Meat intake and bladder cancer risk in 2 prospective cohort studies[1–3]

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ABSTRACT

Background: Nitrosamines, which are known bladder carcinogens, or their precursors are found in certain meat items, and concentrations of these compounds are especially high in bacon. Only 3 cohort studies, all with <100 case subjects, have examined the relation between meat intake and bladder cancer, and few studies have examined the relation of different meat types with bladder cancer.

Objective: The aim was to examine the association between specific meat items and bladder cancer in 2 large prospective studies.

Design: We analyzed data from 2 cohorts with up to 22 y of follow-up and 808 incident bladder cancer cases. Detailed data on meat were obtained from multiple food-frequency questionnaires administered over time. Multivariate relative risks (RRs) and 95% CIs were estimated by using Cox proportional hazards models with control for potential confounders, including detailed smoking history.

Results: Men and women with a high intake of bacon (≥5 servings/wk) had an elevated risk of bladder cancer compared with those who never ate bacon (multivariate RR = 1.59; 95% CI = 1.06, 2.37), although the overall association was not statistically significant (*P* for trend = 0.06). However, the association with bacon was stronger and became statistically significant after the removal of individuals who indicated having "greatly" changed their red meat (men) or bacon (women) intake during the 10 y before baseline (multivariate RR = 2.10; 95% CI = 1.24, 3.55; *P* for trend = 0.006). A positive association was also detected for intake of chicken without skin, but not for chicken with skin or for other meats, including processed meats, hot dogs, and hamburgers.

Conclusions: In these 2 cohorts combined, frequent consumption of bacon was associated with an elevated risk of bladder cancer. Other studies with data on specific meat items are necessary to confirm our findings. *Am J Clin Nutr* 2006;84:1177–83.

KEY WORDS Processed meats, bacon, bladder cancer, cohort study

INTRODUCTION

N-Nitrosamines are known bladder carcinogens in animal models (1), are present in cigarette smoke (2, 3), and are found in the urine of patients who are at high risk of bladder cancer, namely patients with indwelling catheters (4) or schistosomiasis infections (5). Bacon is the major food source of preformed nitrosamines (6, 7). In addition, processed meats contain varying concentrations of nitrites, added for preservation, which can be endogenously converted to nitrosamines (8). In a case-control study by Wilkens et al (9), processed meat intake was positively associated with bladder cancer risk, and nitrosamine intake was associated with a 2- and 3-fold increase in bladder cancer risk among Japanese women and men, respectively. The association with nitrosamines and bladder cancer risk was not apparent among whites; however, a statistically nonsignificant increase in risk was observed for bacon intake among white women (odds ratio for the highest compared with the lowest category of intake = 1.8; 95% CI = 0.7, 5.1) (9).

To date, epidemiologic studies on meat consumption and bladder cancer risk are few and inconsistent, and studies have typically had limited data on different types of meat intake. To our knowledge, only one study reported on the relation between bacon intake (as a separate item) and the risk of bladder cancer (9). To examine prospectively whether different meats, particularly those with potential to generate nitrosamines, are associated with the risk of bladder cancer in men and women, we examined the relation in 2 US cohort studies with detailed dietary data.

SUBJECTS AND METHODS

Two ongoing cohort studies provided data for our analyses: the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS). The HPFS was initiated in 1986 when 51 529 US men aged 40–75 y responded to a mailed questionnaire. Participants of the HPFS study are dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%). The NHS was established in 1976 when 121 700 female registered nurses aged 30–55 y responded to a mailed questionnaire. To date, both cohorts are actively followed with biennial questionnaires. Individual and behavioral characteristics such as age, weight, height, medical history, medication use, menopausal status, physical activity, and vitamin use were obtained on the baseline questionnaires and on subsequent questionnaires. For each of the follow-up questionnaires, up to 6 mailings were sent to nonrespondents. All men (HPFS cohort) completed a food-frequency questionnaire (FFQ) at baseline (1986), and

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98 462 women (NHS cohort) completed a FFQ in 1980. In addition, dietary data were collected in subsequent years of follow-up, usually every 4 y.

Deaths of cohort members are frequently reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index is searched biennially for nonrespondents; this method was shown to have a sensitivity of 98% (10). Through 2002, the total (active + death) follow-up rate was >96% in each dietary cohort. The present study was approved by the Human Research Committee of the Brigham and Women's Hospital and the Human Subjects Committee of the Harvard School of Public Health.

Dietary assessment: semiquantitative food-frequency questionnaire

In 1980, women in the NHS completed a 61-item semiquantitative FFQ. Expanded versions (≈130 food items) of the FFQs were mailed to NHS participants in 1984, 1986, 1990, 1994, and 1998. For the HPFS cohort, the baseline (1986) and follow-up FFQs (1990, 1994, and 1998) included 131 food items.

The participants were asked how often, on average, they had consumed each food, given a standard portion size, over the past year (eg, the serving size for bacon is 2 slices). Participants select from 9 prespecified frequency categories ranging from "never" to "6 or more" times per day. Nutrient intakes were calculated by multiplying the frequency of intake for each item by the nutrient content for the specified portion size. Food composition data were primarily based on values obtained from the US Department of Agriculture supplemented with our own data. Intakes of meat and fish were calculated by multiplying the frequency of intake for individual items by their weights, which were estimated from the specified portion size (and by using additional data from the validation studies to determine mean values for portion size to verify that the specified sizes were accurate). Total meat consisted of the following food items: processed meats; bacon; hot dogs; hamburger; beef, pork, or lamb in a sandwich or mixed dish; beef, pork, or lamb as a main dish; chicken or turkey with skin; and chicken or turkey without skin. Red meat consisted of the total meat items minus the chicken or turkey items. Seafood was not included in the total meat category because these foods contain low heterocyclic amine concentrations and have different nutritional compositions.

The FFQ was validated among a subset ($n = 127$) of the HPFS cohort from the Boston area (11). For this validation study, men completed two 1-wk dietary records ≈6 mo apart and completed a FFQ at the end of the year. The intraclass correlation coefficient between energy-adjusted total fat intake measured by the dietary records and the FFQ was 0.61 (11). Correlations for the meat items ranged from 0.56 for chicken or turkey without skin to 0.83 for processed meats (12).

In a validity study conducted in 173 women, the FFQ was compared with four 1-wk diet records. Correlation coefficients between the average intake assessed by two 1-wk diet records completed 6 mo apart and the 1980 FFQ (which was corrected for within-person variation in the diet records) were as follows: 0.70 for bacon, 0.56 for hot dogs, 0.55 for processed meats, 0.46 for meat (from a main dish or mixed dish), and 0.38 for hamburgers (13).

Smoking history and other risk factors

At baseline, and biennially thereafter, the participants provided information on their current smoking status, smoking intensity, medication use, weight, height, and geographic location. In addition, detailed information on past smoking habits, time since quitting, and average number of cigarettes smoked per day (for previous decades) was obtained on the baseline questionnaires. To control for smoking, total pack-years of smoking was derived to incorporate all past smoking experience. One pack-year is equivalent to having smoked 1 pack or 20 cigarettes/d over one year.

Identification of cases of bladder cancer

The participants in the 2 cohorts were asked to report specified medical conditions including cancers that were diagnosed in the 2-y period between each follow-up questionnaire. We confirmed the self-reported diagnosis of bladder cancer by review of medical records (87% of cases in HPFS; 85% of cases in NHS). When permission to obtain medical records was denied, we attempted to confirm the initial self-reported cancer and date of diagnosis from a secondary source (eg, death certificate, physician, or telephone interview of a family member). If the primary cause (or secondary cause) of death as reported by a death certificate was a previously unreported bladder cancer case, we contacted a family member to obtain permission to retrieve medical records or at least to confirm the cancer diagnosis. On the basis of pathology reports, >95% of bladder cancer cases were transitional cell carcinomas. Carcinoma in situ tumors were included because these superficial lesions have a high risk of progression. Between the return of the 1986 questionnaire and 31 January 2002, 504 incident bladder cancer cases were confirmed in the HPFS cohort. In the NHS cohort, 304 incident bladder cancer cases were confirmed between the return of the 1980 FFQ and 31 May 2002.

Statistical analysis

For these analyses, a total of 47 422 men (from the HPFS cohort) and 88 471 women (from the NHS cohort) were eligible after excluding participants diagnosed with cancer (other than nonmelanoma skin cancer) before baseline (1986 for HPFS; 1980 for NHS) or those with implausibly high or low daily caloric intake (<800 or >4200 kcal/d for men; <500 or >3500 kcal/d for women).

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of bladder cancer diagnosis, death from any cause, or the end of follow-up (31 January 2002 for the men, and 31 May 2002 for the women), whichever came first. Incidence rates of bladder cancer were calculated by dividing the number of incident cases by the number of person-years in each category of exposure. We computed the relative risk for each of the upper quintiles by dividing the rates in these categories by the rate in the lowest quintile. Our primary analyses were conducted using cumulative updated dietary intake [this method, which uses baseline and follow-up FFQs, reduces measurement error in dietary assessment (14)]; in addition, secondary analyses were conducted using baseline dietary data only.

Relative risks (RRs) adjusted for potential confounders were approximated by Cox proportional hazards regression. A new data record was created for every questionnaire cycle at which a

TABLE 1
Characteristics at study baseline by bacon intake in the Health Professionals Follow-Up Study (HPFS; 1986) and the Nurses' Health Study (NHS; 1980)[1]

	Bacon intake in the HPFS (men) cohort				Bacon intake in the NHS (women) cohort			
	None	1 serving/wk	≥5 serving/wk	*P* for trend[2]	None	1 serving/wk	≥5 serving/wk	*P* for trend[2]
n	16 767	8628	1013		28 162	21 280	1964	
Bacon intake (median; in g/d)	0	1.9	13		0	1.9	11.6	
Age (y)	54.9 ± 9.9[3]	53.8 ± 9.6	56.0 ± 9.4	<0.001	47.4 ± 7.2	46.4 ± 7.2	47.6 ± 7.2	<0.001
BMI (kg/m^2)	25.2 ± 3.3	25.8 ± 3.4	25.7 ± 3.5	<0.001	24.4 ± 4.5	24.5 ± 4.5	24.8 ± 5.0	<0.001
Height (in)	69.9 ± 2.8	70.4 ± 2.7	70.5 ± 2.7	<0.001	64.4 ± 2.4	64.6 ± 2.4	64.7 ± 2.4	<0.001
Physical activity (METs)[4]	22.0 ± 27.2	17.9 ± 22.7	15.3 ± 19.6	<0.001	15.0 ± 20.9	13.8 ± 20.9	12.5 ± 15.1	<0.001
Current smokers (%)	5.8	13.4	21.2	<0.001	24.8	31.7	35.4	<0.001
Pack-years of cigarettes[5]	23.3 ± 18.5	26.5 ± 19.5	31.4 ± 21.7	<0.001	19.6 ± 16.7	20.9 ± 16.4	23.8 ± 18.0	<0.001
Multivitamin users (%)	44	40	37	<0.001	36	33	35	<0.001
Dietary intakes (per day)								
Total fat (%)	29.4	33.7	37.7	<0.001	36.5	40.0	45.0	<0.001
Saturated fat (%)	9.7	11.8	13.4	<0.001	14.7	16.1	17.8	<0.001
Carbohydrate (%)	50.0	44.9	40.7	<0.001	40.6	38.2	33.3	<0.001
Chicken (median; in g)	37.4	23.7	18.7	<0.001	27.2	17.6	18.6	<0.001

[1] All variables (except age) are age-standardized. MET, metabolic equivalent. One serving = 2 slices of bacon.
[2] Generalized linear models were used for continuous variables and chi-square tests for categorical variables.
[3] $\bar{x}$ ± SD (all such values).
[4] MET-h/wk, sum of the average time per week spent in each activity × MET value of each activity (from the 1986 NHS questionnaire).
[5] No. of packs smoked per day × no. of years smoked among past and current smokers.

participant was at risk, with covariates set to their values at the time that the questionnaire was returned. All models were stratified by age and calendar time. In addition, we performed analyses with a 2-y lag to exclude preclinical cases at baseline. Tests for multiplicative interaction were evaluated by using the likelihood ratio test (LRT). Tests for linear trend were performed by using the median value of each intake category and modeling these as continuous variables. All statistical procedures were performed with the use of SAS version 8 (SAS Institute Inc, Cary, NC). All *P* values are based on two-sided statistical tests.

We pooled the data from the 2 cohorts by use of a random-effects model for the logarithm of the relative risks (15). Tests of heterogeneity by using the *Q* statistic (15) were conducted before pooling; none of the pooled coefficients for the associations [ie, ln(RR)] showed statistically significant heterogeneity.

RESULTS

Men and women with a high intake of processed meats or bacon were more likely to be current smokers, have a higher lifetime exposure to tobacco smoke, and exercised less than did men and women, respectively, with low intakes of these foods (**Table 1** for bacon; data for processed meats not shown). Within each cohort, the percentage of total and saturated fat intakes was higher, and multivitamin intake lower, among persons with high processed meats or bacon intake compared with persons with low intakes (Table 1 for bacon). Other characteristics, including age, BMI, and height, did not vary substantially by intake of processed meat or bacon (however, the *P* for trends were statistically significant).

Total and red meat intakes were not significantly related to the risk of bladder cancer in either cohort when using baseline (data not shown) or cumulative updated diet data (highest compared with lowest quintile; pooled multivariate RR for total meat intake: 1.15; 95% CI: 0.87, 1.51; *P* for trend = 0.28; pooled multivariate RR for red meat intake: 0.83; 95% CI: 0.64, 1.08; *P* for trend = 0.19). Control for known risk factors in these analyses had little effect on the associations. Furthermore, stratifying by smoking status did not uncover any significant association for total or red meat intake (data not shown).

Although the NHS and HPFS cohorts used different FFQs at baseline, both questionnaires included 8 identical questions on meat consumption (not including fish; **Table 2**). In a cumulative updated diet analysis, no overall significant association was observed for bacon intake (*P* for trend = 0.06), but persons consuming ≥5 servings of bacon/wk had a higher risk of bladder cancer than did those who ate no bacon (pooled multivariate RR: 1.59; 95% CI: 1.06, 2.37; Table 2). Associations were similar in each cohort (*P* > 0.05 for tests of heterogeneity). By using baseline diet only, associations with bacon intake were similar to those found with the use of cumulative updated diet, as reported in Table 2. Neither hot dogs nor other processed meats (eg, sausage, salami, and bologna) were significantly associated with bladder cancer risk in the 2 cohorts with the use of cumulative updated diet (Table 2) or baseline diet (data not shown). Other individual red meat items were not significantly related to the risk of bladder cancer in either cohort (Table 2).

Elevated risks of bladder cancer were observed among men and women who consumed chicken without skin ≥5 times/wk compared with those who did not consume chicken without skin (using cumulative updated diet; Table 2). The pooled multivariate RR for the top compared with the bottom category of chicken without skin intake was statistically significant (1.52; 95% CI: 1.09, 2.11). We examined chicken with skin separately from chicken without skin because heterocyclic amines are more elevated in chicken cooked without skin (16); no significant associations were observed for chicken with skin in either cohort. With the use of baseline diet only, no overall significant associations were observed between chicken without skin and bladder cancer risk in either cohort (multivariate RR in a comparison of ≥5 servings/wk with none in the NHS cohort: 1.90; 95% CI:

TABLE 2
Intake of meat categories (based on cumulative updated diet) and bladder cancer risk for the Health Professionals Follow-Up Study (HPFS; 1986–2002) and the Nurses' Health Study (NHS; 1980–2002) cohorts[1]

	Frequency of intake					*P* for trend[2]
	0	1–3 servings/mo	1 servings/wk	2–4 servings/wk	≥5 servings/wk	
Processed meats (eg, sausage, salami, bologna)						
Men						
Cases/person-years	117/145 515	152/205 070	101/154 999	105/145 290	29/39 928	
Multivariate RR (95% CI)[3]	1.0	0.98 (0.76, 1.25)	0.94 (0.71, 1.23)	0.98 (0.74, 1.30)	1.09 (0.71, 1.69)	
Women						
Cases/person-years	48/335 371	115/652 181	71/386 132	60/408 885	10/88 823	
Multivariate RR (95% CI)[3]	1.0	1.07 (0.76, 1.52)	1.25 (0.86, 1.84)	0.98 (0.65, 1.46)	0.81 (0.40, 1.63)	
Pooled multivariate RR (95% CI)[4]	1.0	1.01 (0.82, 1.23)	1.03 (0.83, 1.29)	0.98 (0.74, 1.30)	1.01 (0.70, 1.45)	0.81
Bacon						
Men						
Cases/person-years	158/225 068	150/216 561	105/145 251	69/86 722	22/17 199	
Multivariate RR (95% CI)[4]	1.0	1.08 (0.86, 1.37)	1.09 (0.84, 1.41)	1.10 (0.82, 1.49)	1.63 (1.02, 2.62)	
Women						
Cases/person-years	55/380 262	117/760 055	78/445 492	46/252 823	8/32 760	
Multivariate RR (95% CI)[3]	1.0	0.90 (0.65, 1.25)	1.06 (0.74, 1.51)	1.00 (0.67, 1.51)	1.48 (0.70, 3.16)	
Pooled multivariate RR (95% CI)[4]	1.0	1.02 (0.84, 1.23)	1.08 (0.88, 1.33)	1.07 (0.84, 1.36)	1.59 (1.06, 2.37)	0.06
Hot dogs						
Men						
Cases/person-years	173/241 129	211/278 267	87/121 401	33/50 005		
Multivariate RR (95% CI)[3]	1.0	1.02 (0.83, 1.25)	1.02 (0.78, 1.34)	0.86 (0.58, 1.27)		
Women						
Cases/person-years	58/348 970	143/830 044	77/515 410	26/176 968		
Multivariate RR (95% CI)[3]	1.0	0.91 (0.66, 1.24)	0.89 (0.63, 1.27)	0.77 (0.47, 1.24)		
Pooled multivariate RR (95% CI)[4]	1.0	0.98 (0.83, 1.17)	0.97 (0.78, 1.20)	0.82 (0.61, 1.11)		0.47
Hamburger						
Men						
Cases/person-years	54/64 701	148/169 378	171/248 312	131/208 411		
Multivariate RR (95% CI)[3]	0.99 (0.72, 1.36)	1.0	0.86 (0.68, 1.08)	0.91 (0.70, 1.17)		
Women						
Cases/person-years	7/48 011	44/273 677	142/847 202	111/702 503		
Multivariate RR (95% CI)[3]	1.07 (0.48, 2.41)	1.0	1.13 (0.80, 1.60)	0.96 (0.66, 1.38)		
Pooled multivariate RR (95% CI)[4]	1.00 (0.75, 1.35)	1.0	0.93 (0.77, 1.13)	0.92 (0.75, 1.14)		0.17
Beef, pork, or lamb (main dish)						
Men						
Cases/person-years	45/48 071	88/115 197	153/223 129	196/266 494	22/37 910	
Multivariate RR (95% CI)[3]	1.35 (0.94, 1.96)	1.0	1.01 (0.78, 1.33)	1.11 (0.85, 1.45)	0.93 (0.57, 1.52)	
Women						
Cases/person-years	6/27 526	15/120 438	60/377 233	173/993 024	50/353 172	
Multivariate RR (95% CI)[3]	2.28 (0.88, 5.92)	1.0	1.35 (0.76, 2.39)	1.23 (0.71, 2.11)	1.01 (0.56, 1.85)	
Pooled multivariate RR (95% CI)[4]	1.45 (1.02, 2.04)	1.0	1.07 (0.84, 1.36)	1.13 (0.89, 1.44)	0.96 (0.66, 1.41)	0.35
Beef, pork, or lamb (sandwich or mixed dish)						
Men						
Cases/person-years	71/80 313	133/156 694	137/239 935	151/191 148	12/22 712	
Multivariate RR (95% CI)[3]	1.06 (0.79, 1.43)	1.0	0.83 (0.65, 1.06)	1.26 (0.98, 1.63)	0.95 (0.51, 1.75)	
Women						
Cases/person-years	16/79 887	66/386 800	105/619 487	108/705 637	9/79 581	
Multivariate RR (95% CI)[3]	1.61 (0.92, 2.81)	1.0	1.03 (0.75, 1.41)	0.92 (0.66, 1.27)	0.83 (0.40, 1.71)	
Pooled multivariate RR (95% CI)[4]	1.16 (0.90–1.51)	1.0	0.90 (0.74, 1.09)	1.12 (0.91, 1.37)	0.90 (0.56, 1.43)	0.52
Chicken without skin						
Men						
Cases/person-years	56/80 102	65/91 628	116/177 339	221/291 821	46/49 911	
Multivariate RR (95% CI)[3]	1.0	0.97 (0.68, 1.40)	0.91 (0.66, 1.26)	1.02 (0.75, 1.38)	1.45 (0.96, 2.17)	
Women						
Cases/person-years	26/236 376	41/282 832	74/504 694	137/749 405	26/98 084	
Multivariate RR (95% CI)[3]	1.0	0.94 (0.57, 1.57)	0.97 (0.61, 1.54)	1.07 (0.68, 1.68)	1.66 (0.94, 2.95)	
Pooled multivariate RR (95% CI)[3]	1.0	0.96 (0.72, 1.29)	0.93 (0.71, 1.21)	1.03 (0.80, 1.33)	1.52 (1.09, 2.11)	0.01
Chicken with skin						
Men						
Cases/person-years	167/213 633	93/122 524	125/182 972	119/171 673		
Multivariate RR (95% CI)[3]	1.0	1.03 (0.79, 1.33)	1.04 (0.82, 1.32)	1.10 (0.86, 1.41)		
Women						
Cases/person-years	77/520 510	70/434 094	96/528 511	61/388 277		
Multivariate RR (95% CI)[3]	1.0	0.92 (0.66, 1.28)	1.24 (0.92, 1.68)	1.01 (0.72, 1.43)		
Pooled multivariate RR (95% CI)[4]	1.0	0.99 (0.80, 1.21)	1.11 (0.92, 1.34)	1.07 (0.88, 1.31)		0.26

[1] RR, relative risk. The reference category is based on the lowest category of intake unless it is too unstable because of few cases in one of the two cohorts (in that case, the next lowest category serves as the reference). One serving = 2 slices of bacon.
[2] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazard model.
[3] Cox proportional hazard model adjusted for age, caloric intake (quintiles), and pack-years of smoking and for geographic region and total fluid intake in the HPFS.
[4] Results obtained from pooling the β-coefficient and SE estimates for men and women by using the DerSimonian and Laird random-effects model; tests of heterogeneity across cohort (ie, sex) were not statistically significant ($P > 0.05$).

TABLE 3
Bacon intake (based on cumulative updated diet) and bladder cancer risk for the Nurses' Health Study (NHS; 1980–2002) and Health Professionals Follow-up Study (HPFS; 1986–2002) cohorts, after removing individuals who indicated having greatly increased or decreased bacon intake (NHS) or red meat intake (HPFS) over the past 10 y (before the baseline food-frequency questionnaire)

	Frequency of bacon intake[1]					*P* for trend[2]
	0	1–3 servings/mo	1 serving/wk	2–4 servings/wk	≥5 servings/wk	
Men (n = 164)						
Multivariate RR (95% CI)[3]	1.0	0.99 (0.60, 1.63)	1.07 (0.64, 1.76)	1.37 (0.80, 2.32)	2.11 (1.05, 4.25)	
Women (n = 233)						
Multivariate RR (95% CI)[3]	1.0	1.05 (0.70, 1.59)	1.21 (0.78, 1.88)	1.15 (0.71, 1.88)	2.08 (0.94, 4.62)	
Pooled multivariate RR (95% CI)[4]	1.0	1.03 (0.75, 1.41)	1.15 (0.82, 1.60)	1.25 (0.87, 1.79)	2.10 (1.24, 3.55)	0.006

[1] One serving = 2 slices of bacon.
[2] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazard model.
[3] Cox proportional hazard model adjusted for age, caloric intake (quintiles), pack-years of smoking, and current smoking status and for US geographic region and total fluid intake in the HPFS.
[4] Results obtained from pooling the β-coefficient and SE estimates for men and women by using the DerSimonian and Laird random-effects model; tests of heterogeneity across cohort (ie, sex) were not statistically significant ($P > 0.05$).

1.01, 3.57; *P* for trend = 0.27; multivariate RR in a comparison of ≥5 servings/wk with none in the HPFS cohort: 1.14; 95% CI: 0.71, 1.83; *P* for trend = 0.99).

In another analysis, we removed those persons who reported (at baseline) having greatly decreased or increased their bacon (NHS) or red meat (HPFS; change in bacon intake per se was not asked) intake (**Table 3**). Although total case numbers are lower in these analyses, the associations for the highest intake of bacon intake, compared with the lowest category, were stronger in each cohort (RR > 2.0) than those of the main analysis (associations were statistically significant for men and the pooled RRs; Table 2).

Stratification by smoking history (never, light, or heavy smoker) was performed for bacon to evaluate the potential effect modification and residual confounding by smoking (**Table 4**). In both cohorts, the association with bacon was strongest among never smokers, was not apparent among light smokers, and was only suggestive among heavy smokers in the HPFS cohort. Never smokers experienced a >2-fold increase in risk when consuming 1 serving of bacon ≥2 times/wk compared with those who did not consume any bacon (multivariate RR: 2.08; 95% CI: 1.26, 3.44; *P* value for trend < 0.001). The test for interaction was statistically significant in the HPFS cohort (*P* value for interaction = 0.05 for HPFS and 0.06 for NHS).

In a secondary analysis, we removed the first 2 y of follow-up using baseline diet as the exposure. The associations were similar or stronger for bacon than those observed with the baseline diet analysis in each cohort (data not shown).

DISCUSSION

In 2 large prospective studies, we observed consistent elevated risks of bladder cancer among men and women who consumed ≥5 servings of bacon/wk compared with those who consumed none, although the overall association was not statistically significant. However, the association with bacon was statistically significant among never smokers and after removing persons who indicated having changed their diet over the past 10 y. Other meat items were not related to bladder cancer risk, with the exception of an association with consumption of chicken without skin.

To date, 3 cohort studies have examined meat intake and bladder cancer risk. A high intake of "meat, poultry or fish" (≥3 times/wk) was associated with an 85% increase in bladder cancer risk in one cohort study (17); however, this finding was based on 52 case subjects and was not statistically significant. In another cohort study, an increase in risk was observed for persons who consumed both beef and pork (RR in a comparison of those who consumed both beef and pork and those who consumed no beef or pork: 2.2; 95% CI: 1.1, 4.4) (18); no information was available on poultry. In a third cohort study, meat intake was associated with a statistically non-significant increase in bladder cancer risk (RR in a comparison of intakes of ≥5 times/wk with ≤1 time/wk: 1.57; 95% CI: 0.78, 3.15; 96 case subjects) (19); but "ham, bacon or sausage" intake was not associated with risk (19).

Positive associations between bladder cancer risk and bacon, ham, and sausage intake (3 separate items) were observed among Japanese men in one case-control study, but not among Japanese women or whites (9). Most case-control studies to date have reported no associations for meat intake and bladder cancer (20, 21). Most studies, however, did not have data on individual meat items (22–25).

Because nitrosamines are known bladder carcinogens and bacon contains detectable and often high concentrations of various preformed nitrosamine compounds (7), this may explain our finding with bacon. Although processed meats other than bacon often contain elevated concentrations of nitrites that can be endogenously converted to nitrosamines, the formation of these compounds is influenced by several factors, such as stomach pH and the presence of vitamins (26). The large interindividual variability in endogenous nitrosamine formation may be sufficient to prevent detection of an association with processed meats (ie, too much measurement error). Given that the strongest associations were observed in the subgroup of men and women who had consistently consumed high amounts of bacon in the past (Table 3), exposure to nitrosamines may have occurred many years before cancer detection. This is consistent with the fact that nitrosamine concentrations in bacon have decreased over time.

Alternatively, heterocyclic amines could be responsible for our findings with bacon and could potentially explain the association observed for chicken without skin. A wide range of heterocyclic amines can be found in cooked meats; the formation of

TABLE 4
Bacon intake (based on cumulative updated diet) and bladder cancer risk for the Health Professionals Follow-Up Study (HPFS; 1986–2002) and the Nurses' Health Study (1980–2002) cohorts by smoking history

	Frequency of bacon intake[1]				*P* for trend[2]
	0	1–3 servings/mo	1 serving/wk	≥2 servings/wk	
Never smokers					
Men					
Cases/person-years	34/96 994	34/87 902	25/54 222	18/34 562	
Multivariate RR (95% CI)[3]	1.0	1.21 (0.73, 2.00)	1.60 (0.92, 2.75)	1.70 (0.91, 3.19)	
Women					
Cases/person-years	9/172 423	27/332 492	18/190 069	17/120 562	
Multivariate RR (95% CI)[3]	1.0	1.56 (0.72, 3.38)	1.77 (0.78, 4.05)	2.99 (1.28, 6.95)	
Pooled multivariate RR (95% CI)[4]	1.0	1.31 (0.86, 1.99)	1.65 (1.04, 2.60)	2.08 (1.26, 3.44)	<0.001
Light smokers (<25 pack-years)					
Men					
Cases/person-years	52/77 632	49/74 313	26/49 289	17/32 996	
Multivariate RR (95% CI)[5]	1.0	1.18 (0.78, 1.79)	0.94 (0.57, 1.54)	0.84 (0.47, 1.52)	
Women					
Cases/person-years	16/134 638	36/266 314	22/151 424	7/87 057	
Multivariate RR (95% CI)[5]	1.0	0.96 (0.53, 1.76)	1.19 (0.61, 2.32)	0.64 (0.26, 1.58)	
Pooled multivariate RR (95% CI)[4]	1.0	1.11 (0.79, 1.56)	1.02 (0.69, 1.52)	0.78 (0.47, 1.27)	0.32
Heavy smokers (≥25 pack-years)					
Men					
Cases/person-years	64/37 543	60/42 584	45/33 978	52/30 414	
Multivariate RR (95% CI)[5]	1.0	1.03 (0.72, 1.46)	1.09 (0.74, 1.58)	1.42 (0.96, 2.10)	
Women					
Cases/person-years	30/73 201	54/161 249	38/104 000	30/77 964	
Multivariate RR (95% CI)[5]	1.0	0.70 (0.44, 1.11)	0.82 (0.50, 1.35)	0.80 (0.47, 1.36)	
Pooled multivariate RR (95% CI)[4]	1.0	0.89 (0.67, 1.18)	0.98 (0.73, 1.32)	1.16 (0.85, 1.59)	0.06

[1] One serving = 2 slices of bacon.
[2] Based on the median value of each intake category and modeling these as continuous variables in a Cox proportional hazard model.
[3] Cox proportional hazard model adjusted for age and caloric intake (quintiles) and for US geographic region and total fluid intake in the HPFS only.
[4] Results obtained from pooling the β-coefficient and SE estimates for men and women by using the DerSimonian and Laird random-effects model; tests of heterogeneity across cohort (ie, sex) were not statistically significant ($P > 0.05$). The bacon × smoking interaction was significant, $P = 0.02$.
[5] Cox proportional hazard model adjusted for age, caloric intake (quintiles), and pack-years of smoking and for US geographic region and total fluid intake in the HPFS.

different types depends on the type of meat and the cooking method. In a recent study that used US national dietary data, chicken contributed 35–40% of the most common heterocyclic amine [2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)], and, of the different cooking methods, pan-fried meats contributed ≈50% (27). Moreover, chicken and bacon combined were estimated to contribute an average of 66% and 70% of the dietary exposure to 2-amino-3,4,8-dimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx) for men and women, respectively (27). Unlike nitrosamines, however, heterocyclic amines such as PhIP and DiMeIQx have not been clearly linked to bladder carcinogenesis in animal studies.

The lack of association for chicken with skin in the present study may be explained by low heterocyclic amine concentrations in chicken cooked with skin, compared with chicken without skin, under the same cooking conditions (16). Despite also being a major contributor to heterocyclic amines, "beef" was not associated with bladder cancer in the present study. Misclassification may have been more of a problem for beef because the FFQs in the 2 cohorts do not separate beef from pork and include several different cooking methods. Hamburgers, which were asked as a separate question, do not contribute substantially to heterocyclic amine concentrations (27).

In a case-control study conducted in Sweden, a 40% increase in bladder cancer risk was reported with frequent intake of fried meat (where higher heterocyclic amines concentrations would be expected) (24). To date, the only study to directly examine the relation between heterocyclic amines and bladder cancer found no association for 5 common types of dietary heterocyclic amines (28). However, the estimated average adult daily intake of heterocyclic amine for a Swedish population (2.3 ng · kg^{-1} · d^{-1}) (29) was substantially lower than the estimated intake in the United States (9 ng · kg^{-1} · d^{-1}) (27). This could be due to different patterns of meat intake in Sweden; for example, habitants of Sweden, Denmark, and Germany consume, on average, about one-third less chicken than do the habitants of Spain (30). It is conceivable that the study by Augustsson et al (28) detected no association with heterocyclic amines that are particularly high in chicken, such as PhIP or DiMeIQx, because of the narrow range of chicken intake. In our study, an elevated risk of bladder cancer was only detected among persons who consumed chicken ≥5 times/wk.

The strengths of the present study include a prospective design, a large number of bladder cancer cases (including a large number of female cases), detailed and updated data on diet and smoking, minimal loss to follow-up, and the comparison and

pooling of 2 entirely separate cohort studies. This is the largest study to date on meat intake and bladder cancer risk. In the present study, however, we were not able to estimate specific concentrations of nitrosamines or heterocyclic amine exposure because we had insufficient data on cooking practices. Therefore, we can only speculate that these compounds may explain our findings for bacon and chicken without skin.

In the present study, we observed strong associations between bacon intake and bladder cancer when using cumulative updated data on diet. In the NHS cohort, we observed a slightly weaker association between bacon intake and bladder cancer when using baseline dietary data than with the cumulative updated dietary data (Table 2). Because dietary intake fluctuates daily and over time and cannot be measured without error, using cumulative updated dietary intakes with multiple dietary assessments during the follow-up reduces measurement error and better reflects long-term intake (31). Because the association was further strengthened after removal of the women who had changed bacon intake before baseline, and given the consistent finding in the HPFS cohort, it is unlikely that these findings are due to chance. Furthermore, residual confounding by smoking is unlikely to explain our findings, given that the associations between bacon intake and smoking and between smoking and bladder cancer are not strong enough for residual confounding to explain the observed association in the present study.

For the 2 cohorts combined, we observed elevated risks of bladder cancer among persons who frequently consume bacon. The associations were more pronounced after restricting analyses to persons who had not changed their dietary intake for these items. Although we were unable to determine which compounds were responsible for our observations, we speculate that nitrosamines, heterocyclic amines, or both may play a role. Because our findings have not been previously reported in other studies, they need to be confirmed.

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