

Dietary intake of meat, fruits, vegetables, and selective micronutrients and risk of bladder cancer in the New England region of the United States

JW Wu¹, AJ Cross¹, D Baris¹, MH Ward¹, MR Karagas², A Johnson³, M Schwenn⁴, S Cherala⁵, JS Colt¹, KP Cantor^{1,6}, N Rothman¹, DT Silverman¹ and R Sinha^{*,1}

¹National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 6120 Executive Blvd, Rockville, MD 20852, USA;

²Dartmouth Medical School, Section of Biostatistics and Epidemiology, 1 Medical Center Drive, 7927 Rubin Building, Lebanon, NH 03756, USA;

³Vermont Cancer Registry, 108 Chery Street, Burlington, VT 05402, USA; ⁴Maine Cancer Registry, 286 Water Street, Fourth Floor, 11 State House

Station, Augusta, ME 04333, USA; ⁵New Hampshire department of Health and Human Services, 129 Pleasant Street, Concord, NH 03301, USA;

⁶KP Cantor Environmental LLC, 708 Bonifant Street, Silver Spring, MD 20910, USA

BACKGROUND: Despite many studies on diet and bladder cancer, there are areas that remain unexplored including meat mutagens, specific vegetable groups, and vitamins from diet.

METHODS: We conducted a population-based case–control study of bladder cancer in Maine, New Hampshire, and Vermont. A total of 1171 cases were ascertained through hospital pathology records and cancer registries from 2001 to 2004. Overall, 1418 controls were identified from the Department of Motor Vehicles (<65 years) and Center for Medicaid and Medicare Services (65–79 years) and were frequency-matched to cases by state, sex, and age (within 5 years). Diet was assessed with a self-administered Diet History Questionnaire. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI).

RESULTS: Processed meat intake was positively associated with bladder cancer (highest vs lowest quartile OR: 1.28; 95% CI: 1.00–1.65; $P_{\text{trend}} = 0.035$), with a stronger association for processed red meat (OR: 1.41; 95% CI: 1.08–1.84; $P_{\text{trend}} = 0.024$). There were no associations between intake of fruits or vegetables and bladder cancer. We did, however, observe an inverse association with vitamin B12 intake (OR: 0.77; 95% CI: 0.61–0.99; $P = 0.019$).

CONCLUSION: Vitamin B12 from diet may be protective against bladder cancer, whereas consuming processed meat may increase risk.

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Over the past few decades, the incidence of bladder cancer has been relatively constant, with an estimated 70 530 Americans (52 760 men and 17 770 women) diagnosed with bladder cancer in 2010 (Howlader *et al*, 2010). Diet is a source of carcinogenic and anticarcinogenic compounds, which may be excreted through the urine (Pelucchi *et al*, 2006). However, there is a lack of consensus on the effects of diet on bladder cancer risk. In a 2007 review of the literature, no dietary components were ‘convincingly’, or even ‘probably’, associated with risk of bladder cancer (Marmot *et al*, 2007).

With the exception of one prospective cohort (Ferrucci *et al*, 2010) and one case–control study, (García-Closas *et al*, 2007) cooking preferences of meats, which determines the formation of mutagens such as heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), have not been studied extensively in relation to bladder cancer risk. However, these meat mutagens have been associated with an increased risk of breast, colorectal, upper gastrointestinal, lung, pancreatic, and prostate cancer (Alaejos *et al*, 2008; Zheng and Lee, 2009). Furthermore, HCAs

induce tumours in multiple organs in animal studies (Ohgaki *et al*, 1987), including the urinary tract (Hashida *et al*, 1982; Takahashi *et al*, 1993).

In general, prospective cohort and case–control studies have demonstrated inconsistent results for the association between fruits and vegetables and bladder cancer (Riboli *et al*, 1991; Shibata *et al*, 1992; Chyou *et al*, 1993; Bruemmer *et al*, 1996; Michaud *et al*, 1999; Nagano *et al*, 2000; Wakai *et al*, 2000; Balbi *et al*, 2001; Zeegers *et al*, 2001b; García-Closas *et al*, 2007). There is also a lack of consistent epidemiologic data that demonstrate one particular fruit or vegetable group is protective against bladder cancer, despite the fact that clinical studies that have shown specific vegetable groups, such as brassica and allium, activate glutathione S-transferases (GSTs), which act to minimise oxidative stress (Lampe *et al*, 2000; Asaduzzaman Khan *et al*, 2010). Furthermore, a recent meta-analysis has shown that deletion of GST M1 (GSTM1) may increase the risk of bladder cancer (Jiang *et al*, 2011).

Similarly, several prospective cohort and case–control studies have evaluated the role of micronutrients in bladder cancer with variable results (Steineck *et al*, 1990; Nomura *et al*, 1991; Riboli *et al*, 1991; Shibata *et al*, 1992; Bruemmer *et al*, 1996; Michaud *et al*, 1999; Michaud *et al*, 2000; Zeegers *et al*, 2001a;

*Correspondence: Dr R Sinha; E-mail: sinhar@mail.nih.gov

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Michaud *et al*, 2002; García-Closas *et al*, 2007; Brinkman *et al*, 2010; Hotaling *et al*, 2011); however, there is evidence from laboratory and epidemiological studies that demonstrate certain micronutrients are associated with a reduced risk of specific cancer sites including the bladder (Greenwald *et al*, 2001; Leppert *et al*, 2006).

In the Spanish bladder cancer study (García-Closas *et al*, 2007), the authors found that higher compared with lower intakes of folate and B-vitamins were protective against bladder cancer and so our study aimed to confirm some of the results from that study. The Spanish bladder cancer study also analysed the role of meat cooking and related carcinogens. Therefore, we evaluated a range of dietary components, including meat (by cooking method and meat mutagens), fruits, vegetables, and micronutrients in relation to bladder cancer in a large population-based case-control study in northern New England.

MATERIALS AND METHODS

Study population

The details of the design of the New England Bladder Cancer Study have been published elsewhere (Baris *et al*, 2009). Briefly, newly diagnosed, histologically confirmed cases of urinary bladder carcinoma (including carcinoma *in situ*) aged 30–79 years were enrolled in Maine, Vermont, and New Hampshire. Enrolment of cases occurred between 1 September 2001 and 31 October 2004 in Maine and Vermont and between 1 January 2002 and 31 July 2004 in New Hampshire. Cases were ascertained through hospital pathology departments, hospital cancer registries, and the state cancer registries. Out of 1878 patients who were eligible for study, 1213 (65%) were interviewed. Reasons for non-participation included individuals who refused (50%), were deceased (22%), too ill (12%), did not speak English fluently (5.5%), had a physician refused (5%), or could not be located (5%). An expert pathologist conducted a blind review of the cases to confirm diagnosis, histological classification, and tumour stage and grade. After the review, 20 patients who were judged not to have bladder cancer and 22 who did not have urothelial carcinomas were excluded. We further excluded an additional 84 cases (7%) because they did not complete the Diet History Questionnaire (DHQ) resulting in 1087 cases.

Controls aged 30–64 and 65–79 years were identified from Department of Motor Vehicles (DMV) records and by the Centers for Medicare and Medicaid Services (CMS), respectively. Controls had no previous history of bladder cancer and were frequency-matched to the bladder cancer cases by state, sex, and within 5 years of age at diagnosis of patients. There were 1418 control subjects interviewed, which accounted for 65% of the eligible individuals from the DMV and CMS (594 and 824, respectively). A total of 319 and 444 individuals from DMV and CMS, respectively, were eligible but did not participate, including refusals (DMV – 70% and CMS – 65%), those who could not be located (DMV – 24% and CMS – 11%), who did not speak English fluently (DMV – 3% and CMS – 10%), who were too ill (DMV – 1% and CMS – 7%), or deceased (DMV – 1% and CMS – 7%). Similar to the cases, 125 controls (9%) were not included in the analysis because the individuals did not complete the DHQ ensuing in 1293 control subjects.

Individuals who agreed and consented to the study were interviewed at home by a trained interviewer using a detailed computer-assisted personal interview. The interviewer obtained information on demographics, use of tobacco products, occupational and residential histories, fluid intake, use of hair-colouring products, family history of cancer, and medication use.

Dietary assessment

Food intake over the past 5 years was assessed with a modified version of the self-administered 124 food item DHQ created by the National Cancer Institute, which included portion size and dietary supplement questions (Subar *et al*, 2001). In general, we asked, 'During the last 5 years, how often did you eat...' in order to capture usual diet over the past 5 years. The DHQ was validated among an American population aged 50–71 years old from six states that did not include the New England region (Thompson *et al*, 2008); however, the New England study population is similar to the validation population such that they were generally older, White non-Hispanic participants. Correlations between the DHQ and 24 h dietary recalls for fruits and vegetables were 0.61 and 0.72 and for red meat was 0.70 and 0.62 for women and men, respectively (Thompson *et al*, 2008; Ferrucci *et al*, 2010).

The MyPyramid Equivalents Database (MPED 2.0) was utilised as a guideline to create food groups. Fruits were categorised as citrus/berries/melons (cantaloupe, melons, grapefruit, orange, and strawberry) and other fruits (apple, apricots, avocado, banana, grapes, peaches, nectarine, plum, pear, and plantain). Vegetables were grouped as cruciferous (coleslaw, cabbage/sauerkraut, broccoli, and cauliflower/brussel sprouts), dark green (spinach (cooked and raw) and broccoli), orange (carrots and sweet potatoes), starchy (corn, peas, and potatoes), other vegetables (green beans, celery, olives, onions, lettuce, peppers, and tomatoes), and beans. Meat and fish were categorised as red (beef, veal, pork, and lamb), white (chicken and turkey), tuna, and other fish (fried and non-fried fish). Processed meat included red processed (ham, bacon, sausage, hot dog, and cold cuts) and white processed (turkey sausages and hot dogs, and poultry cold cuts). Vitamins from the diet were estimated by linking food codes from the United States Department of Agriculture's 1994 to 1996 Continuing Survey of Food Intakes by Individuals (CSFII) to those from the Nutrient Data Systems for Research (NDS-R) (Dixon *et al*, 2003).

Information was collected on how the meat and fish was cooked – baked, broiled, microwaved, pan-fried, or barbecued. Heterocyclic amines included 2-amino-3,4,8-trimethylimidazo(4,5-f)quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo(4,5-f)quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) and benzo(a)pyrene (B(a)P) intake was estimated as a marker for PAH. Total mutagenic activity, which measures mutagenicity from all meat-related mutagens, was also estimated (Ferrucci *et al*, 2010). Meat-cooking methods, HCAs, B(a)P, and total mutagenic activity were analysed using Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) (Sinha *et al*, 2005).

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression. For the meat variables, all models summed to total meat; for example, red and white meat were included in the same model, as was tuna and other fish. Dietary variables were energy-adjusted using the multivariate nutrient-density method. We excluded individuals with energy intake that fell in the 1st or 99th percentiles ($n=44$). Quartiles were created for the dietary variables and determined based on the distribution among the controls. Multivariate models were adjusted for gender, age (0–54, 55–64, 65–74, or 75+ years), region (Maine, Vermont, New Hampshire), race (White or other), Hispanic status (yes or no), smoking status (never, occasional, former, or current), usual body mass index (BMI – kg m^{-2} , continuous), and total energy (kcal per day, continuous). For the smoking status variable, 'never smokers' were defined as individuals who had <100 cigarettes in their lifetime. 'Occasional smokers' consumed >100 cigarettes but not on a regular basis

(i.e. at least one cigarette per day for at least 6 months). 'Former smokers' were individuals who quit smoking 1 year or more before the diagnosis date for case patients or selection date for control subjects, whereas 'current smokers' were regularly smoking at the time of their interview or had quit < 1 year before the reference date. More refined adjustment for smoking, including pack-years and number of cigarettes, for example, did not alter our results. Missing or unknown values were imputed with the median value of the variable. Individuals who did not have a known smoking status were excluded ($n = 2$). Adjustment for education, occupation, and use of non-steroidal anti-inflammatory drugs did not affect the association; therefore, these covariates were not included in the final model. P -values for linear trends were calculated using the quartile median values. Test for interactions were also conducted using the Wald statistic. Data analyses were calculated using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA) and all P -values were two-tailed with an α level of 0.05.

RESULTS

A total of 1068 cases (811 men and 257 women) and 1266 controls (927 men and 339 women) were included in our analysis (Table 1). The cases and controls were mostly from Maine and New Hampshire. The majority of the study subjects were White (94.5% and 94.7% for cases and controls, respectively). Cases were more likely to be current smokers compared with controls (30.1% vs 13.5%, $P < 0.001$). BMI was similar among cases ($26.2 \pm 4.4 \text{ kg m}^{-2}$) and controls ($26.0 \pm 4.1 \text{ kg m}^{-2}$). Total energy intake among cases and controls was 2041 ± 793 and

Table 1 Characteristics of cases and controls^a

Variable	Cases	Controls	P_{value}^c
<i>N</i> (%)	1068 (45.8)	1266 (54.2)	
<i>Region</i>			0.138
Maine	523 (49.0)	664 (52.5)	
Vermont	188 (17.6)	226 (17.8)	
New Hampshire	357 (33.4)	376 (29.7)	
<i>Age (years)</i>			0.662
30–54	158 (14.8)	195 (15.4)	
55–64	274 (25.7)	305 (24.1)	
65–74	404 (37.8)	504 (39.8)	
75+	232 (21.7)	262 (20.7)	
<i>Gender</i>			0.134
Male	811 (75.0)	927 (73.2)	
Female	257 (24.1)	339 (26.8)	
<i>Race</i>			0.386
White	1009 (94.5)	1197 (94.7)	
Native Americans	52 (4.9)	53 (4.2)	
Other	7 (0.7)	14 (1.1)	
<i>Hispanic status</i>			0.587
Yes	20 (1.9)	20 (1.6)	
No	1048 (98.1)	1246 (98.4)	
<i>Smoking status</i>			<0.001
Non-smoker	162 (15.2)	425 (33.6)	
Occasional	18 (1.7)	39 (3.1)	
Former	567 (53.1)	631 (49.8)	
Current	321 (30.1)	171 (13.5)	
Usual BMI (kg m^{-2}) ^b	26.2 ± 4.4	26.0 ± 4.1	0.189
Energy (kcal per day) ^b	2041 ± 793	1987 ± 711	0.081

Abbreviation: BMI = body mass index. ^aThe numbers in brackets are percentages. ^bThis is a continuous variable and a mean and a SD are given in the format of mean \pm SD. ^c P -values were tabulated using χ^2 tests (categorical variables) or t -tests (continuous variables).

1987 ± 711 kcal per day, respectively. A comparison between the controls recruited from the DMV vs CMS showed no difference in the baseline characteristics except for region and total energy intake; a higher proportion of controls from the DMV were from Vermont compared with CMS controls, and controls from the DMV had a higher total energy intake compared with those from CMS (2089 ± 707 and 1920 ± 706 kcal, respectively).

Individuals in the highest, compared with those in the lowest, quartile of processed meat intake had an increased risk of bladder cancer in multivariate models (OR: 1.28; 95% CI: 1.00–1.65; $P_{\text{trend}} = 0.035$; Table 2); the association was slightly stronger for processed red meat specifically (OR: 1.41; 95% CI: 1.08–1.84; $P_{\text{trend}} = 0.024$). In contrast, no association with bladder cancer was

Table 2 Meat and fish intake and risk of bladder cancer^{a,b}

Quartiles of intake	Median (g per 1000 kcal)	Cases	Controls	Multivariate model ^c	
				OR	95% CI
<i>Red meat</i>					
Q1	17.2	241	316	1.00	
Q2	27.6	254	317	0.97	(0.76, 1.24)
Q3	37.4	269	317	1.04	(0.81, 1.33)
Q4	53.0	304	316	1.14	(0.89, 1.46)
P_{trend}				0.258	
<i>White meat</i>					
Q1	9.6	320	316	1.00	
Q2	17.6	267	317	0.94	(0.73, 1.20)
Q3	27.7	236	316	0.85	(0.65, 1.11)
Q4	51.0	245	317	0.89	(0.67, 1.18)
P_{trend}				0.428	
<i>Processed meat</i>					
Q1	2.9	226	316	1.00	
Q2	6.1	246	317	1.01	(0.78, 1.30)
Q3	10.1	287	316	1.19	(0.92, 1.53)
Q4	18.4	309	317	1.28	(1.00, 1.65)
P_{trend}				0.035	
<i>Red, processed</i>					
Q1	1.9	200	316	1.00	
Q2	4.3	263	317	1.24	(0.96, 1.60)
Q3	7.4	289	316	1.39	(1.07, 1.81)
Q4	13.5	316	317	1.41	(1.08, 1.84)
P_{trend}				0.024	
<i>White, processed</i>					
Q1	0	278	317	1.00	
Q2	0.5	243	316	0.99	(0.77, 1.26)
Q3	1.5	270	317	1.07	(0.84, 1.36)
Q4	5.8	277	316	1.17	(0.91, 1.49)
P_{trend}				0.192	
<i>Total tuna</i>					
Q1	0.3	262	316	1.00	
Q2	1.1	254	317	1.11	(0.87, 1.43)
Q3	2.2	295	317	1.23	(0.96, 1.58)
Q4	5.3	257	316	1.10	(0.85, 1.43)
P_{trend}				0.975	
<i>Other fish</i>					
Q1	0.8	356	316	1.00	
Q2	2.2	224	317	0.65	(0.51, 0.83)
Q3	4.1	235	317	0.74	(0.57, 0.94)
Q4	8.9	253	316	0.84	(0.65, 1.10)
P_{trend}				0.452	

Abbreviations: CI = confidence intervals; OR = odds ratios. ^a P_{trends} were calculated using the median value for each quartile. ^bAll models included total meat and fish intakes. ^cAdjusted for gender (female/male), age (0–54, 55–64, 65–74, 75+ years), region (Maine, Vermont, New Hampshire), race (White/other), Hispanic status (yes/no), smoking status (never, occasional, former, current), usual BMI (kg m^{-2} – continuous), and total energy (kcal per day – continuous).

Table 3 Meat-cooking methods and risk of bladder cancer^a

Quartiles of intake	Median (g per 1000 kcal)	Cases	Controls	Multivariate model ^b	
				OR	95% CI
<i>Baking/microwaving/broiling</i>					
Q1	0.4	261	317	1.00	
Q2	2.2	270	316	1.07	(0.84, 1.36)
Q3	5.0	286	317	1.13	(0.89, 1.44)
Q4	12.6	251	316	1.00	(0.78, 1.29)
<i>P</i> _{trend}				0.814	
<i>Barbequed</i>					
Q1	0	260	317	1.00	
Q2	1.5	298	316	1.15	(0.91, 1.47)
Q3	4.1	265	316	1.04	(0.81, 1.32)
Q4	10.2	245	317	1.00	(0.78, 1.29)
<i>P</i> _{trend}				0.649	
<i>Pan-fried</i>					
Q1	0.2	228	317	1.00	
Q2	1.6	290	316	1.23	(0.96, 1.57)
Q3	3.9	239	316	0.92	(0.71, 1.18)
Q4	9.5	311	317	1.10	(0.86, 1.40)
<i>P</i> _{trend}				0.942	

Abbreviations: CI = confidence intervals; OR = odds ratios. ^a*P*_{trends} were calculated using the median value for each quartile. ^bAdjusted for gender (female/male), age (0–54, 55–64, 65–74, 75+ years), region (Maine, Vermont, New Hampshire), race (White/other), Hispanic status (yes/no), smoking status (never, occasional, former, current), usual BMI (kg m⁻² – continuous), and total energy (kcal per day – continuous).

apparent for intake of processed white meat (high vs low intake: OR: 1.17; 95% CI: 0.91–1.49; *P*_{trend} = 0.192). Given that a positive association for processed red meat was observed, we investigated specific processed meat groups. There was no significant linear, increased risk of bladder cancer associated with intake of bacon, or sausages; however, those in the highest intake category of ham (not lunchmeat), cold cuts, and hot dog compared with the lowest had a moderate, non-significant increase in risk (OR: 1.29; 95% CI: 1.00–1.68; *P*_{trend} = 0.072; OR: 1.21; 95% CI: 0.94–1.55; *P*_{trend} = 0.047; and OR: 1.18; 95% CI: 0.91–1.53; *P*_{trend} = 0.026, respectively). We did not observe any association between consumption of tuna or other types of fish and bladder cancer.

Barbequed and pan-fried meats were not associated with bladder cancer when comparing those in the highest with those in the lowest quartile (OR: 1.00; 95% CI: 0.78–1.29; *P*_{trend} = 0.649 and OR: 1.10; 95% CI: 0.86–1.40; *P*_{trend} = 0.942; respectively) (Table 3). Furthermore, there was no association between intakes of MeIQx, DiMeIQx, PhIP, B(a)P, total mutagenicity, or haeme iron intake and bladder cancer (Table 4).

Although the unadjusted models indicated inverse associations between the 'citrus, melons and berries' food group, as well as 'cruciferous vegetables', 'dark green vegetables' and 'orange vegetables' and bladder cancer (data not shown), these associations were attenuated after multivariate adjustment (Table 5). The smoking variable was the strongest confounder for the association between the fruit and vegetable groups and bladder cancer.

In general, vitamins and minerals obtained from the diet were not associated with bladder cancer after multivariate adjustment (Table 6), with the exception of vitamin B12. Individuals in the highest, compared with the lowest, quartile of vitamin B12 intake had a lower risk of bladder cancer (OR: 0.77; 95% CI: 0.61–0.99; *P* = 0.019). Vitamins acquired from supplements were not associated with bladder cancer, including vitamin B12 (data not shown).

For most dietary variables, we did not find any differences by smoking status, except among never smokers we observed decreased risks for those in the highest vs lowest category of vegetables, vitamin E, and α -carotene (Supplementary Table 1), but none

Table 4 Meat mutagens and haeme iron in relation to bladder cancer^a

Quartiles of intake	Median	Cases	Controls	Multivariate model ^b	
				OR	95% CI
<i>MeIQx (ngs)</i>					
Q1	2.9	243	317	1.00	
Q2	8.4	265	316	1.10	(0.86, 1.41)
Q3	17.6	252	317	0.95	(0.74, 1.22)
Q4	43.7	308	316	1.04	(0.81, 1.33)
<i>P</i> _{trend}				0.999	
<i>DiMeIQx (ngs)</i>					
Q1	0	245	317	1.00	
Q2	0.4	274	317	1.10	(0.86, 1.40)
Q3	1.0	265	316	1.02	(0.80, 1.30)
Q4	3.0	284	316	1.01	(0.79, 1.30)
<i>P</i> _{trend}				0.822	
<i>PhIP (ngs)</i>					
Q1	5.2	250	317	1.00	
Q2	17.2	246	316	0.95	(0.74, 1.21)
Q3	39.1	329	317	1.26	(0.99, 1.60)
Q4	117.6	243	316	0.90	(0.70, 1.17)
<i>P</i> _{trend}				0.334	
<i>B(a)P (ngs)</i>					
Q1	0.3	264	317	1.00	
Q2	1.8	278	316	1.06	(0.83, 1.34)
Q3	8.9	266	317	1.01	(0.79, 1.28)
Q4	39.7	260	316	1.02	(0.80, 1.31)
<i>P</i> _{trend}				0.969	
<i>Mutagenic activity</i>					
Q1	430.1	258	317	1.00	
Q2	1087.7	243	316	0.92	(0.72, 1.18)
Q3	2166.0	291	317	1.04	(0.82, 1.33)
Q4	5415.2	276	316	0.93	(0.72, 1.19)
<i>P</i> _{trend}				0.652	
<i>Haeme iron (mcg)</i>					
Q1	111.6	243	317	1.00	
Q2	220.5	257	316	1.01	(0.78, 1.28)
Q3	338.1	262	317	0.99	(0.77, 1.28)
Q4	565.5	306	316	1.08	(0.82, 1.42)
<i>P</i> _{trend}				0.558	

Abbreviations: CI = confidence intervals; OR = odds ratios. ^a*P*_{trends} were calculated using the median value for each quartile. ^bAdjusted for gender (female/male), age (0–54, 55–64, 65–74, 75+ years), region (Maine, Vermont, New Hampshire), race (White/other), Hispanic status (yes/no), smoking status (never, occasional, former, current), usual BMI (kg m⁻² – continuous), and total energy (kcal per day – continuous).

of the interaction terms were statistically significant (*P* > 0.05). Other results stratified by age, gender, region, or BMI were not materially different from the overall findings (data not shown).

DISCUSSION

In this large population-based case-control study, higher intake of processed meat, and processed red meat in particular, was associated with an increased risk of bladder cancer; although meat-cooking methods, HCAs and B(a)P were not associated with risk. We found no statistically significant associations between fruits or vegetables and bladder cancer. Individuals in the highest quartile of dietary vitamin B12 intake had a decreased risk of bladder cancer.

In agreement with our findings, many previous studies have not found an association between total or red meat and bladder cancer (Riboli *et al*, 1991; Chyou *et al*, 1993; Tavani *et al*, 2000; Wakai *et al*, 2000; Balbi *et al*, 2001; Cross *et al*, 2007;

Table 5 Fruit and vegetable intake and risk of bladder cancer^a

Quartiles of intake	Median (g per 1000 kcal)	Cases	Controls	Multivariate model ^b	
				OR	95% CI
Total Fruits					
Q1	33.6	295	317	1.00	
Q2	83.0	267	316	1.11	(0.87, 1.42)
Q3	135.4	256	316	1.11	(0.86, 1.42)
Q4	227.7	250	317	1.13	(0.88, 1.46)
<i>P</i> _{trend}				0.404	
Citrus, melons, and berries					
Q1	3.9	298	317	1.00	
Q2	8.6	281	316	1.06	(0.84, 1.35)
Q3	15.5	262	317	1.03	(0.81, 1.31)
Q4	38.5	227	316	0.94	(0.73, 1.21)
<i>P</i> _{trend}				0.444	
Other fruits					
Q1	7.9	304	316	1.00	
Q2	24.4	259	317	1.01	(0.79, 1.27)
Q3	49.3	262	317	1.16	(0.91, 1.48)
Q4	94.6	243	316	1.08	(0.84, 1.39)
<i>P</i> _{trend}				0.447	
Total vegetables					
Q1	64.6	290	316	1.00	
Q2	99.1	261	317	0.97	(0.76, 1.23)
Q3	130.3	282	316	1.06	(0.84, 1.35)
Q4	187.8	235	317	0.90	(0.70, 1.16)
<i>P</i> _{trend}				0.495	
Cruciferous vegetables					
Q1	2.6	305	316	1.00	
Q2	7.6	264	317	0.93	(0.74, 1.18)
Q3	13.4	274	316	0.99	(0.78, 1.25)
Q4	23.3	225	317	0.84	(0.65, 1.07)
<i>P</i> _{trend}				0.192	
Dark green vegetables					
Q1	1.2	325	317	1.00	
Q2	4.1	248	316	0.86	(0.68, 1.09)
Q3	9.0	265	316	0.89	(0.70, 1.13)
Q4	22.7	230	317	0.82	(0.64, 1.05)
<i>P</i> _{trend}				0.199	
Orange vegetables					
Q1	0.7	329	316	1.00	
Q2	1.8	268	317	0.92	(0.72, 1.16)
Q3	3.5	251	317	0.90	(0.71, 1.14)
Q4	8.3	220	316	0.82	(0.64, 1.06)
<i>P</i> _{trend}				0.150	
Starchy vegetables					
Q1	14.4	264	316	1.00	
Q2	27.5	275	317	0.98	(0.77, 1.24)
Q3	41.4	272	317	1.03	(0.81, 1.31)
Q4	63.9	247	316	0.93	(0.73, 1.20)
<i>P</i> _{trend}				0.662	
Other vegetables					
Q1	14.9	283	317	1.00	
Q2	26.6	267	316	1.02	(0.81, 1.31)
Q3	39.7	251	317	0.99	(0.78, 1.26)
Q4	66.3	267	316	1.03	(0.81, 1.32)
<i>P</i> _{trend}				0.822	
Total Beans					
Q1	0.6	302	316	1.00	
Q2	2.5	269	317	0.97	(0.77, 1.24)
Q3	5.6	241	317	0.88	(0.69, 1.12)
Q4	12.1	256	316	0.95	(0.75, 1.22)
<i>P</i> _{trend}				0.686	

Abbreviations: CI = confidence intervals; OR = odds ratios. ^a*P*_{trends} were calculated using the median value for each quartile. ^bAdjusted for gender (female/male), age (0–54, 55–64, 65–74, 75+ years), region (Maine, Vermont, New Hampshire), race (White/other), Hispanic status (yes/no), smoking status (never, occasional, former, current), usual BMI (kg m⁻² – continuous), and total energy (kcal per day – continuous).

Table 6 Vitamins from diet and risk of bladder cancer^a

Quartiles of intake	Median	Cases	Controls	Multivariate model ^b	
				OR	95% CI
Vitamin A (mcg per 1000 kcal)					
Q1	279.8	307	316	1.00	
Q2	356.4	276	317	0.98	(0.78, 1.24)
Q3	432.9	257	317	0.94	(0.74, 1.20)
Q4	551.3	228	316	0.85	(0.66, 1.08)
<i>P</i> _{trend}				0.165	
Vitamin B2 (mg per 1000 kcal)					
Q1	0.7	293	317	1.00	
Q2	0.9	289	316	1.05	(0.83, 1.33)
Q3	1.0	265	317	1.00	(0.79, 1.27)
Q4	1.3	221	316	0.90	(0.70, 1.15)
<i>P</i> _{trend}				0.308	
Vitamin B6 (mg per 1000 kcal)					
Q1	0.7	307	317	1.00	
Q2	0.9	295	316	1.11	(0.88, 1.41)
Q3	1.1	241	316	0.96	(0.75, 1.22)
Q4	1.4	225	317	0.93	(0.72, 1.20)
<i>P</i> _{trend}				0.372	
Vitamin B12 (mcg per 1000 kcal)					
Q1	1.8	315	316	1.00	
Q2	2.4	282	317	0.92	(0.73, 1.17)
Q3	3.1	233	317	0.76	(0.60, 0.97)
Q4	4.1	238	316	0.77	(0.61, 0.99)
<i>P</i> _{trend}				0.019	
Vitamin C (mg per 1000 kcal)					
Q1	32.3	288	317	1.00	
Q2	53.1	261	316	1.06	(0.83, 1.35)
Q3	71.6	257	316	1.10	(0.86, 1.40)
Q4	104.6	262	317	1.15	(0.90, 1.47)
<i>P</i> _{trend}				0.265	
Vitamin E (mg per 1000 kcal)					
Q1	2.9	335	317	1.00	
Q2	3.6	266	316	0.91	(0.72, 1.15)
Q3	4.2	223	317	0.79	(0.62, 1.00)
Q4	5.6	244	316	0.91	(0.71, 1.15)
<i>P</i> _{trend}				0.405	
Folate (mcg per 1000 kcal)					
Q1	138.8	286	317	1.00	
Q2	174.4	286	316	1.10	(0.87, 1.40)
Q3	205.7	259	317	1.10	(0.86, 1.41)
Q4	255.8	237	316	1.06	(0.82, 1.37)
<i>P</i> _{trend}				0.708	
α-Carotene (mcg per 1000 kcal)					
Q1	99.3	283	316	1.00	
Q2	171.9	282	317	1.08	(0.85, 1.37)
Q3	262.2	277	316	1.06	(0.84, 1.35)
Q4	468.1	226	317	0.94	(0.73, 1.20)
<i>P</i> _{trend}				0.449	
β-Carotene (mcg per 1000 kcal)					
Q1	615.9	292	317	1.00	
Q2	986.0	273	316	1.04	(0.82, 1.32)
Q3	1439.6	259	316	0.99	(0.77, 1.26)
Q4	2347.6	244	317	0.99	(0.77, 1.27)
<i>P</i> _{trend}				0.838	

Abbreviations: CI = confidence intervals; OR = odds ratios. ^a*P*_{trend} were calculated using the median value for each quartile. ^bAdjusted for gender (female/male), age (0–54, 55–64, 65–74, 75+ years), region (Maine, Vermont, New Hampshire), race (White/other), Hispanic status (yes/no), smoking status (never, occasional, former, current), usual BMI (kg m⁻² – continuous), and total energy (kcal per day – continuous).

García-Closas *et al*, 2007; Aune *et al*, 2009; Larsson *et al*, 2009; Ferrucci *et al*, 2010; Jakszyn *et al*, 2011). However, one cohort study found a positive association between total meat intake and bladder cancer (Mills *et al*, 1991), and another found an increased risk for high total processed meat intake (Hu *et al*, 2011). Consumption of specific processed meat groups, such as bacon, cold cuts, ham, hot dogs, or sausages, have previously been linked to bladder cancer risk in some (Chyou *et al*, 1993; Michaud *et al*, 2006; Larsson *et al*, 2009; Ferrucci *et al*, 2010) but not all studies (Chyou *et al*, 1993; Michaud *et al*, 2006; Larsson *et al*, 2009; Ferrucci *et al*, 2010).

Meat is a source of multiple mutagenic compounds such as HCAs, PAHs, and *N*-nitroso compounds (NOCs). Previous animal studies have demonstrated HCAs, such as MeIQx and PhIP, affects the urinary system as well as other organ systems (Ohgaki *et al*, 1987; Takahashi *et al*, 1993; Shirai *et al*, 1998). However, similar to our data, meat cooking preferences and mutagens have not been associated with bladder cancer in other studies (Augustsson *et al*, 1999; García-Closas *et al*, 2007; Ferrucci *et al*, 2010). Dietary intake of MeIQx, DiMeIQx, and PhIP in our study was lower than in a previous study in Spain (García-Closas *et al*, 2007), but was higher compared with another US study population (Ferrucci *et al*, 2010). Processed meat is also a source of NOCs, which are formed from nitrate and nitrite, and they can cause tumours at multiple organ sites in many animal species (Bogovski and Bogovski, 1981), including the urinary bladder (Mirvish, 1995). In a recent cohort study, processed meat intake was not associated with bladder cancer, but total nitrate and nitrite intake from processed meats had a borderline positive association with bladder cancer (RR: 1.29; 95% CI: 1.00–1.67; $P=0.110$) (Ferrucci *et al*, 2010). In contrast, another recent cohort study that estimated NOC exposure in relation to bladder cancer was null (Jakszyn *et al*, 2011). Although the findings between HCAs, PAHs, and NOCs in relation to bladder cancer have been null or inconsistent, the weakness of effect may be due to the inherent design of epidemiological studies where exposures are measured from self-reported dietary intake of individual foods ensuing in non-differential misclassification of exposure and dilution of the observed effect (Eichholzer and Gutzwiller, 1998; Sinha, 2002).

In our study, we did not find any associations between fruit intake and bladder cancer. Other studies have also found null results (Shibata *et al*, 1992; Michaud *et al*, 1999; Nagano *et al*, 2000; Michaud *et al*, 2002); only one study has shown a statistically significant reduction in bladder cancer risk for individuals in the highest category of fruit intake compared with the lowest (Zeegers *et al*, 2001b). Other research studies have shown that specific fruit or vegetable groups have some protective effects but the findings are highly variable across the studies (Michaud *et al*, 1999; Nagano *et al*, 2000); for example, in a Spanish case-control study, berries were inversely related to bladder cancer, whereas in a Finnish cohort study there was no association (Michaud *et al*, 2002; García-Closas *et al*, 2007). We did not find any specific fruit or vegetable group to be protective against bladder cancer, which is similar to the findings of other prospective cohort studies (Shibata *et al*, 1992; Zeegers *et al*, 2001b; Michaud *et al*, 2002).

Two case-control and cohort studies have observed inverse associations with specific vitamins such as A, B12, C and E (Shibata *et al*, 1992; Bruemmer *et al*, 1996; Michaud *et al*, 2000; García-Closas *et al*, 2007); however, other studies have found no evidence for a protective effect of vitamins (Nomura *et al*, 1991; Riboli *et al*, 1991; Michaud *et al*, 1999; Wakai *et al*, 2000; Zeegers *et al*, 2001b; Michaud *et al*, 2002; Brinkman *et al*, 2010; Hotaling *et al*, 2011). Micronutrients can potentially prevent carcinogenesis and inhibit tumour growth through a multitude of biological mechanisms (Greenwald *et al*, 2001; Steinmetz and Potter, 1991); for example, carotenoids increase cell differentiation, vitamin C prevents formation of NOCs, vitamin E has intracellular

antioxidant properties, and vitamin D and calcium decrease cellular proliferation (Steinmetz and Potter, 1991; Greenwald *et al*, 2001).

Dietary vitamin B12 was inversely associated with bladder cancer in our study; this association was also observed in a Spanish population in diet and vitamin supplements (García-Closas *et al*, 2007). The main sources of vitamin B12 include fish, meat, poultry, eggs, milk, and milk products, with 27% of the micronutrient coming from beef (Subar *et al*, 1998). Vitamin B12, as well as folic acid, is needed for methylation in DNA metabolism (Fenech, 2001; Fenech *et al*, 1998). Deficiencies in vitamin B12 may result in high incorporation of uracil into the DNA, thus leading to chromosomal breakage, which has implications for cancer risk. However, more studies are needed to elucidate the biological mechanism between vitamin B12 and bladder cancer specifically.

The strengths of this study are the large sample size and the comprehensive validated dietary questionnaire. Furthermore, this study was located in a region with high bladder cancer incidence and mortality (Brown *et al*, 1995). One of the limitations of our study is the 60% participation rate, although this was approximately the same among both the cases and controls. The main reason for non-participation in the cases was because 22% of the eligible cases had died before entry to the study. The main reason for non-participation among the controls was refusals, with 23.5% of eligible controls refusing to participate. Using data on some of the non-respondent cases from the state cancer registries, we observed that non-respondent cases did not seem to differ by sex or cancer stage compared with respondents. We also found a low percent of cancers were at high stage, and this was similar among those who participated and those who did not. Selection bias is a potential limitation in case-control studies; however, the characteristics of our study participants are similar to the NHANES 1999–2002 study population, which is representative of the general population in the USA (Ong *et al*, 2007; Seligman *et al*, 2007). In comparison with a cohort study, our study population characteristics, dietary intake and the associations observed was similar (Ferrucci *et al*, 2010). Moreover, the aggressive and non-aggressive bladder cancer cases in our study did not differ by major dietary factors (red and processed meat, fruits, and vegetables), age, race, Hispanic status, region, smoking, and BMI except for gender. As in most case-control studies of diet, there is also a concern regarding differential recall bias between cases and controls, which is a potential weakness of our study. Issues of measurement error associated with assessing usual dietary intake in large epidemiologic studies are also a concern but it will most likely be non-differential misclassification resulting in an underestimation of the true association. Furthermore, since we investigated multiple exposures, there is a possibility that associations may have been observed by chance.

In summary, we observed a positive association between processed meat intake and bladder cancer, especially for processed red meat. Furthermore, individuals who consumed larger amounts of vitamin B12 had a decreased risk for this malignancy. Future studies are needed to clarify the role of processed meat and vitamin B12 in bladder carcinogenesis as we have seen some inconsistencies in the current literature.

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