Cancer Causes Control (2009) 20:35–40
DOI 10.1007/s10552-008-9214-x

ORIGINAL PAPER

Meat intake and bladder cancer risk in a Swedish prospective cohort

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Received: 21 May 2008 / Accepted: 19 July 2008 / Published online: 15 August 2008

Abstract
Background High meat consumption could potentially increase the risk of bladder cancer, but findings from epidemiologic studies are inconsistent. We prospectively examined the association between meat intake and bladder cancer risk in a population-based cohort study.
Methods We prospectively followed 82,002 Swedish women and men who were free from cancer and completed a food-frequency questionnaire in 1997. Incident cases of bladder cancer were identified in the Swedish cancer registries. Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI), adjusted for age, sex, education, smoking status, pack-years of smoking, and total energy intake.
Results During a mean follow-up of 9.4 years, 485 incident cases of bladder cancer (76 women and 409 men) were ascertained in the cohort. We observed no association between the intake of total or any specific type of meat and the risk of bladder cancer. The multivariate HRs (95% CIs) comparing the highest and the lowest category of intake were 1.05 (0.71–1.55) for total meat, 1.00 (0.71–1.41) for red meat, 1.01 (0.80–1.28) for processed meats, 0.96 (0.70–1.30) for chicken/poultry, and 0.92 (0.65–1.30) for fried meats/fish. The associations did not vary by sex or smoking status.
Conclusions These results do not support the hypothesis that intake of red meat, processed meat, poultry, or fried meats/fish is associated with the risk of developing bladder cancer.

Keywords Bladder cancer · Diet · Epidemiology · Meat · Prospective studies

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Introduction

High meat consumption has been associated with higher risk of several malignancies [1] and could plausibly increase the risk of bladder cancer. Meat may be involved in bladder carcinogenesis via several biological mechanisms. One possible mechanism involves the formation of heterocyclic amines and polycyclic aromatic hydrocarbons when meat is cooked at a high temperature or over an open flame [2, 3]. Heterocyclic amines and polycyclic aromatic hydrocarbons are mutagenic and carcinogenic in animal studies [2, 3]. Certain processed meat and fish products contain *N*-nitrosamines as well as nitrites, which can be endogenously converted to nitrosamines [4]. Nitrosamines have been shown to cause a wide range of tumors, including cancer of the bladder, in over 40 animal species [5, 6]. Although a high meat consumption may be a risk factor for bladder cancer, evidence from prospective cohort studies is inconclusive [7–12].

The aim of the present study was to examine the association between meat intake and bladder cancer incidence in a large prospective study of Swedish women and men.

Subjects and methods

Study population

Our study population included participants of the Swedish Mammography Cohort (SMC) and the Cohort of Swedish

Men (COSM). The SMC was established between 1987 and 1990, when all women born between 1914 and 1948 and residing in central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire on diet, body size, and education [13]. In the late autumn of 1997, all surviving participants received a new expanded questionnaire that included about 350 items concerning diet and other lifestyle factors (including cigarette smoking); 39,227 women answered the questionnaire. The COSM was initiated in the late autumn of 1997, when all men born between 1918 and 1952 and living in central Sweden (Västmanland and Örebro counties) received a questionnaire by mail that was identical (except for some sex-specific questions) to the SMC questionnaire from 1997; 48,850 men returned a completed questionnaire.

Because the SMC 1987–1990 questionnaire did not include data on smoking and because smoking is a strong risk factor for bladder cancer, eligible participants for the present analyses were women and men who completed the 1997 questionnaire. We excluded those with an erroneous or missing National Registration Number (243 women and 260 men) and those with implausible values for total energy intake [i.e., three SDs from the $\log_e$-transformed mean energy intake in women ($n = 483$) and men ($n = 568$)]. Furthermore, we excluded women diagnosed with cancer (except nonmelanoma skin cancer) between enrollment and 1 January 1998 ($n = 1{,}837$) and men with a diagnosis of cancer (except nonmelanoma skin cancer) before 1 January 1998 ($n = 2{,}684$). After these exclusions, 82,002 participants (36,664 women and 45,338 men) remained for analyses. The present study was approved by the Ethics Committee at the Karolinska Institutet in Stockholm, Sweden.

Dietary assessment

In 1997, diet was assessed using a self-administered food-frequency questionnaire (FFQ) on which participants reported their average frequency of consumption of 96 foods and beverages over the past year. Participants could choose from eight prespecified frequency categories ranging from "never" to "three or more times per day." Energy intake was calculated by multiplying the average frequency of consumption of each food by the energy content of age- and sex-specific portion sizes. Values for energy content of foods were obtained from the Swedish Food Administration Database [14]. Total meat consisted of the following food items: meatballs or hamburger; beef, pork, or veal; liver or kidney; sausage (fried, grilled, or boiled); ham, salami, or other cold cuts; and chicken or other poultry. Red meat consisted of meatballs or hamburger; beef, pork, or veal; and kidney or liver. Processed meat included sausage; and ham, salami, or cold cuts. The FFQ also elicited information on consumption of fried foods, including beef, pork, sausage, fish, and chicken. In a validation study of the FFQ, the corrected Pearson correlation coefficients between the FFQ and the mean intake assessed by four 1-week diet records ranged from 0.3 to 0.7 for meat items (Wolk A, unpublished data).

Ascertainment of bladder cancer cases

Incident bladder cancer cases were identified by computerized record linkage of the study population (using the National Registration Number assigned to each Swedish resident) to the National Swedish Cancer Register and the Regional Cancer Register covering the study area. The completeness of cancer follow-up was estimated to be almost 100% [15]. The endpoint for the present analyses was incident bladder cancer coded according to the 2nd revision of the International Classification of Disease for Oncology (ICD-O-2, codes C67.0–C67.9). We excluded participants who were diagnosed with in situ bladder cancer ($n = 20$). From information in the regional bladder cancer registry, we were able to determine tumor-node-metastasis (TNM) stage for 90.3% of the cases and grade for 88.5% of the cases. Cases with missing stage or grade were included in the analyses for total bladder cancer but were excluded from the analyses for stage or grade. We categorized cases into two groups according to the TNM stage: superficial bladder cancer ($n = 337$; stages Ta and T1) and invasive/advanced bladder cancer ($n = 101$; stages T2–T4). We also categorized disease as lower grade ($n = 132$; grade I) or higher grade ($n = 297$; grades II and III). Information on dates of death for deceased participants was obtained from the Swedish Death Registry.

Statistical analysis

We computed person-time of follow-up for each participant from 1 January 1998 until the date of bladder cancer diagnosis, death from any cause, or the end of follow-up (31 December 2007), whichever occurred first. Participants were categorized into four predetermined categories of total meat intake ($\leq$2 servings/week, 3–6 servings/week, 1–1.4 servings/day, and $\geq$1.5 servings/day) and into three predetermined categories of red meat, processed meat, specific meat items, fried meats/fish, and chicken/poultry (0–3 servings/month, 1–4 servings/week, and $\geq$5 servings/week for meat items and never, <2 servings/week, and $\geq$2 servings/week for chicken/poultry). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards models [16] with time since entry (person-time) as the underlying time metric. Analyses using age as the underlying time scale yielded almost identical HRs. We adjusted for age as a continuous

variable in the Cox model. We found no statistically significant differences in HRs between women and men. Therefore, we report HRs for both sexes combined, with adjustment for sex as a stratum variable in the model to allow for different baseline hazard rates. Besides age and sex, multivariate models were adjusted for education (primary school, high school, or university), smoking status (never, past, or current), pack-years of smoking history (i.e., number of packs of cigarettes smoked per day multiplied by the number of years of smoking; <20, 20–39, or ≥40 pack-years), and total energy intake. In addition, models were adjusted for body mass index, history of diabetes, physical activity, aspirin use, and intakes of alcohol, fruits, vegetables, fish, and milk products. However, risk estimates changed only marginally, and therefore, these adjustments were not included in the final models. We tested the proportional hazard assumption using the likelihood ratio test and found no departure from the assumption.

Tests for linear trend were conducted by using the median value of each intake category and modeling these as continuous variables in the Cox model. Tests for interaction were assessed by examining stratum-specific estimates and formally by using the likelihood ratio test. All statistical procedures were performed with SAS version 9.1 (SAS Institute, Cary, NC). All reported *p*-values are two-sided.

Results

Among the 82,002 participants included in the analysis, 485 developed incident bladder cancer (76 women and 409 men) during a mean follow-up of 9.4 years (772,272 person-years). Characteristics of the study population in 1997 by categories of total meat intake are presented in Table 1. Women and men with a high meat intake were less likely to have a postsecondary education and had higher body mass index compared with those with a low meat intake. They also had higher intakes of energy and alcohol.

We found no significant association between intakes of total meat, red meat, processed meat, or fried meats/fish and the risk of bladder cancer (Table 2). Likewise, individual red and processed meat items and chicken/poultry were not associated with bladder cancer risk. Results did not change appreciably when we excluded all cases diagnosed during the first two years of follow-up to avoid bias due to potential changes in diet and meat intake due to preclinical disease (HR for the highest vs. lowest category of total meat intake = 1.15; 95% CI, 0.74–1.78). We observed no associations for any type of meat in subgroups defined by sex or smoking status (data not shown).

The association between meat intake and bladder cancer risk did not vary significantly by stage or grade of disease. For example, the multivariate HRs comparing the highest with the lowest category of total meat intake were 1.04 (95% CI, 0.65–1.66) for superficial bladder cancer and 0.76 (95% CI, 0.34–1.73) for invasive and advanced bladder cancer. The corresponding HRs for low-grade and high-grade disease were 1.40 (95% CI, 0.59–3.35) and 0.89 (95% CI, 0.55–1.43), respectively.

Table 1 Age-standardized characteristics by category of total meat intake in 1997

	Total meat intake			
	≤2 Servings/week	3–6 Servings/week	1.0–1.4 Servings/day	≥1.5 Servings/day
No. of individuals	6,847	38,058	22,747	14,350
Sex (% men)	45.5	50.2	60.0	66.6
Age (years)	64.9	61.1	59.9	60.4
Postsecondary education (%)	20.4	18.0	16.7	16.0
Smoking status (%)				
Never	45.7	44.8	43.3	42.1
Past	29.0	31.6	32.3	33.6
Current	25.3	23.6	24.4	24.3
Pack-years of smoking[a]	17.4	17.9	19.3	19.7
Body mass index (kg/m^2)	25.0	25.3	25.6	25.7
Total physical activity (METs)[b]	42.3	42.1	41.8	41.9
Aspirin use (%)	40.6	43.0	42.8	42.4
Total energy intake (kcal/day)	1,820	2,062	2,364	2,762
Alcohol intake (g/day)	5.3	6.9	8.4	9.2

[a] Among past and current smokers only; pack-years = number of packs of cigarettes smoked per day multiplied by the number of years of smoking

[b] MET-h/day; sum of the average time per day spent in each activity multiplied by its typical energy expenditure requirements expressed in metabolic equivalents

Table 2 HR and 95% CI for incident bladder cancer by meat intake

	Cases	Person-years	HR (95% CI)[a]	HR (95% CI)[b]
Total meat				
≤2 servings/week	40	62,500	1.00	1.00
3–6 servings/week	206	359,981	1.08 (0.77–1.51)	1.04 (0.74–1.47)
1.0–1.4 servings/day	144	215,393	1.22 (0.86–1.74)	1.14 (0.80–1.64)
≥1.5 servings/day	95	134,398	1.15 (0.79–1.67)	1.05 (0.71–1.55)
p-value for trend			0.34	0.72
Red meat				
0–3 servings/month	45	66,145	1.00	1.00
1–4 servings/week	276	422,831	1.15 (0.84–1.57)	1.11 (0.81–1.52)
≥5 servings/week	164	283,296	1.11 (0.79–1.55)	1.00 (0.71–1.41)
p-value for trend			0.86	0.57
Processed meats				
0–3 servings/month	113	181,936	1.00	1.00
1–4 servings/week	157	309,374	0.87 (0.68–1.10)	0.87 (0.68–1.11)
≥5 servings/week	215	280,962	1.04 (0.83–1.31)	1.01 (0.80–1.28)
p-value for trend			0.26	0.40
Beef, pork, or veal				
0–3 servings/month	89	121,602	1.00	1.00
1–4 servings/week	375	610,655	1.16 (0.92–1.47)	1.11 (0.87–1.40)
≥5 servings/week	21	40,015	0.89 (0.56–1.44)	0.79 (0.48–1.28)
p-value for trend			0.95	0.50
Hamburger or meat balls				
0–3 servings/month	172	248,991	1.00	1.00
1–4 servings/week	274	461,149	0.97 (0.90–1.17)	0.96 (0.79–1.16)
≥5 servings/week	39	62,132	0.89 (0.63–1.27)	0.85 (0.59–1.21)
p-value for trend			0.52	0.36
Sausage (fried, grilled, or boiled)				
0–3 servings/month	219	352,151	1.00	1.00
1–4 servings/week	225	375,004	1.00 (0.83–1.21)	0.99 (0.82–1.20)
≥5 servings/week	41	45,117	1.28 (0.91–1.78)	1.21 (0.86–1.71)
p-value for trend			0.23	0.37
Chicken/poultry				
Never	102	118,634	1.00	1.00
< 2 servings/week	311	510,427	1.03 (0.82–1.29)	0.98 (0.78–1.23)
≥2 servings/week	72	143,211	1.03 (0.76–1.40)	0.96 (0.70–1.30)
p-value for trend			0.87	0.78
Fried meats/fish[c]				
0–3 servings/month	67	116,869	1.00	1.00
1–4 servings/week	349	548,649	1.06 (0.81–1.37)	1.01 (0.78–1.32)
≥5 servings/week	69	106,754	1.06 (0.76–1.49)	0.92 (0.65–1.30)
p-value for trend			0.77	0.55

[a] Adjusted for age and sex

[b] Adjusted for age, sex, education, smoking status, pack-years of smoking, and total energy intake

[c] Including fried beef, pork, sausage, fish, and chicken

Discussion

In this prospective cohort study of Swedish women and men, we observed no association between intake of total meat, red meat, processed meat, chicken/poultry, or fried meats/fish and risk of bladder cancer. The associations did not vary by sex or smoking status.

Few cohort studies have investigated associations between meat and processed meat intakes and the risk of bladder cancer. With regard to fresh meat intake and bladder cancer risk, three large cohort studies observed no associations with red meat, beef, pork, or lamb intakes [8, 9], whereas one study found a statistically significant positive association with high beef and pork intakes [7].

Two small cohort studies reported a nonsignificant increase in bladder cancer risk associated with a high intake of meat, poultry, and fish (≥3 times/week vs. none, relative risk = 1.85; 95% CI, 0.87–3.95) [10] or total meat (≥5 vs. ≤1 times/week, relative risk = 1.57; 95% CI, 0.78–3.15) [11]. In a nested case–control study, within the EPIC cohort [12], total meat intake was not associated with bladder cancer risk in the whole study population; however, a high intake of meat was associated with an increased risk of bladder cancer among those with the rapid *NAT2* genotype (odds ratio in a comparison of highest vs. lowest quartile of meat intake = 3.5; 95% CI, 1.2–9.7). Processed meat intake was not significantly associated with risk of bladder cancer in three US cohort studies [8, 9]. However, in one of those studies [9], which consisted of two cohorts combined, men and women with high intakes of bacon (≥5 servings/week) had a statistically significant 59% increased risk of bladder cancer compared with those who never consumed bacon. Case–control studies on meat intake and risk of bladder cancer have been inconsistent. One case–control study showed positive associations of bacon, ham, and sausage intake with bladder cancer risk in Japanese men but not in Japanese women or whites [17]. Three other case–control studies found an increased risk of bladder cancer associated with high intakes of red meat [18], pork [19], or fried meats [20]. No significant positive association between meat intake and bladder cancer risk was observed in five other case–control studies [21–25].

The strengths of this study include a population-based and prospective design, a large sample size, detailed information on diet and smoking history, and the completeness of case ascertainment through record linkage to Swedish cancer registries. The prospective design eliminates recall bias, and the virtually complete follow-up minimizes the likelihood that our findings have been affected by bias due to differential follow-up.

The use of a food-frequency questionnaire as an assessment instrument can cause diet to be measured with error, and measurement error is certainly present in our data. We have observed positive associations between red and processed meat intakes and risk of cancers of the colorectum, pancreas, and stomach in this study population [26–28], suggesting that failure to observe an association in the present study was not due to an inability to assess meat intake. However, we may have overlooked a weak association between meat intake and risk of bladder cancer. The food-frequency questionnaire used to assess dietary intake in 1997 did not elicit information on bacon intake. Nevertheless, this would not be much of an issue as bacon is not frequently consumed in the Swedish population; 39% never consume bacon and only 1.5% consume two or more servings per week [26]. We also did not have information on total fluid intake, which might be a potential confounder. Finally, our study is limited by the relatively short follow-up.

In conclusion, our findings do not support the hypothesis that consumption of red meat, processed meat, poultry, or fried meats/fish is associated with the risk of developing bladder cancer.

Acknowledgments This work was supported by the Swedish Cancer Foundation, Örebro County Council Research Committee, and the Swedish Research Council Committee for Infrastructure.

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