the previous 12 months.[10] A lifestyle questionnaire[8] was used to collect information about sociodemographic characteristics, lifestyles (smoking habits) and medical history. Anthropometric measures and blood samples were taken at recruitment.

Total red meat included all types of unprocessed (beef, pork and lamb) and processed meat (bacon, cold cuts, ham, hot dogs, meatballs, hamburgers and sausages). White meat included chicken and turkey. Heme iron, *N*-nitrosodimethylamine (NDMA) and endogenous nitroso compounds (ENOC) intakes for each subject was estimated as previously described.[11]

Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for the development of EAC were estimated by Cox proportional hazards regression. The correct sentence are: Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) for the development of EAC were estimated by Cox proportional hazards regression models. We treated meat (unprocessed red, processed and white) and heme iron intake as categorical variables (in tertiles) and continuous variables in the regression models. Tests for trend were performed by creating a continuous variable from the medians of the categories. All dietary variables were adjusted for total energy using the nutrient density method. Models for the continuous variables of meat (unprocessed red, white and processed) (for 25 g/2,000 kcal) and heme iron (1 mg/2,000 kcal) were performed. Recognized as potential risk factors for EAC[3] were considered as potential confounders including sex, smoking status (never, former, smoker and unknown), number of cigarettes (cig/d), time since quitting smoking (y), body mass index (BMI)(kg/m^2), total energy intake (kcal/d), fresh fruits (g/2,000 kcal) and vegetables intake (g/2,000 kcal) and educational level (none, primary school, technical/professional school, secondary school, longer educational and not specified) and included in the mode in the final model. To eliminate the possibility that undiagnosed cases might have changed their dietary habits before completing the baseline questionnaire, which could bias the observed association, sensitivity analyses were performed excluding the first 2 years of follow-up.

Results of a detailed computerized 24-hr diet recall method[12] that was performed as a second dietary assessment (between 1995 and 1999) in a random sample of the cohort (7.1% of total cohort; n = 36,994 participants) were used to calibrate dietary measurements across countries and to correct observed uncalibrated risk estimates for measurement error of dietary intakes.[13] This approach was applied to calibrate meat (and meat types) and heme iron intakes as previously described.[14]

Results

During a mean follow-up of 11 years, a total of 137 EAC cases were identified. The number of cases by country and the related mean consumption of types of meat are summarized in Table 1. Overall, intakes of all meat types were higher in men than in women. The highest consumption of all meats was found in Spain, Denmark and Netherlands and the lowest in the United Kingdom (health conscious cohort). Baseline characteristics of the cohort participants according to tertiles of dietary intake of heme iron, unprocessed red, white and processed red meat are reported in Table 2 (descriptive analysis). Subjects with the highest intake of heme iron tended to be older, had a higher mean BMI, had a lower educational level, drank more alcohol and more frequently smoked. Subjects with higher red meat intake were older, also tended to consume more white meat, had a lower educational level, were more likely to be current smokers and smoked more cigarettes. Subjects with higher dietary intake of white meat were mainly women, reported a higher consumption of vegetables and fruit and were less likely to be current smokers. Finally, subjects with a higher intake of processed meats consumed fewer vegetables and fruits, were less educated and more likely to be current smokers.

Table 3 shows the HRs and 95% CI for the association between dietary intakes of heme iron, unprocessed red, white and processed meat and EAC risk. After adjustment for potential confounders, processed meat was positively associated with EAC (HR for the highest *vs.* lowest tertile: 2.27, 95% CI: 1.33–3.89, p-trend = 0.004). However, estimated risks for unprocessed red and white meats were not statistically significant. In the continuous analysis, we observed a positive significant association with processed meat (HR for 25 g/2,000 kcal: 1.29, 95% CI: 1.08–1.54), which became borderline in the calibrated model (HR for 25 g/2,000 kcal: 1.33, 95% CI: 0.97–1.82).

Dietary intake of heme iron was associated with an increased risk of EAC, HR for the highest *vs.* lowest tertile: 1.67, 95% CI: 1.05–2.68, p-trend = 0.022 in the categorical analysis. In the continuous analysis, the association was positive but borderline significant in the uncalibrated and calibrated models (HR for 25 g/2,000 kcal: 1.24, 95% CI: 0.97–1.59 and $HR_{calibrated}$: 1.30, 95% CI: 0.98–1.73). The positive association between processed meat and EAC remained significant even after adjustment for heme iron intake ($HR_{calibratedl}$ 1 mg/2,000 kca: 1.34, 95% CI: 1.00–1.78) (data not shown).

Excluding the first 2 years of follow-up (resulting in the exclusion of 17 cases) did not change the uncalibrated

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Table 1. Description of the EPIC cohort

Country	Cohort	PY	Adenocarcinoma	Heme iron,[1] mean (mg/d)	Red meat intake, mean (g/d)	White meat intake, mean (g/d)	Processed meat intake, mean (g/d)	Total meat intake, mean (g/d)
France	66,541	690,760	1	1.31	47.81	19.94	30.42	98.17
Italy	44,342	498,149	3	1.3	49.27	25.74	24.76	99.77
Spain	39,074	471,740	4	1.81	41.65	34.77	36.82	113.25
United Kingdom	74,852	832,466	52	0.56	24.93	17.45	16.02	58.39
The Netherlands	36,086	426,283	12	1.18	60.63	12.21	29.97	102.81
Germany	47,700	471,929	8	1.15	29.54	12.1	59.84	101.48
Sweden	48,591	637,782	25	1.24	27.79	10.37	41.24	79.4
Denmark	54,349	594,186	32	1.61	75.69	21.45	26.27	126.4
Total	472,538	5,211,430	137	1.21	42.4	18.77	31.18	92.35

[1]432 missing values and 1 is an adenocarcinoma case.

associations for processed meat (HR for 25 g/200 kcal: 1.29, 95% CI: 1.07–1.57) and heme iron (HR for 1 mg/200 kcal: 1.28, 95% CI: 0.98–1.66) (data not shown).

Discussion

In this large prospective European study, we show a potential association between higher intakes of processed meat and heme iron and risk of EAC.

Several case-control studies have investigated associations between meat intake and EAC risk[3,15] however, results were inconsistent. A prospective study conducted in the United States including more than 600 EAC cases did not show any association between red or processed meat and EAC.[16] Recent findings from Netherlands Cohort study[17] showed that a high consumption of unprocessed and processed red meat was positively associated with the risk of ESCC in men but not with EAC. Our previous analysis based on 65 EAC cases[7] showed a strong positive association with processed meat intake and a weaker and nonsignificant association with red meat intake. This new analysis including a greater number of cases (137 EAC) confirms the previous result for processed meat intake. Moreover, results from a recent EPIC study on ESCC based on 151 cases also found a positive association with processed meat intake (calibrated HR: 1.42, 95% CI: 1.13–1.76).[18]

Regarding dietary heme iron intake, a case-control study (population-based) conducted in Ireland based on 224 EAC cases reported a positive significant association between heme iron intake and EAC (highest *vs.* lowest quartile OR: 3.11; 95% CI: 1.46–6.61, p-trend = 0.009).[19] Another case-control (population-based) study that included 124 EAC cases also suggested a positive significant association with heme iron intake (HR highest *vs.* lowest quintile: 3.04, 95% CI: 1.20–7.72, p-trend = 0.009).[20] The only prospective study published until now on heme iron intake and EAC reported a positive nonsignificant association (HR highest *vs.* lowest quartile: 1.47, 95% CI: 0.99–2.2, p-trend = 0.063).[16]

Heme iron is an organic form of iron and represents about two thirds of total body iron. It has a greater bioavailability than inorganic iron and may well be a more informative marker of potential iron toxicity.[21] Studies carried out by Bingham and coworkers[6] showed that heme iron stimulates endogenous intestinal *N*-nitrosation in humans. In fact, we showed a dose-response relationship between intake of iron from meat and endogenous formation of NOCs.[11] Moreover, iron contributes to the formation of free radicals.[22] Many known risk factors for EAC such as esophageal inflammation due to gastroesophageal reflux and cigarette smoking are all associated with oxidative stress that may act as an unifying underlying mechanism together with heme iron in the esophageal carcinogenesis process.

In the Second World Cancer Research Fund Expert Report,[3] processed meat was defined as meat preserved by

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Table 2. Baseline characteristics by tertiles of heme iron, red, white and processed meat [mean (sd)]

	Heme iron (mg/2,000 kcal)		Red meat (g/2,000 kcal)		White meat (g/2,000 kcal)		Processed meat (g/2,000 kcal)	
	T1	T3	T1	T3	T1	T3	T1	T3
Nonheme iron (mg/2,000 kcal)	11.51 (2.67)	11.96 (2.29)	11.70 (2.72)	11.49 (2.13)	11.50 (2.63)	11.87 (2.28)	12.34 (2.62)	11.16 (2.13)
Heme iron (mg/2,000 kcal)	0.49 (0.26)	1.91 (0.59)	0.73 (0.66)	1.61 (0.57)	0.88 (0.70)	1.39 (0.67)	0.89 (0.72)	1.42 (0.66)
NDMA (μg/2,000 kcal)	0.13 (0.18)	0.19 (0.25)	0.16 (0.24)	0.16 (0.19)	0.19 (0.27)	0.14 (0.18)	0.08 (0.08)	0.30 (0.35)
ENOC (μg/2,000 kcal)	61.59 (17.00)	108.37 (28.34)	71.11 (30.29)	97.82 (23.69)	75.00 (29.44)	91.08 (26.03)	69.83 (24.40)	97.98 (29.52)
Meat (g/2,000 kcal)	47.83 (31.42)	124.96 (39.25)	50.70 (37.13)	126.71 (33.62)	61.62 (45.76)	115.25 (38.10)	59.93 (43.69)	116.06 (37.62)
Fresh meat (g/2,000 kcal)	29.46 (23.99)	86.69 (38.16)	23.65 (21.45)	97.98 (27.76)	32.44 (31.26)	87.13 (32.83)	53.61 (42.03)	57.44 (33.53)
Red meat (g/2,000 kcal)	17.33 (15.62)	62.91 (32.37)	10.38 (7.50)	75.93 (21.86)	29.64 (30.52)	48.20 (28.84)	35.14 (31.53)	40.33 (27.51)
White meat (g/2,000 kcal)	12.14 (15.41)	23.78 (20.17)	13.26 (18.57)	22.05 (17.80)	2.80 (2.95)	38.93 (18.12)	18.47 (20.74)	17.11 (16.16)
Processed meat (g/2,000 kcal)	18.37 (17.07)	38.27 (29.37)	27.05 (26.80)	28.73 (21.78)	29.18 (28.05)	28.12 (22.94)	6.32 (5.06)	58.62 (21.83)
Fruits and vegetables (g/2,000 kcal)	476.44 (289.35)	442.30 (268.43)	472.94 (300.93)	431.29 (248.02)	424.78 (282.75)	505.55 (270.79)	581.25 (308.07)	346.93 (207.31)
Vitamin C (mg/d)	132.36 (71.98)	124.46 (67.97)	131.56 (74.30)	122.07 (63.10)	125.27 (70.01)	132.13 (69.65)	150.82 (81.45)	109.34 (56.96)
Alcohol (g/2,000 kcal)	8.97 (12.62)	12.23 (15.16)	8.56 (12.27)	13.01 (15.55)	10.29 (14.20)	10.45 (13.68)	10.06 (13.89)	10.60 (13.87)
Total energy intake (kcal)	2,034.5 (609.71)	2,085.1 (617.49)	2,009.0 (621.68)	2,114.0 (598.35)	2,083.1 (626.69)	2,027.9 (602.37)	2,022.0 (592.43)	2,088.4 (644.86)
Age at recruitment (y)	49.74 (11.48)	52.09 (8.82)	48.95 (11.08)	52.92 (8.88)	50.06 (11.07)	51.99 (9.06)	50.85 (11.67)	50.86 (8.81)
BMI (kg/m^2)	24.39 (3.95)	26.33 (4.39)	24.64 (4.12)	25.97 (4.30)	24.67 (4.03)	26.05 (4.43)	25.16 (4.37)	25.80 (4.26)
Sex (%)								
Male	24.36	37.14	25.66	35.29	29.87	26.85	25.49	34.86
Female	75.61	62.86	74.34	64.71	70.13	73.15	74.51	65.14
Educational level (%)								
None	2.15	6.68	4.17	3.96	1.65	8.09	6.25	3.58
Primary school	18.55	30.99	19.02	29.52	21.97	28.62	22.98	28.15
Technical/professional school	22.37	20.8	21.13	23.52	23.44	19.3	18.24	26.18
Secondary school	20.84	19.32	21.18	19.85	20.98	20.01	19.87	18.94
Longer education	29.93	20.44	29.7	20.34	28.24	20.35	27.65	21.09
Not specified	6.15	1.77	4.81	2.81	3.73	3.62	5.01	2.06
Smoking status (%)								
Never	52.85	46.47	54.16	44.7	48.92	51.11	53.59	44.48
Former	27.77	25.28	26.51	26.63	26.84	25.82	25.39	27.65
Smoker	17.15	26.52	17.19	26.88	22.27	20.91	18.92	25.88
Unknown	2.23	1.73	2.14	1.79	1.96	2.16	2.1	1.99
Time since quitting (y)[1]	15.03 (10.04)	15.26 (10.11)	15.03 (10.04)	15.33 (10.13)	15.27 (10.23)	15.05 (9.93)	15.20 (10.41)	15.02 (9.86)
No. cigarettes (c/d)[2]	13.37 (8.27)	15.77 (9.34)	13.24 (8.22)	15.92 (9.29)	14.69 (8.76)	14.67 (9.09)	15.22 (10.57)	14.81 (8.24)

[1]Only for formers.
[2]Only for smokers.

Table 3. Multivariable HR and (95% confidence intervals) of EAC for observed and calibrated intakes of heme iron and unprocessed and processed red and white meat in the EPIC cohort

	EAC cases			Categorical[1]			Continuous HR (95% CI)
Tertile 2		Tertile 3		*p*-trend			
		Cases/py	HR (95% CI)	Cases/py	HR (95% CI)		
Heme Iron (mg/2,000 kcal)	136	34/1,773,100	0.96 (0.60–1.53)	59/1,797,648	1.67 (1.05–2.68)	0.048	1.21 (0.92–1.58)
Unprocessed red meat (25 g/200 kcal)[2]	137	40/1,776,344	0.91 (0.57–1.47)	61/1,790,335	1.00 (0.60–1.66)	0.911	1.00 (0.85–1.18)
Processed red meat (25 g/200 kcal)[2]	137	52/1,815,660	1.65 (0.98–2.77)	62/1,789,912	2.27 (1.33–3.89)	0.004	1.31 (1.08–1.58)
White meat (25 g/200 kcal)[2]	137	42/1,787,037	0.82 (0.50–1.20)	50/1,780,967	1.25 (0.81–1.95)	0.241	1.17 (0.92–1.50)

Models adjusted by sex, smoking status (never, former, smoker and unknown), number of cigarettes (cig/d), time since quitting smoking (y), body mass index (BMI)(kg/m^2), total energy intake (kcal/day), fresh fruits (g/2,000 kcal) and vegetables intake (g/2,000 kcal) and educational levels were (none, primary school, technical/professional school, secondary school, longer educational and not specified). py, person years.

[1]For tertile 1 (cases/person year): for: heme iron: 43/1,785,563; unprocessed red meat: 36/1,794,627; processed red meat: 23/1,762,734; white meat: 45/1,793,301.

[2]Models were mutually adjusted.

smoking, curing or salting or addition of chemical preservatives, including that contained in processed foods. This food group is rich in saturated fats and salt. Moreover, processed meat contains higher amounts of preformed nitrosamines.[23] Even though we did not detect a statistically significant association when we explored the association between dietary intake of nitrosamines (endogenous and exogenous sources) and EAC (HR: 1.41, 95% CI: 0.74–2.69 and HR: 1.26, 95% CI: 0.96–1.65) for NDMA and ENOC, respectively), an effect of these factors cannot totally be ruled out. Besides, to further explore possible factors behind the association between processed meat and EAC, we estimated the effect of processed meat adjusted by heme iron intake. The estimate remained significant ($HR_{calibrated}$: 1.34, 95% CI: 1.00–1.78) (data not shown), suggesting that other compounds or mechanisms present in processed meat are responsible for this association.

In the published literature, there is no generally agreed definition of what constitutes "processed meats." Meat products designated as processed meats may have undergone a range of different processing methods and the definitions used in different studies vary. The processed meat category in EPIC includes meatballs and hamburgers, while other epidemiological studies did not include these items. Consumption in EPIC European countries varies from 3 to 75 g/d in men and from 2 to 48 g/d in women.[24] In our study, processed meat consumption in high consumers was 10 times greater than in low consumers (highest *vs.* lowest tertile of intake). In this context, it seems important to promote public health strategies to reduce the consumption of total meat, mainly processed meat, and to increase the consumption of other iron sources such as vegetables and legumes. Moreover, a better understanding of the specific mechanisms and specific compounds behind this association would allow a more useful definition of processed meats for future studies and for clear recommendations to the general population.

The strengths of our study include a wide range of meat intake. Moreover, the prospective design minimizes recall and selection bias. However, as all observational studies, our study may suffer from residual confounding by unknown risk factors of EAC or incomplete information on confounders. For instance, we do not have information on the prevalence of gastresophageal reflux disease and *Helicobacter pylori* infection for the EC cases in the EPIC cohort. Another limitation in our study is the measurement error in dietary intake, although we were able to correct our risk estimates in the calibrated models. However, for some specific food items that are not consume daily (such processed meat), calibration would attenuate our estimations due to its inability to capture variation within days using a single 24-hr recall. In our study, heme iron was calculated using specific factors for each type of meat.[14] However, since we did not perform any direct measure of the heme content of the meat, we cannot overcome the limitation of assigning values using published data. Another limitation could be lack of information on cooking method that hampered the possibility to explore other compounds related to processed meat such as heterocyclic amineas or polycicic aromatic hydrocarbons.

In summary, in this large cohort study, higher intakes of processed meat and heme iron may be associated with an increased risk of developing EAC. Further studies are needed to confirm this tentative association and to elucidate which specific components present in processed meat are implicated.

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Short Report