

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

Paula Jakszyn¹, Carlos A. González¹, Leila Luján-Barroso¹, Martine M. Ros^{2,3}, H. Bas Bueno-de-Mesquita², Nina Roswall⁴, Anne M. Tjønneland⁴, Frederike L. Büchner^{2,3}, Lars Egevad⁵, Kim Overvad⁶, Ole Raaschou-Nielsen⁴, Françoise Clavel-Chapelon^{7,8}, Marie-Christine Boutron-Ruault^{7,8}, Marina S. Touillaud^{7,8}, Jenny Chang-Claude⁹, Naomi E. Allen¹⁰, Lambertus A. Kiemeny^{3,11,12}, Timothy J. Key¹³, Rudolf Kaaks⁹, Heiner Boeing¹⁴, Steffen Weikert^{14,15}, Antonia Trichopoulou^{16,17}, Eleni Oikonomou¹⁶, Dimosthenis Zylis¹⁶, Domenico Palli¹⁸, Franco Berrino¹⁹, Paolo Vineis^{20,21}, Rosario Tumino²², Amalia Mattiello²³, Petra H.M. Peeters²⁴, Christine L. Parr²⁵, Inger T. Gram²⁶, Guri Skeie²⁶, Maria-Jose Sánchez²⁷, Nerea Larrañaga^{28,29}, Eva Ardanaz^{30,31}, Carmen Navarro^{30,31}, Laudina Rodríguez³², David Ulmert³³, Roy Ehrnström³⁴, Göran Hallmans³⁵, Borje Ljungberg³⁶, Andrew Wilfred Roddam³⁷, Sheila A. Bingham³⁸, Kay-Tee Khaw³⁹, Nadia Slimani⁴⁰, Paolo A. Boffetta⁴⁰, Mazda Jenab⁴⁰, Traci Mouw²¹, Dominique S. Michaud²¹, and Elio Riboli²¹

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.

Authors' Affiliations: ¹Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Barcelona, Spain; ²National Institute for Public Health and the Environment (RIVM), Bilthoven; ³Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; ⁴Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; ⁵Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; ⁶Department of Clinical Epidemiology, Aarhus University Hospital, Ålborg, Denmark; ⁷INSERM (Institut National de la Santé et de la Recherche Médicale), Paris; ⁸Institut de canc_erologie Gustave Roussy, Villejuif, France; ⁹Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany; ¹⁰Cancer Research UK Epidemiology Unit, University of Oxford, Oxford, United Kingdom; ¹¹Department of Urology, Radboud University Nijmegen Medical Centre; ¹²Comprehensive Cancer Center East, Nijmegen, the Netherlands; ¹³Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; ¹⁴German Institute of Human Nutrition, Potsdam-Rehbrücke; ¹⁵Department of Urology, Charité-University Medicine Berlin, Berlin, Germany; ¹⁶WHO Collaborating Center for Food and Nutrition Policies, Department of Hygiene and Epidemiology, Medical School, University of Athens; ¹⁷Hellenic Health Foundation, Athens, Greece; ¹⁸Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute (ISPO), Florence; ¹⁹Department of Preventive &

Predictive Medicine and Epidemiology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan; ²⁰Cancer Epidemiology Department, University of Turin, Turin, Italy; ²¹Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom; ²²Cancer Registry and Histopathology Unit, Department of Oncology, "Civile M.P. Arezzo" Hospital, Ragusa; ²³Department of Clinical and Experimental Medicine, Federico II University Naples, Italy; ²⁴Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; ²⁵Institute of Basic Medical Sciences, Department of Biostatistics, University of Oslo, Oslo; ²⁶Department of Community Medicine, University of Tromsø, Tromsø, Norway; ²⁷Andalusian School of Public Health, Granada; ²⁸Public Health Department of Gipuzkoa, Basque Government, Gipuzkoa; ²⁹CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona; ³⁰Public Health Institute of Navarra, Pamplona; ³¹Epidemiology Department, Murcia Health Council, Murcia; ³²Public Health and Participation Directorate, Health and Health Care Services Council, Asturias, Spain; ³³Lund University, Department of Urology, UMAS; ³⁴University and Regional Laboratories Region Skåne, Department of Pathology, Skåne University Hospital, Malmö; Departments of ³⁵Public Health and Clinical Medicine, Nutritional Research and ³⁶Surgical and Perioperative Sciences, Urology and Andrology, University of Umeå, Umeå, Sweden; ³⁷Cancer Research UK Epidemiology Unit, University of Oxford, Oxford;

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)
<i>P</i> _{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)
<i>P</i> _{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)
<i>P</i> _{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)

^aThe 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.

^bHeme iron (mg/d): Q1, 0–<0.6; Q2, >0.6–<1.02; Q3, >1.02–<1.53; Q4, >1.53–4.

^cRed meat intake (g/d): Q1, 0–57.86; Q2, 57.86–91.42; Q3, 91.42–130.63; Q4, 130.63–754.79.

^dENOC (μg/d): Q1, 40.52; Q2, 62.91–78.27; Q3, 78.27–98.45; Q4, 98.46–201.41.

^eNDMA (μg/d): Q1, 0–0.05; Q2, 0.05–0.1; Q3, 0.10–0.19; Q4, 0.19–21.11.

^fTwo missing values for ENOC.

^gExcludes 46 cases that could not be classified into prognostically high- or low-risk bladder cancer.

^hOne missing value for ENOC.

³⁸MRC Dunn Human Nutrition Unit, Cambridge; ³⁹Department of Public Health and Primary Care, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom; and ⁴⁰International Agency for Research on Cancer, Lyon, France

Corresponding Author: Dr. Paula Jakszyn, Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute

of Oncology, AV gran via 199 (08907), L'Hospitalet de Llobregat, Barcelona, Spain. Phone: 34932607401; Fax: 349326077787. E-mail: pajak@iconcologia.net

doi: 10.1158/1055-9965.EPI-10-0971

©2011 American Association for Cancer Research.

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
<i>Tobacco smoking</i>								
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)
<i>P</i> _{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)
<i>P</i> _{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)
<i>P</i> _{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)
<i>Sex</i>								
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)
<i>P</i> _{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)
<i>P</i> _{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)
<i>Occupational exposure risk</i>								
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)
<i>P</i> _{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)
<i>P</i> _{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)

^aThe 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.

^bIncluding fresh and processed meat.

^cWorked 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 red 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.

Grant Support

The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue contre le Cancer, 3M, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la Recherche Médicale (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF; the Netherlands); Statistics Netherlands; Norwegian Cancer Society (Norway); Health Research Fund (FIS) of the Spanish Ministry of Health (Exp

P10710130), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, La Caixa (BM 06-130), RTICCC-C03/10, R06/0020; Spain); Swedish Cancer Society, Swedish Scientific Council and Regional Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council, Stroke Association, British Heart

Foundation, Department of Health, Food Standards Agency, and Wellcome Trust (United Kingdom).

Received September 10, 2010; accepted September 30, 2010; published OnlineFirst January 14, 2011.

References

1. World Cancer Research Fund American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research; 2007.
2. Bingham SA, Hughes R, Cross AJ. Effect of white versus red meat on endogenous N-nitrosation in the human colon and further evidence of a dose response. *J Nutr* 2002;132Suppl:3522S-5S.
3. Mirvish SS. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. *Cancer Lett* 1995;93:17-48.
4. Steineck G, Norell SE, Feychting M. Diet, tobacco and urothelial cancer. A 14-year follow-up of 16, 477 subjects. *Acta Oncol* 1988; 27:323-7.
5. Larsson SC, Johansson JE, Andersson SO, Wolk A. Meat intake and bladder cancer risk in a Swedish prospective cohort. *Cancer Causes Control* 2009;20:35-40. [Epub 2008 Aug 15].
6. Ferrucci LM, Sinha R, Ward MH, Graubard BI, Hollenbeck AR, Kilfoy BA, et al. Meat and components of meat and the risk of bladder cancer in the NIH-AARP Diet and Health Study. *Cancer* 2010;116:4345-53.
7. Bingham S, Riboli E. Diet and cancer—the European Prospective Investigation into Cancer and Nutrition. *Nat Rev Cancer* 2004;4:206-15.
8. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. study populations and data collection. *Public Health Nutr* 2002; 5:1113-24.
9. Jakszyn P, Bingham S, Pera G, Agudo A, Luben R, Welch A, et al. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. *Carcinogenesis* 2006;27:1497-501.
10. Carpenter CE, Clark E. Evaluation of methods used in meat iron analysis and iron content of raw and cooked meats. *J Agric food Chem* 1995;43:1824-27.
11. Kongkachuichai R, Napatthalung P, Charoensirini R. Heme and non heme iron content in animal products commonly consumed in Thailand. *J Food Comp Anal* 2002;15:389-98.
12. Büchner FL, Bueno-de-Mesquita HB, Ros MM, Kampman E, Egevad L, Overvad K, et al. Consumption of vegetables and fruit and the risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2009;125:2643-51.
13. Kiemeny LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. *Nat Genet* 2008;40:1307-12.
14. Lumbreras B, Garte S, Overvad K, Tjønneland A, Clavel-Chapelon F, Linseisen JP, et al. Meat intake and bladder cancer in a prospective study: a role for heterocyclic aromatic amines? *Cancer Causes Control* 2008;19:649-56.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association
for Cancer Research

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

Paula Jakszyn, Carlos A. González, Leila Luján-Barroso, et al.

Cancer Epidemiol Biomarkers Prev 2011;20:555-559. Published OnlineFirst January 14, 2011.

Updated version Access the most recent version of this article at:
doi:[10.1158/1055-9965.EPI-10-0971](https://doi.org/10.1158/1055-9965.EPI-10-0971)

Cited articles This article cites 13 articles, 1 of which you can access for free at:
<http://cebp.aacrjournals.org/content/20/3/555.full#ref-list-1>

Citing articles This article has been cited by 4 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/20/3/555.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/20/3/555>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.