Cancer Epidemiology, Biomarkers & Prevention

Red Meat, Dietary Nitrosamines, and Heme Iron and Risk of Bladder Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Abstract

Background: Previous epidemiologic studies found inconsistent results for the association between red meat intake, nitrosamines [NDMA: *N*-nitrosodimethylamine, and ENOC (endogenous nitroso compounds)], and the risk of bladder cancer. We investigated the association between red meat consumption, dietary nitrosamines, and heme iron and the risk of bladder cancer among participants of the European Prospective Investigation into Cancer and Nutrition (EPIC).

Methods: Data on food consumption and complete follow-up for cancer occurrence were available for a total of 481,419 participants, recruited in 10 European countries. Estimates of HRs were obtained by proportional hazard models, stratified by age at recruitment, gender, and study center and adjusted for total energy intake, smoking status, lifetime intensity of smoking, duration of smoking, educational level, and BMI.

Results: After a mean follow-up of 8.7 years, 1,001 participants were diagnosed with bladder cancer. We found no overall association between intake of red meat ($\log_2$ HR: 1.06; 95% CI: 0.99–1.13), nitrosamines ($\log_2$ HR: 1.09; 95% CI: 0.92–1.30 and HR: 0.98; 95% CI: 0.92–1.05 for ENOC and NDMA, respectively) or heme iron ($\log_2$ HR: 1.05; 95 CI: 0.99–1.12) and bladder cancer risk. The associations did not vary by sex, high- versus low-risk bladder cancers, smoking status, or occupation (high vs. low risk).

Conclusions: Our findings do not support an effect of red meat intake, nitrosamines (endogenous or exogenous), or heme iron intake on bladder cancer risk. *Cancer Epidemiol Biomarkers Prev; 20(3); 555–9. ©2011 AACR.*

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Introduction

Meat may be involved in bladder carcinogenesis via several biological mechanisms (1). One possible mechanism involves the formation of endogenous nitrosamines from heme contained in fresh and processed meat (2). Nitrosamines have been shown to cause a wide range of tumors, including cancer of the bladder, in more than 40 animal species (3). Intake of red meat (the most important source of heme iron) has shown inconsistent results with bladder cancer in epidemiologic studies (4, 5). A recent study has shown a positive association between dietary nitrite from processed meat and bladder cancer risk (6). The aim of the present study was to examine the association between red meat intake, dietary nitrosamines (endogenous and exogenous), heme iron intake, and

Table 1. Adjusted HRs for full cohort and prognostically high- and low-risk bladder cancer by quartiles of heme iron and red meat intake, ENOC, and NDMA[a]

	Heme iron[b]		Red meat intake[c] (fresh and processed meat)		ENOC[d]		NDMA[e]	
	Cases	HR	Cases	HR	Cases	HR	Cases	HR
Full cohort (n = 481,419)								
Q1	171	1.00	144	1.00	157	1.00	165	1.00
Q2	219	1.04 (0.84–1.28)	233	1.20 (0.96–1.49)	214	1.05 (0.84–1.30)	190	1.14 (0.91–1.42)
Q3	268	1.09 (0.88–1.35)	269	1.14 (0.91–1.42)	274	1.12 (0.90–1.39)	226	1.07 (0.85–1.34)
Q4	343	1.10 (0.88–1.39)	355	1.15 (0.90–1.45)	354	1.12 (0.89–1.42)	420	1.12 (0.88–1.44)
P_{trend}		0.39		0.49		0.30		0.49
log_2	1,001	1.05 (0.99–1.12)	1,001	1.06 (0.99–1.13)	999[f]	1.09 (0.92–1.30)	1,001	0.98 (0.92–1.05)
High risk[g]								
Q1	72	1.00	64	1.00	67	1.00	89	1.00
Q2	111	1.16 (0.86–1.56)	111	1.16 (0.86–1.58)	113	1.15 (0.85–1.55)	97	1.11 (0.83–1.49)
Q3	140	1.19 (0.88–1.59)	137	1.13 (0.84–1.53)	144	1.18 (0.87–1.59)	113	1.03 (0.76–1.40)
Q4	161	1.00 (0.73–1.37)	172	1.05 (0.76–1.44)	160	1.00 (0.73–1.37)	185	0.99 (0.72–1.36)
P_{trend}		0.88		0.15		0.92		0.98
log_2	484	1.07 (0.97–1.19)	484	1.09 (0.98–1.21)	484	0.95 (0.73–1.22)	484	1.00 (0.91–1.10)
Low risk[g]								
Q1	77	1.00	64	1.00	73	1.00	69	1.00
Q2	110	1.04 (0.77–1.40)	112	1.19 (0.87–1.62)	100	0.95 (0.70–1.29)	87	1.11 (0.81–1.53)
Q3	112	0.92 (0.68–1.25)	120	1.07 (0.78–1.47)	118	0.92 (0.67–1.25)	105	1.04 (0.75–1.44)
Q4	172	1.10 (0.81–1.51)	175	1.16 (0.84–1.61)	179	1.04 (0.76–1.43)	210	1.16 (0.83–1.63)
P_{trend}		0.22		0.28		0.37		0.16
log_2	471	1.05 (0.95–1.15)	471	1.06 (0.96–1.17)	470[h]	1.24 (0.96–1.59)	471	0.99 (0.90–1.09)

[a]The Cox regression model stratified by age at recruitment, sex, and center and adjusted for educational level, BMI (as continuous variable), smoking status, lifetime intensity of smoking (number of cigarettes per day), time since quitting or duration of smoking, and total energy intake.
[b]Heme iron (mg/d): Q1, 0–<0.6; Q2, >0.6–<1.02; Q3, >1.02–<1.53; Q4, >1.53–4.
[c]Red meat intake (g/d): Q1, 0–57.86; Q2, 57.86–91.42; Q3, 91.42–130.63; Q4, 130.63–754.79.
[d]ENOC (μg/d): Q1, 40.52; Q2, 62.91–78.27; Q3, 78.27–98.45; Q4, 98.46–201.41.
[e]NDMA (μg/d): Q1, 0–0.05; Q2, 0.05–0.1; Q3, 0.10–0.19; Q4, 0.19–21.11.
[f]Two missing values for ENOC.
[g]Excludes 46 cases that could not be classified into prognostically high- or low-risk bladder cancer.
[h]One missing value for ENOC.

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Table 2. Adjusted[a] HRs for bladder cancer by heme iron and red meat intake, ENOC, and NDMA

	Heme iron		Red meat intake[b]		ENOC		NDMA	
	Cases	HR	Cases	HR	Cases	HR	Cases	HR
Tobacco smoking								
Current smokers (n = 108,011)								
Q1	41	1.00	43	1.00	40	1.00	48	1.00
Q2	87	1.16 (0.79–1.71)	80	1.04 (0.70–1.52)	79	1.04 (0.71–1.54)	63	0.96 (0.65–1.43)
Q3	105	1.03 (0.70–1.53)	101	0.92 (0.63–1.35)	112	1.07 (0.73–1.57)	94	0.99 (0.67–1.45)
Q4	187	1.20 (0.80–1.79)	196	1.12 (0.76–1.65)	189	1.18 (0.79–1.75)	215	1.06 (0.71–1.58)
P_{trend}		0.43		0.54		0.35		0.67
log_2	420	1.07 (0.94–1.23)	420	1.06 (0.92–1.21)	420	1.12 (0.85–1.48)	420	0.98 (0.89–1.09)
Former smokers (n = 128,094)								
Q1	76	1.00	57	1.00	72	1.00	60	1.00
Q2	81	0.94 (0.67–1.32)	87	1.16 (0.82–1.66)	79	0.94 (0.67–1.33)	69	1.29 (0.90–1.21)
Q3	106	1.12 (0.81–1.56)	112	1.25 (0.88–1.79)	107	1.07 (0.76–1.50)	87	1.21 (0.83–1.75)
Q4	105	0.95 (0.65–1.37)	112	1.01 (0.69–1.49)	110	0.94 (0.64–1.37)	152	1.24 (0.83–1.86)
P_{trend}		0.87		0.95		0.90		0.41
log_2	368	1.03 (0.94–1.14)	368	1.07 (0.97–1.18)	368	0.97 (0.73–1.30)	368	1.01 (0.91–1.12)
Never smokers (n = 235,401)								
Q1	51	1.00	41	1.00	41	1.00	55	1.00
Q2	49	1.01 (0.67–1.54)	64	1.50 (1.00–2.26)	55	1.30 (0.85–2.00)	55	1.32 (0.88–1.97)
Q3	57	1.22 (0.81–1.85)	55	1.35 (0.86–2.10)	55	1.38 (0.88–2.16)	45	1.11 (0.70–1.76)
Q4	50	1.13 (0.71–1.80)	47	1.25 (0.75–2.08)	54	1.36 (0.83–2.21)	52	1.06 (0.62–1.80)
P_{trend}		0.51		0.52		0.24		0.94
log_2	207	1.06 (0.94–1.20)	207	1.04 (0.93–1.17)	205	1.24 (0.86–1.79)	207	0.95 (0.82–1.10)
Sex								
Male (n = 142,010)								
Q1	90	1.00	70	1.00	76	1.00	78	1.00
Q2	128	1.09 (0.82–1.45)	135	1.29 (0.95–1.75)	130	1.01 (0.60–1.70)	106	1.23 (0.90–1.67)
Q3	185	1.16 (0.87–1.54)	190	1.26 (0.93–1.71)	188	0.90 (0.53–1.54)	158	1.23 (0.91–1.66)
Q4	302	1.22 (0.91–1.64)	310	1.26 (0.92–1.72)	309	0.94 (0.54–1.61)	363	1.24 (0.90–1.69)
P_{trend}		0.18		0.36		0.80		0.30
log_2	705	1.06 (0.97–1.15)	705	1.05 (0.97–1.14)	703	0.99 (0.88–1.12)	705	1.00 (0.93–1.08)
Female (n = 339,409)								
Q1	81	1.00	74	1.00	81	1.00	87	1.00
Q2	91	1.05 (0.76–1.44)	98	1.20 (0.87–1.64)	84	0.93 (0.67–1.28)	84	1.18 (0.85–1.64)
Q3	83	1.10 (0.79–1.54)	79	1.06 (0.75–1.50)	86	1.10 (0.79–1.54)	68	0.96 (0.66–1.41)
Q4	41	0.89 (0.58–1.36)	45	0.98 (0.64–1.50)	45	0.91 (0.60–1.34)	57	1.02 (0.66–1.57)
P_{trend}		0.70		0.87		0.99		0.85
log_2	296	1.05 (0.94–1.16)	296	1.07 (0.97–1.19)	296	0.95 (0.68–1.32)	296	0.95 (0.84–1.08)
Occupational exposure risk								
High (n = 389,996)[c]								
Q1	21	1.00	12	1.00	19	1.00	29	1.00
Q2	25	0.61 (0.33–1.12)	32	1.28 (0.65–2.53)	35	0.92 (0.52–1.64)	31	0.97 (0.56–1.69)
Q3	44	0.66 (0.37–1.17)	52	1.27 (0.66–2.45)	46	0.73 (0.41–1.31)	30	0.58 (0.32–1.06)
Q4	113	0.93 (0.52–1.67)	107	1.32 (0.68–2.57)	103	0.90 (0.50–1.63)	113	0.77 (0.43–1.37)
P_{trend}		0.27		0.54		0.85		0.33
log_2	203	1.10 (0.89–1.35)	203	1.09 (0.88–1.34)	203	0.98 (0.64–1.50)	203	0.98 (0.85–1.14)
Low (n = 167,236)								
Q1	64	1.00	54	1.00	64	1.00	66	1.00
Q2	77	0.78 (0.56–1.11)	85	0.91 (0.64–1.29)	85	0.88 (0.63–1.23)	66	1.19 (0.82–1.72)
Q3	117	0.96 (0.69–1.34)	106	0.91 (0.64–1.28)	115	0.95 (0.68–1.32)	105	1.45 (1.00–2.10)
Q4	147	0.91 (0.63–1.31)	160	1.01 (0.70–1.45)	140	0.96 (0.67–1.38)	168	1.39 (0.93–2.09)
P_{trend}		0.99		0.8		0.97		0.11
log_2	405	1.00 (0.89–1.12)	405	0.99 (0.89–1.09)	404	1.10 (0.82–1.47)	405	1.01 (0.91–1.12)

[a]The Cox regression model stratified by age at recruitment, sex, and center and adjusted for educational level, BMI, smoking status, lifetime intensity of smoking (number of cigarettes per day), time since quitting or duration of smoking, and total energy intake.
[b]Including fresh and processed meat.
[C]Worked in foundries, electroplating, refinery, dye production, rubber industry, textile dying, fiber preparation or weaving, leather and tanning industry, turning/metal engineering, welding shop, as asphalt worker, as truck driver, as bus/taxi driver, as welder, as hairdresser, as gasoline station worker, and as car repair worker.

bladder cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC).

Material and Methods

EPIC rationale and details were described elsewhere (7). Briefly, the EPIC study involves more than a half million people from 23 centers in 10 European countries. A lifestyle questionnaire was used to collect information about sociodemographic characteristics, lifestyle factors, and medical history. Dietary data collected by validated country-specific questionnaires recording the usual diet over the previous 12 months (8) were used to estimate red meat intake (fresh and processed meat). NDMA (*N*-nitrosodimethylamine), the most available exogenous nitroso compound, and ENOC (endogenous nitroso compounds), both in micrograms per day, were obtained from previous estimation in the EPIC-EURGAST study (9). Published information on measured values of different types of meat (10, 11) was used to estimate heme iron. The proportion of heme iron from total iron was 65% in cooked beef, 39% in pork and chicken, and 26% in fish. For those foods with mixed composition of meat (beef and pork), we applied an average factor.

After a mean follow-up of 8.7 years, 1,049 bladder cancer cases were identified. Bladder cancer ascertainment was described previously (12). We excluded 6,220 individuals without dietary or nondietary exposure information and 3,220 participants with implausible dietary data (below or above 3 SD sex-specific log of mean energy intake). We also excluded 3,500 individuals with an extreme heme iron intake (>4 mg/d). After the exclusion, we had a sample of 481,419 subjects, of which 1,001 subjects developed primary bladder cancer. Other variables such as occupational exposures were defined as previously (12). Proportional hazards models were used to estimate the association between meat intake, nitrosamines (NDMA and ENOC), and heme iron and bladder cancer risk. The time scale was age; the entry time was age at recruitment and the exit time was, for cases, age at first bladder tumor, and for noncases, age at death or last complete follow-up. All models were stratified by age, sex, and center and adjusted for educational level (none, primary school, technical/professional school, secondary school, longer education, and unknown), BMI (as continuous variable), smoking status (never, former, and current), lifetime intensity of smoking (for current smokers, <20 cigarettes per day and >20) and time since quitting (for former smokers, <10 years and >10 years), and total energy intake. The Statistical Analysis System (version 9; SAS Institute) was used for analyses.

Results

In multivariable models, the HR for highest versus lowest quartile of intake was 1.15 (95% CI: 0.90–1.45) for read meat, 1.12 (95% CI: 0.89–1.42) for ENOC, 1.12 (95% CI: 0.88–1.44 for NDMA, and 1.10 (95 CI: 0.88–1.39) for heme iron. This lack of association was supported by analyses of continuous variables (Table 1).

No differences were observed when fresh meat and processed red meat were assessed separately (data not shown). Calibration of dietary variables did not change our findings (data not shown), Furthermore, similar findings were found when stratifying bladder cancer cases by risk of progression (13). There was no association between heme iron and bladder cancer risk (Table 2) within strata of sex (male vs. female), tobacco smoking (never, former, current), and occupational exposure (high vs. low risk).

Discussion

In this prospective study, we found no overall association between intake of red meat (fresh and processed meat), nitrosamines, or heme iron and bladder cancer risk. The results did not vary by sex, risk of progression, smoking status, or occupational exposure (high vs. low risk). Although there was no association between the intake of red meat and bladder cancer risk in a previously published analysis in EPIC (14), it does not preclude an association with certain aspects of meat intake, such as its content of heme iron, or nitrosamines. However, we were not able to find an association with any particular meat-related compound.

To our knowledge, this is the first prospective study of heme iron intake and bladder cancer risk. The strengths of this study include its large size, prospective design, and inclusion of potential confounding variables.

In summary, our findings do not support the hypothesis that red meat and meat-related compounds are associated with the risk of developing bladder cancer. Considering the biological plausibility of an association between red meat intake and bladder cancer risk, further investigation is warranted, given the limited available evidence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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