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Meat and haem iron intake in relation to glioma in the European Prospective Investigation into Cancer and Nutrition study

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Data sharing: For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php

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Abstract

Background—Diets high in red or processed meat have been positively associated with some cancers and several possible underlying mechanisms have been proposed, including iron-related pathways. However, the role of meat intake on adult glioma risk has yielded conflicting findings due to small sample sizes and heterogeneous tumor classifications.

Objective—The study objective was to examine red meat, processed meat and iron intake in relation to glioma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Methods—In this prospective cohort study, 408,751 individuals from nine European countries completed demographic and dietary questionnaires at recruitment. Multivariable Cox proportional hazards models were used to examine intake of red meat, processed meat, total dietary iron and haem iron in relation to incident glioma.

Results—During an average follow-up of 14.1 years, 688 incident glioma cases were diagnosed. There was no evidence that any of the meat variables (red, processed meat, or subtypes of meat) or iron (total or haem) were associated with glioma; results were unchanged when the first two years of follow-up was excluded.

Conclusion—This study suggests that there is no association between meat or iron intake and adult glioma. This is the largest prospective analysis of meat and iron in relation to glioma and as such provides a substantial contribution to a limited and inconsistent literature.

Keywords

EPIC; glioma; brain cancer; N-nitroso compounds; processed meat; red meat; dietary iron; haem iron

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Introduction

Diets high in red or processed meat have been positively associated with several cancers (Abid et al., 2014), through complex mechanisms that include haem iron and the formation of *N*-nitroso compounds (NOCs)(Cross et al., 2003). The International Agency for Research on Cancer recently classified red meat and processed meat as class 2A and 1 carcinogens, respectively (Bouvard et al., 2015). Exposure to NOCs occurs from endogenous formation, which is directly related to red meat intake, and from exogenous exposure from nitrate- and nitrite-preserved meats. Haem iron, which is primarily found in red meat, has been shown to increase endogenous NOC formation (Cross, Pollock, & Bingham 2003) and may increase the risk of some common cancers (Fonseca-Nunes et al., 2014). NOCs may be highly carcinogenic and able to pass through the blood-brain barrier (McKinney, 2004), thus providing a mechanism through which the dietary components under examination could have been associated with glioma risk. A recent meta-analysis reported that processed meat may be positively associated with glioma (Wei et al., 2015); however, the majority of evidence available is from case-control studies, and iron intake has not been examined. Our aim was to examine intake of red meat, processed meat, total iron, and haem iron in relation to adult incident glioma risk in the large European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Methods

From 1992-2000, the EPIC study recruited 521 448 adults (aged 25-70 years) from Denmark, France, Germany, Greece, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom (Riboli et al., 2002). Questionnaires on demographics, diet and other lifestyle factors were completed by participants at baseline. All EPIC centers measured height, weight, waist, and hip circumference except France, Norway, and Oxford where they were self-reported. The study was approved by all relevant ethical review boards, and all participants provided consent for the retention of acquired data and follow-up for incidence of cancer and death.

Dietary intake over the past year was assessed at baseline through country-specific questionnaires (Riboli, Hunt, Slimaniet al. 2002). Red and processed meat definitions within EPIC are described elsewhere (Rohrmann et al., 2013). The proportion of total iron that is haem iron was estimated to be 65% in cooked beef, 39% in pork and chicken, and 26% in fish (Balder et al., 2006).

Each participant was followed from baseline to cancer diagnosis, emigration, loss to follow-up, death, or end of study follow-up (which varied by center from June 2008-December 2013), whichever came first. Incident glioma cases were identified as site code C71 using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and morphology codes 9380-9460 from the International Classification of Diseases for Oncology (ICD-O).

France was not included in the present analysis as there were insufficient data to distinguish tumor histology (n=74,523). Among the remaining participants, we excluded those with prevalent cancer at baseline (n=11.479), incomplete questionnaire data (n=6,837) or cancer follow-up data (n = 23,566) or if their energy intake versus energy requirement values were in the top or bottom 1% of the distribution (n=8,219). The analytical sample size was 408, 751.

We examined energy-adjusted meat and iron as continuous variables and within fifths derived from the distribution among the total cohort; tests for linear trend were obtained using a continuous variable with values equal to the median intake within each fifth. Hazard ratios (HR) and 95% confidence intervals (CI) for glioma were estimated by Cox proportional hazards regression models, with person-years as the underlying time variable, stratified by age (rounded to one year), sex, and country. Smoking status, education, body mass index (kg/m^2), physical activity, and intake of alcohol, total fat, saturated fat, fruit, vegetables and vitamin C were not included as covariates as none of them substantially (>10%) altered the risk estimates of the primary exposures. As sensitivity analyses, the first two years of follow-up were excluded to reduce the likelihood of dietary reports being influenced by potential changes in appetite related to undiagnosed glioma (reverse causality). The proportional hazards assumption was validated through examination of Martingale residuals.

Results

Descriptive characteristics of the cohort are presented in Table 1. During an average of 14.1 years of follow-up (5770398 person years), there were 324 glioma cases among men and 364 glioma cases among women.

Intake of red meat, processed meat, total iron, or haem iron was not associated with glioma (Table 2). These null results persisted for sex-specific dietary fifths, subtypes of meat and processed meat, after excluding incident glioma cases occurring within two years of recruitment (data not shown) and when absolute amounts of meat and iron were analyzed. No interactions were detected for age (above/below median) or smoking status for red meat, processed meat, or total iron (p values > 0.10). For haem iron, interactions were null by age (p 0.29). A marginally significant interaction by smoking status (p 0.08) suggested the potential for differences in the haem-glioma association by smoking status; however subgroup results are not provided given the lack of statistical significance.

Discussion

In this large prospective European study, red meat, processed meat, and total iron were not associated with the risk of glioma. The majority of previous studies to evaluate the NOC hypothesis in relation to glioma are retrospective studies; limited evidence supported the presence of an association (Lee et al., 1997) . The results of the present study are consistent with other prospective results for red meat (Dubrow et al., 2010;Michaud et al., 2009)and processed meat (Wei, Zou, Caoet al. 2015); to the best of our knowledge, no other prospective investigations of total iron and haem iron in relation to glioma have been conducted.

The present study is the largest and only the fourth prospective cohort study to investigate the association between meat intake and adult glioma. Furthermore, it is the first study to assess this association in relation to total dietary iron intake. The prospective design precluded recall bias, and selection bias was minimized by the very high rate of follow-up over a long period of time. Equivalent baseline characteristics among exposure groups allowed for adequate comparisons to be made. The large number of incident cases of glioma was clearly defined and recorded which allowed for stratified analyses. A wide detailed range of meat intake was assessed in country-specific FFQs, which allowed for inclusion of a wide variety of dietary habits. A number of potential dietary and non-dietary factors were assessed for confounding, including measured height and weight for the majority of participants.

However, this study had several limitations. Food and nutrient intake was measured via multiple FFQs, which are subject to measurement error and may explain the lack of associations in the current study. However, the validation of these FFQs has been discussed previously and dietary estimates have been shown to be representative of European diets (Riboli, Hunt, Slimaniet al. 2002). In addition, direct estimates of dietary intake of individual NOCs were not calculated. Unrecorded information on cooking methods provided a limitation to explore other compounds related to meat such as heterocyclic amines or polycyclic aromatic hydrocarbons. Furthermore, usual dietary intake in the past year was assessed only at recruitment with no repeated measures, and may therefore not have captured diet during the etiologically relevant exposure period. Haem iron was calculated using specific factors for each type of meat, not measured directly, thus results are limited in interpretation due to assigning values using reported levels in the literature. In the future, the use of biomarkers of dietary intake may address some of limitations described above.

In summary, this study provides no indication that red meat or processed meat is associated with risk of adult glioma. Moreover, no significant associations were observed between iron intake and risk of glioma. These results do not provide support for the NOC hypothesis in relation to meat intake and adult glioma; however, future studies are warranted in order to confirm these findings and to determine whether specific biological mechanisms related to meat intake may be important.

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Table 1

Baseline characteristics according to study-wide fifths of red meat, processed meat, total iron and haem iron intake

	Red meat intake			Processed meat intake			Total iron intake			Heme iron intake		
Characteristic [a]	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
No. of individuals	81748	81749	81751	81751	81751	81749	81748	81750	81751	81750	81751	81750
Age (years)	47.1	51.7	53.1	49.1	51.9	50.6	50.2	51.2	51.4	47.8	51.7	52.1
Height (cm)	166.9	166.0	167.8	164.8	167.2	168.1	168.7	166.9	164.5	166.9	166.3	167.4
BMI (kg/m^2)	24.5	26.0	26.7	25.5	25.8	26.3	25.2	25.6	26.8	24.2	26.0	26.9
Female (%)	71.9	67.8	55.1	71.3	64.2	59.0	59.2	67.0	67.0	73.4	67.7	52.7
Smoking status (%) [b]												
Never	54.9	45.3	38.6	55.0	44.4	40.5	42.2	46.0	50.3	53.6	44.6	41.9
Former	27.6	28.1	28.6	24.6	28.6	29.3	26.4	29.2	26.4	29.2	27.8	26.4
Current	16.3	24.9	31.9	18.5	25.7	28.8	29.8	23.6	21.8	15.7	26.0	30.7
Highest education level (%) [b]												
None	4.8	5.6	4.0	9.1	4.0	4.2	1.4	3.6	12.2	2.1	5.5	7.2
Primary school	16.3	31.0	33.6	22.8	29.2	31.0	30.5	26.9	29.5	15.0	30.5	35.2
Technical/professional school	23.3	25.8	29.7	17.9	28.1	30.5	28.0	27.6	20.9	24.2	27.5	25.1
Secondary school	16.7	16.1	13.8	15.7	16.4	13.8	18.6	16.2	12.1	17.0	16.4	13.5
Longer education	33.6	19.4	17.0	29.9	19.8	19.6	19.2	23.3	22.1	35.0	18.4	18.1
Physical activity (%) [b]												
Inactive	19.7	22.8	20.3	27.8	19.5	18.8	19.6	19.3	28.1	19.4	21.3	23.2
Moderately inactive	33.1	31.6	31.4	30.7	32.1	32.3	31.2	32.4	31.4	32.5	31.1	32.4
Moderately active	26.3	26.3	22.1	22.7	24.9	28.8	26.9	25.5	22.6	25.6	26.5	22.9
Active	19.5	17.2	22.9	17.6	21.1	17.7	19.5	20.7	16.8	20.5	18.6	19.9
Alcohol intake (g/day) [c]	3.7	4.9	8.6	3.7	6.0	5.1	3.6	6.3	4.9	4.1	5.2	6.9
Total fat intake (g/day) [c]	74.6	76.6	78.5	74.1	76.0	78.1	84.1	76.4	66.7	69.5	77.6	78.1
Saturated fat intake (g/day) [c]	28.5	28.4	29.4	24.9	29.1	30.3	34.5	29.2	21.9	26.4	29.0	28.4
Vitamin C intake (g/day) [c]	107.4	111.0	101.6	148.0	105.9	92.8	91.2	109.3	137.3	123.8	108.7	101.9
Vegetable intake (g/day) [c]	139.8	158.1	160.5	280.2	152.5	122.1	113.7	161.3	249.3	196.2	153.6	155.9
Fruit intake (g/day) [c]	180.5	192.7	161.0	276.1	183.1	125.2	144.7	186.7	234.8	212.6	185.5	162.3

[a] Values are mean unless otherwise noted

[b] Data does not sum to 100% due to missing data

[c] Median values

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Table 2

Meat and iron intake and the risk of incident glioma in the EPIC study

	Continuous [c]	Fifth of intake					P for trend
		1	2	3	4	5	
Red meat							
Intake, g/1000kcals [a]	20.2	2.67	10.18	17.36	26.52	44.46	
Cases	688	135	127	125	146	155	
HR [b] (95% CI)	1.01 (0.96,1.07)	1.00	1.00 (0.79,1.29)	1.02 (0.79,1.32)	0.99 (0.76,1.30)	0.99 (0.75,1.31)	0.93
Processed meat							
Intake, g/1000kcals [a]	15.3	1.11	6.48	12.28	19.68	36.89	
Cases	688	109	145	138	152	144	
HR [b] (95% CI)	1.02 (0.99,1.05)	1.00	0.99 (0.75,1.31)	1.04 (0.79,1.38)	1.02 (0.77,1.36)	1.12 (0.83,1.51)	0.36
Total Iron							
Intake, mg/1000kcals [a]	6.33	4.72	5.60	6.19	6.86	8.23	
Cases	688	133	142	149	143	121	
HR [b] (95% CI)	1.00 (0.94,1.07)	1.00	1.06 (0.84,1.35)	1.09 (0.85,1.38)	1.04 (0.81,1.34)	0.94 (0.71,1.24)	0.63
Heme Iron							
Intake, mg/1000kcals [a]	0.54	0.14	0.36	0.50	0.67	1.04	
Cases	688	134	114	144	154	142	
HR [b] (95% CI)	0.95 (0.74,1.22)	1.00	0.88 (0.68,1.15)	1.03 (0.80,1.35)	1.15 (0.90,1.49)	0.96 (0.73,1.26)	0.78

[a]Median intake.

[b]Hazard ratios (HRs) and 95% confidence intervals (CI) from Cox proportional hazards models were adjusted for caloric intake (energy-adjusted quintiles), age, sex and country.

[c]Red meat intake (per 10g/day), processed meat intake (per 5g/day), total iron (per g/day), haem iron (per g/day)