American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2009.

Vol. 170, No. 9
DOI: 10.1093/aje/kwp280
Advance Access publication:
October 6, 2009

Original Contribution

Meat and Meat-related Compounds and Risk of Prostate Cancer in a Large Prospective Cohort Study in the United States

Rashmi Sinha*, Yikyung Park, Barry I. Graubard, Michael F. Leitzmann, Albert Hollenbeck, Arthur Schatzkin, and Amanda J. Cross

* Correspondence to Dr. Rashmi Sinha, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Rockville, MD 20892 (e-mail: sinhar@nih.gov).

Initially submitted January 28, 2009; accepted for publication July 31, 2009.

The authors examined associations between meat consumption (type, cooking method, and related mutagens), heme iron, nitrite/nitrate, and prostate cancer in a cohort of 175,343 US men aged 50–71 years. During 9 years of follow-up (1995–2003), they ascertained 10,313 prostate cancer cases (1,102 advanced) and 419 fatal cases. Hazard ratios comparing the fifth intake quintile with the first revealed elevated risks associated with red and processed meat for total (red meat: hazard ratio (HR) = 1.12, 95% confidence interval (CI): 1.04, 1.21; processed meat: HR = 1.07, 95% CI: 1.00, 1.14) and advanced (red meat: HR = 1.31, 95% CI: 1.05, 1.65; processed meat: HR = 1.32, 95% CI: 1.08, 1.61) prostate cancer. Heme iron, barbecued/grilled meat, and benzo[*a*]pyrene were all positively associated with total (HR = 1.09 (95% CI: 1.02, 1.17), HR = 1.11 (95% CI: 1.03, 1.19), and HR = 1.09 (95% CI: 1.00, 1.18), respectively) and advanced (HR = 1.28 (95% CI: 1.03, 1.58), HR = 1.36 (95% CI: 1.10, 1.69), and HR = 1.28 (95% CI: 1.00, 1.65), respectively) disease. Nitrite (HR = 1.24, 95% CI: 1.02, 1.51) and nitrate (HR = 1.31, 95% CI: 1.07, 1.61) intakes were associated with advanced prostate cancer. There were no clear associations for fatal prostate cancer. Red and processed meat may be positively associated with prostate cancer via mechanisms involving heme iron, nitrite/nitrate, grilling/barbecuing, and benzo[*a*]pyrene.

amines; benzo(*a*)pyrene; heme; meat; nitrates; nitrites; polycyclic hydrocarbons, aromatic; prostatic neoplasms

Abbreviations: B[*a*]P, benzo[*a*]pyrene; CI, confidence interval; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; HR, hazard ratio; NIH, National Institutes of Health; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; NOCs, *N*-nitroso compounds; PAHs, polycyclic aromatic hydrocarbons; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; PSA, prostate-specific antigen.

Prostate cancer is the most common cancer among men in the United States, with an estimated 186,320 incident cases and 28,660 deaths occurring during 2008 (1). Results of ecologic and migrant studies suggest that environmental exposures, including diet, play an important role in the etiology of this malignancy (2–4).

In 2007, an international panel of experts noted "impressive recent evidence from cohort studies and trials demonstrating effects of specific foods and nutrients in prostate cancer" (5, p. 305). However, the panel indicated that there was "limited suggestive" evidence for an association between processed meat intake and prostate cancer. Case-control (6–9) and cohort (8–13) studies generally have found a positive association between red meat intake and prostate cancer; however, after reviewing prospective studies, Dagnelie et al. (8) concluded that this association was not convincing. There is some evidence that intake of meat from different meat groups, such as hamburgers or processed meat, is positively associated with prostate cancer (8, 14, 15).

There are various mechanisms by which meat consumption may be related to prostate cancer. High-temperature cooking methods, such as pan-frying and grilling/barbecuing, produce compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons (PAHs) (16–22), which are known animal carcinogens (23–26). The second group of potential carcinogens is *N*-nitroso compounds (NOCs), which are formed endogenously from red meat or from preservatives added to processed meats (27–29). The third possible mechanism operates via heme iron, which can promote endogenous production of NOCs; in addition, any source of iron can also catalyze free radical formation (27, 30–33).

We prospectively investigated whether types of meat (red, white, or processed) and possible mechanisms related to meat (heme iron, nitrite/nitrate, and meat cooking carcinogens) were associated with prostate cancer in the National Institutes of Health (NIH)-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. Because red meat intake has been reported to be more strongly related to metastatic prostate cancer than incident prostate cancer (9), we evaluated associations according to prostate tumor characteristics by studying 3 main endpoints: total prostate cancer, advanced prostate cancer, and fatal prostate cancer.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health Study was initiated by mailing a questionnaire to AARP members aged 50–71 years residing in one of 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) in 1995–1996 (34). The participants returned a self-administered food frequency questionnaire that asked about diet, medical history, and lifestyle factors. Within 6 months of mailing the first questionnaire, a risk factor questionnaire was mailed to participants who did not have self-reported prostate, breast, or colon cancer at baseline. Of men who returned both the baseline questionnaire and the risk factor questionnaire (n = 196,851), we excluded persons whose questionnaires were completed by proxies (n = 8,734), persons who had any prevalent cancer, except nonmelanoma skin cancer (n = 9,832), and persons who had died of cancer but did not have a cancer incidence record in the registry (n = 1,515). In addition, we excluded persons who reported extreme total energy intakes (beyond 2 times the interquartile ranges of sex-specific Box-Cox log-transformed intake) (n = 1,427). After these exclusions, our analytic cohort consisted of 175,343 men.

Cancer ascertainment

Cancer cases were identified through probabilistic linkage with state cancer registry databases that are certified by the North American Association of Central Cancer Registries as being at least 90% complete within 2 years of cancer occurrence. Our case ascertainment method was described in a previous study, which demonstrated that approximately 90% of cancers were identified through the registries (35). Causes of death were ascertained through annual linkage of the cohort to the Social Security Administration Death Master File, follow-up searches of the National Death Index Plus for participants who were matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

We identified 10,313 incident cases of prostate cancer (*International Classification of Diseases for Oncology*, Third Edition, code C619) with information on cancer stage and histology during follow-up through December 31, 2003. Fatal cases were defined as those in persons who died of prostate cancer through December 31, 2005, with additional follow-up information obtained through National Death Index searches. Advanced cases were defined as those in persons with clinical stages of T3, T4, N1, or M1 according to the American Joint Committee on Cancer 1997 tumor-node-metastasis classification system (36); the remaining cases were considered nonadvanced cases.

Dietary assessment

A 124-item food frequency questionnaire (37) with information on the usual consumption of foods and drinks over the past 12 months was administered at baseline. The risk factor questionnaire collected information on cooking methods used for different meats.

"Red meat" included all types of beef and pork (bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, steak, and meats in foods such as pizza, chili, lasagna, and stew) (38). "White meat" included chicken and turkey (poultry cold cuts, chicken mixtures, low-fat sausages, and low-fat hot dogs made from poultry) and fish. "Processed meat" included bacon, red-meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. In a calibration study of the food frequency questionnaire used in the NIH-AARP Diet and Health Study, the correlations between red meat intake assessed from the food frequency questionnaire and intake assessed from 24-hour recalls were 0.62 for men and 0.70 for women (39).

Using the risk factor questionnaire, we estimated quantities of meat in grams according to cooking method used (grilled/barbequed, pan-fried, microwaved, or broiled) and doneness level (well-done or medium/rare) (40). We estimated levels of heterocyclic amines (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)), levels of benzo[*a*]pyrene (B[*a*]P), and mutagenic activity (a measure of total mutagenic potential incorporating all meat-related mutagens) from meats with known cooking details by multiplying grams of intake and the appropriate mutagen content provided in the National Cancer Institute's CHARRED database (http://charred.cancer.gov/).

Heme iron concentrations in meat can vary depending on cooking method and degree of doneness, as heme iron in meat can be converted to nonheme iron (41–43). In most epidemiologic studies, investigators have estimated heme iron content by applying a standard factor to total iron from meat (44, 45). To estimate heme iron intake, we used a database based on measured values from meat samples cooked by different methods and to varying doneness levels (unpublished data). We estimated nitrate and nitrite intake from processed meats using a separate National Cancer Institute database (unpublished data) containing measured values of nitrate and nitrite for 10 types of processed meats, which represent 90% of processed meats consumed in the United States (46).

Statistical analysis

We used Cox proportional hazards regression models, with age as the underlying time metric, to estimate hazard ratios and 95% confidence intervals. Person-years of follow-up for cancer incidence were calculated from the date on which the risk factor questionnaire was returned to the date of prostate cancer diagnosis, death, moving out of the study area, or the end of follow-up, whichever came first. For the fatal cancer analyses, person-years were calculated from the date on which the risk factor questionnaire was returned to the date of death, relocation out of the study area, or the end of follow-up, whichever came first. We evaluated the proportional hazards assumption by modeling interaction terms of time and meat variables. The interactions were not statistically significant, which validated the use of proportional hazards.

In the baseline questionnaire, we inquired about race/ethnicity, educational level, marital status, smoking status, vigorous physical activity, medical history (including diabetes), family history of prostate cancer, and current body weight and height. In the risk factor questionnaire, we also asked the subject whether he had undergone prostate-specific antigen (PSA) testing during the past 3 years (47).

Hazard ratios were estimated within quantiles of meat and meat-related exposures, and tests for linear trend were performed by assigning the median value of each category to each participant, constructing a continuous variable based on that assignment, and then entering that variable in a regression model. Intakes of red and white meat and processed and nonprocessed meat were mutually adjusted for each other. Food intakes were energy-adjusted using the nutrient density method, and nutrients were adjusted by the residual method (48).

The multivariate model included age, education, marital status, family history of prostate cancer, self-reported history of diabetes, PSA testing, race/ethnicity, body mass index (weight (kg)/height (m)^2), smoking, vigorous physical activity, and intakes of total energy, alcohol, tomatoes, vitamin E, α-linolenic acid, zinc, selenium, and calcium. The largest confounders of the association between meat intake and prostate cancer were a family history of prostate cancer, undergoing a PSA test in the past 3 years, and self-reported history of diabetes. All statistical analyses were carried out using SAS software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Among 10,313 prostate cancer cases (1,135,051 person-years), there were 1,102 participants with advanced disease. In addition, we ascertained 419 fatal prostate cancers (1,579,590 person-years).

We observed a wide range in red meat consumption; mean intake was 10.8 g/1,000 kcal in the first quintile and 70.9 g/1,000 kcal in the fifth quintile (Table 1). Consumption of more red meat was associated with being married, being non-Hispanic white, being less educated, being a current smoker, having a higher body mass index, being less physically active, and not having undergone a PSA test in the past 3 years. Men consuming more red meat also had higher intakes of processed meat, total calories, α-linolenic acid, and selenium and lower amounts of white meat, calcium, vitamin E, and alcohol.

Red meat intake was associated with an increased risk for all prostate cancer (Table 2), especially in the top 2 deciles, compared with the first decile (ninth decile: hazard ratio (HR) = 1.14, 95% confidence interval (CI): 1.04, 1.26; 10th decile: HR = 1.13, 95% CI: 1.02, 1.25; *P*-trend = 0.003). The associations were stronger for advanced disease, with an approximately 30% higher risk being observed among men in the fifth quintile as compared with those in the first. Processed meat intake was associated with an increased risk of advanced prostate cancer, especially in the top decile, compared with the first (HR = 1.45, 95% CI: 1.10, 1.92; *P*-trend = 0.006). When we subdivided processed meat into red and white meat, we found that the red processed meat was associated with increased risk among men in the top quintile, as compared with the bottom quintile (HR = 1.28, 95% CI: 0.95, 1.59; *P*-trend = 0.03). Furthermore, in the continuous data, we observed an increased risk of 10% per 10-g increase in red processed meat intake (95% CI: 1.03, 1.17; *P*-trend = 0.003). For fatal prostate cancer, we also observed a suggestive increased risk and linear trend with intake of red meat ($P = 0.08$) but no associations for white meat or processed meat intake.

To investigate possible mechanisms that might explain these positive associations, we investigated iron/heme iron, nitrate/nitrite, and cooking-related carcinogens. There was no association between total iron intake and the risk of total, advanced, or fatal prostate cancer (Table 3). In contrast, heme iron intake was associated with an increased risk of 9% for total prostate cancer and 28% for advanced disease. We also observed increased risks of 24% and 31% for nitrite and nitrate, respectively, but only for advanced prostate cancer (Table 3). There were no associations for fatal prostate cancer with either heme iron or nitrite/nitrate from meat.

The only meat-cooking method associated with increased risk was grilled/barbecued meats for total (11% increased risk) and advanced (36% increased risk) prostate cancer (Table 4). The doneness of the meat did not appear to play a role in this association. Estimated intake of B[*a*]P, a marker of PAHs, was also associated with increased risk for total (9%) and advanced (28%) prostate cancer. However, none of the heterocyclic amines or meat-derived mutagenicity was associated with this malignancy. We did not find any association for fatal prostate cancer for cooking methods, doneness, or meat mutagens.

Sensitivity analyses, excluding men who were diagnosed in the first 2 years of follow-up, did not attenuate the associations. In many instances the risks were further elevated; for example, the hazard ratios for advanced cancer in the top quintiles of red meat, processed meat, and heme iron were 1.60 (95% CI: 1.21, 2.11), 1.46 (95% CI: 1.16, 1.85), and 1.38 (95% CI: 1.07, 1.79), respectively.

Table 1. Selected Characteristics[a] of Men ($n = 175{,}343$) by Quintile of Red Meat Consumption in the NIH-AARP Diet and Health Study, 1995–2003

Characteristic	Quintile of Red Meat Intake				
	1	2	3	4	5
Mean meat intake, g/1,000 kcal					
Red meat	10.8	24.1	34.5	46.4	70.9
White meat	35.6	31.7	30.6	30.3	30.8
Processed meat	5.4	8.4	11.0	14.2	20.1
Age, years	63.5	63.4	63.1	62.9	62.2
Race, %					
Non-Hispanic white	90.7	93.3	94.2	95.1	94.9
Non-Hispanic black	3.2	2.5	2.1	1.7	1.6
Hispanic	4.9	3.3	2.7	2.4	2.5
Asian/Pacific Islander, American Indian/Alaskan Native, or unknown	1.3	1.0	0.9	0.8	1.0
Family history of prostate cancer, %	8.4	8.4	8.6	8.2	8.3
Self-reported history of diabetes, %	6.8	7.7	8.8	10.8	14.3
Having a prostate-specific antigen test in the past 3 years, %	75.1	73.3	72.5	70.1	66.6
Currently married, %	81.3	84.9	86.6	86.8	85.6
Body mass index[b]	25.9	26.7	27.2	27.6	28.3
Smoking history, %					
Never smoker	34.6	30.9	29.5	28.2	26.4
Former smoker	56.1	56.8	56.2	55.5	54.5
Current smoker or former smoker who quit <1 year previously	5.8	8.8	11.0	12.8	15.6
College graduation or postgraduate study, %	54.8	49.5	47.6	44.6	41.4
Vigorous physical activity ≥5 times per week, %	31.1	23.8	20.7	19.0	16.9
Use of ≥1 vitamin supplement per month	68.0	62.3	59.2	56.6	52.8
Dietary variables (mean intake)					
Energy, kcal/day	1,899	1,957	2,000	2,046	2,119
Alcohol, g/day	19.7	19.5	17.0	15.0	12.8
Tomatoes, servings/1,000 kcal	0.35	0.33	0.33	0.33	0.33
Saturated fat, g/1,000 kcal	7.7	9.6	10.6	11.5	12.7
α-Linolenic acid, g/1,000 kcal	0.62	0.67	0.71	0.73	0.75
Total calcium, mg/day[c]	1,052	970	912	856	775
Total vitamin E, μg/day[c]	100.5	80.9	72.6	66.7	60.9
Total zinc, mg/day[c]	18.0	17.5	17.6	17.7	18.7
Total selenium, μg/day[c]	102.9	100.9	102.7	106.0	113.5
DiMeIQx, ng/1,000 kcal	0.31	0.48	0.64	0.82	1.25
MeIQx, ng/1,000 kcal	3.2	7.0	10.2	13.9	22.6
PhIP, ng/1,000 kcal	31.8	41.0	51.0	62.9	95.8
Benzo[*a*]pyrene, ng/1,000 kcal	6.7	12.0	17.1	22.9	37.1
Heme iron, μg/1,000 kcal	74.5	128.0	175.7	235.2	372.9
Nitrite, μg/1,000 kcal	49.4	72.4	93.0	118.0	166.9
Nitrate, μg/1,000 kcal	63.3	113.1	151.4	194.5	268.5

Abbreviations: DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; NIH, National Institutes of Health; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine.

[a] Data were obtained from the risk factor questionnaire.

[b] Weight (kg)/height (m)^2.

[c] Energy-adjusted mean amount from the diet plus amount derived from supplements.

Table 2. Hazard Ratios for Relations Between Consumption of Red, White, and Processed Meat and Prostate Cancer in the NIH-AARP Diet and Health Study, 1995–2003

Category (Median Intake)	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		*P*-Trend
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Red meat, g/1,000 kcal	11.6	24.2		34.5		46.1		66.1		
Total prostate cancer										
No. of cases	2,133	2,113		2,065		2,003		1,999		
Age- and energy-adjusted[a]	1	1.00	0.94, 1.06	0.99	0.93, 1.05	0.98	0.92, 1.04	1.02	0.96, 1.08	0.58
Multivariate[b]	1	1.02	0.96, 1.08	1.02	0.96, 1.09	1.04	0.98, 1.12	1.12	1.04, 1.21	0.002
Advanced prostate cancer										
No. of cases	196	233		212		228		233		
Age- and energy-adjusted	1	1.20	1.00, 1.46	1.11	0.91, 1.35	1.20	0.99, 1.46	1.25	1.03, 1.52	0.05
Multivariate	1	1.21	1.00, 1.47	1.12	0.91, 1.37	1.23	1.00, 1.51	1.31	1.05, 1.65	0.04
Fatal prostate cancer										
No. of cases	71	65		97		98		88		
Age- and energy-adjusted	1	0.93	0.66, 1.30	1.44	1.06, 1.96	1.51	1.11, 2.06	1.46	1.07, 2.01	0.002
Multivariate	1	0.88	0.63, 1.24	1.34	0.97, 1.84	1.36	0.98, 1.90	1.25	0.87, 1.82	0.08
White meat, g/1,000 kcal	9.3	17.9		26.3		37.6		60.7		
No. of cases	1,989	2,083		2,108		2,067		2,066		
Age- and energy-adjusted	1	1.06	1.00, 1.13	1.08	1.02, 1.15	1.08	1.01, 1.15	1.10	1.03, 1.17	0.008
Multivariate	1	1.04	0.98, 1.11	1.05	0.99, 1.12	1.04	0.98, 1.11	1.08	1.00, 1.16	0.09
Advanced prostate cancer										
No. of cases	221	213		213		224		231		
Age- and energy-adjusted	1	0.96	0.79, 1.16	0.96	0.79, 1.16	1.02	0.85, 1.23	1.08	0.90, 1.30	0.24
Multivariate	1	0.93	0.77, 1.13	0.93	0.77, 1.13	0.99	0.81, 1.22	1.10	0.88, 1.36	0.21
Fatal prostate cancer										
No. of cases	102	95		69		84		69		
Age- and energy-adjusted	1	0.92	0.69, 1.21	0.67	0.49, 0.91	0.86	0.64, 1.15	0.77	0.56, 1.04	0.11
Multivariate	1	0.99	0.74, 1.32	0.76	0.55, 1.04	1.00	0.73, 1.37	0.92	0.64, 1.31	0.76
Processed meat, g/1,000 kcal	2.2	5.5		9.0		14.1		24.6		
Total prostate cancer										
No. of cases	2,091	2,071		2,063		1,994		2,094		
Age- and energy-adjusted	1	1.00	0.94, 1.07	1.01	0.95, 1.07	0.97	0.91, 1.03	1.02	0.96, 1.09	0.63
Multivariate	1	1.01	0.95, 1.07	1.02	0.96, 1.09	1.00	0.93, 1.06	1.07	1.00, 1.14	0.04
Advanced prostate cancer										
No. of cases	203	226		207		208		258		
Age- and energy-adjusted	1	1.12	0.93, 1.36	1.03	0.84, 1.25	1.03	0.84, 1.25	1.28	1.06, 1.54	0.02
Multivariate	1	1.11	0.91, 1.34	1.02	0.84, 1.25	1.03	0.84, 1.26	1.32	1.08, 1.61	0.008
Fatal prostate cancer										
No. of cases	89	79		81		81		89		
Age- and energy-adjusted	1	0.88	0.65, 1.19	0.89	0.66, 1.22	0.90	0.66, 1.22	1.01	0.75, 1.36	0.60
Multivariate	1	0.81	0.60, 1.11	0.81	0.59, 1.11	0.79	0.58, 1.09	0.86	0.63, 1.18	0.74

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] HRs were adjusted for age (years; continuous) and total energy intake (kcal/day; continuous).

[b] HRs were adjusted for age (continuous); total energy intake (continuous); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown); education (<8 years or unknown, 8–11 years, 12 years, some college, college graduate); marital status (married: yes/no); family history of prostate cancer (yes/no); undergoing prostate-specific antigen testing in the past 3 years (never/ever/missing data); history of diabetes (yes/no); body mass index (weight (kg)/height (m)^2; <18.5, 18.5–<25, 25–<30, 30–<35, or ≥35); smoking history (detailed variable derived from smoking status (never, former, current), time since quitting for former smokers, and smoking dose); frequency of vigorous physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, or ≥5 times/week); and intakes of alcohol (0, <5, 5–<15, 15–<30, or ≥30 g/day); calcium (quintiles), tomatoes (quintiles), α-linolenic acid (quintiles), vitamin E (quintiles), zinc (quintiles), and selenium (quintiles).

Table 3. Hazard Ratios for Relations Between Dietary and Heme Iron, Nitrite and Nitrate, and Prostate Cancer in the NIH-AARP Diet and Health Study, 1995–2003

Category (Median Intake)	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		*P*-Trend
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Total dietary iron, mg/1,000 kcal	11.9	15.7		21.4		31.5		37.4		
Total prostate cancer										
No. of cases	1,973	1,995		2,082		2,106		2,157		
Age- and energy-adjusted[a]	1	0.99	0.93, 1.05	1.03	0.97, 1.10	1.05	0.98, 1.11	1.04	0.98, 1.10	0.06
Multivariate[b]	1	1.01	0.94, 1.08	1.08	0.99, 1.17	1.11	0.97, 1.26	1.08	0.94, 1.25	0.24
Advanced prostate cancer										
No. of cases	218	214		212		213		245		
Age- and energy-adjusted	1	0.96	0.80, 1.17	0.96	0.80, 1.16	0.97	0.80, 1.17	1.09	0.91, 1.31	0.32
Multivariate	1	0.94	0.76, 1.16	0.91	0.70, 1.18	0.86	0.58, 1.29	0.95	0.61, 1.46	0.86
Fatal prostate cancer										
No. of cases	93	87		67		88		84		
Age- and energy-adjusted	1	0.88	0.66, 1.18	0.68	0.50, 0.93	0.90	0.68, 1.21	0.80	0.60, 1.08	0.37
Multivariate	1	1.03	0.74, 1.44	0.77	0.50, 1.18	0.90	0.47, 1.72	0.77	0.38, 1.58	0.35
Heme iron, μg/1,000 kcal	57.9	117.5		171.0		236.8		366.8		
Total prostate cancer										
No. of cases	2,132	2,093		2,046		2,047		1,995		
Age- and energy-adjusted	1	0.99	0.93, 1.05	0.98	0.93, 1.04	1.01	0.95, 1.07	1.03	0.97, 1.09	0.23
Multivariate	1	1.00	0.94, 1.06	1.01	0.95, 1.07	1.04	0.98, 1.11	1.09	1.02, 1.17	0.003
Advanced prostate cancer										
No. of cases	204	217		214		227		240		
Age- and energy-adjusted	1	1.07	0.88, 1.29	1.06	0.88, 1.28	1.14	0.94, 1.38	1.23	1.02, 1.49	0.02
Multivariate	1	1.07	0.88, 1.30	1.07	0.88, 1.30	1.16	0.94, 1.42	1.28	1.03, 1.58	0.02
Fatal prostate cancer										
No. of cases	88	87		80		76		88		
Age- and energy-adjusted	1	1.00	0.74, 1.35	0.96	0.71, 1.29	0.95	0.70, 1.29	1.19	0.89, 1.61	0.26
Multivariate	1	0.95	0.70, 1.28	0.87	0.64, 1.19	0.84	0.61, 1.17	1.00	0.71, 1.40	0.98

Table continues

DISCUSSION

In our study, red meat, processed meat, heme iron, nitrite/nitrate from meat, grilled/barbecued meat, and B[*a*]P were associated with elevated risks of advanced prostate cancer. We observed similar but less strong associations for total prostate cancer but no association for nitrite/nitrate. For fatal prostate cancer, we observed a suggestive positive association for red meat but not for other meat-related variables.

In their 2007 report (5), a World Cancer Research Fund expert panel concluded that the evidence for a role of processed meat in the etiology of prostate cancer was "limited—suggestive," and for red meat the evidence was at an even lower level of "limited—no conclusion." Similar conclusions were reached in a review (8) and some recent cohort studies (49, 50), although a review of fat and meat intake in relation to prostate cancer found that 16 out of 22 case-control and cohort studies showed a positive risk of 1.3 or more with higher total meat intake (9). Few studies disaggregated meat into red and processed meat (9); the studies that did, however, found evidence that different subtypes of meat may be associated with an increased risk (14, 51). Our results provide evidence in support of the premise that analyzing meat by subgroup is important. We found risks around 1.3 among men consuming red and processed meat in the highest quintile, while associations for white meat were null. We also observed that red processed meat specifically may be related to increased risk, providing evidence that specific components of this type of meat may be important.

We observed an increased risk of prostate cancer with heme iron intake but not with total iron from the diet. To our knowledge, the relation between heme iron and prostate cancer has not been previously investigated. Kolonel (9) suggested that red meat may exert its role via other trace minerals such as selenium and zinc (high in red meat), which are essential for testosterone synthesis, but did not specifically address the role of heme in red meat. Tappel (52) suggested that heme iron may damage many organs, including the prostate, by catalyzing free radical formation. Once absorbed, heme iron is transported by the blood to

Table 3. Continued

Category (Median Intake)	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		*P*-Trend
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Nitrite from meat, mg/1,000 kcal	0.017	0.043		0.073		0.117		0.215		
Total prostate cancer										
No. of cases	2,089	2,092		2,048		2,003		2,081		
Age- and energy-adjusted	1	1.02	0.96, 1.08	1.00	0.94, 1.07	0.98	0.93, 1.05	1.02	0.96, 1.09	0.69
Multivariate	1	1.02	0.96, 1.08	1.01	0.95, 1.08	1.00	0.94, 1.07	1.05	0.99, 1.12	0.14
Advanced prostate cancer	0.016	0.043		0.073		0.117		0.215		
No. of cases	205	222		215		210		250		
Age- and energy-adjusted	1	1.09	0.90, 1.32	1.06	0.88, 1.29	1.04	0.86, 1.26	1.23	1.03, 1.49	0.04
Multivariate	1	1.07	0.89, 1.30	1.04	0.86, 1.27	1.02	0.84, 1.25	1.24	1.02, 1.51	0.03
Fatal prostate cancer										
No. of cases	85	81		81		85		87		
Age- and energy-adjusted	1	0.98	0.72, 1.33	1.00	0.74, 1.35	1.04	0.77, 1.41	1.07	0.80, 1.45	0.52
Multivariate	1	0.92	0.67, 1.25	0.92	0.67, 1.25	0.95	0.70, 1.30	0.96	0.70, 1.32	0.97
Nitrate from meat, mg/1,000 kcal	0.032	0.081		0.129		0.192		0.314		
Total prostate cancer										
No. of cases	2,091	2,069		2,084		1,997		2,072		
Age- and energy-adjusted	1	1.01	0.95, 1.07	1.02	0.96, 1.08	0.98	0.92, 1.04	1.02	0.96, 1.08	0.78
Multivariate	1	1.01	0.95, 1.07	1.03	0.97, 1.10	1.00	0.94, 1.06	1.06	0.99, 1.13	0.11
Advanced prostate cancer										
No. of cases	193	236		204		222		247		
Age- and energy-adjusted	1	1.23	1.02, 1.49	1.07	0.88, 1.30	1.16	0.96, 1.41	1.30	1.08, 1.57	0.02
Multivariate	1	1.22	1.01, 1.48	1.06	0.87, 1.30	1.16	0.95, 1.42	1.31	1.07, 1.61	0.03
Fatal prostate cancer										
No. of cases	82	77		73		97		90		
Age- and energy-adjusted	1	0.96	0.70, 1.31	0.92	0.67, 1.26	1.22	0.91, 1.64	1.16	0.86, 1.56	0.12
Multivariate	1	0.89	0.65, 1.22	0.83	0.60, 1.15	1.07	0.79, 1.46	0.93	0.67, 1.28	0.92

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH, National Institutes of Health.

[a] HRs were adjusted for age (years; continuous) and total energy intake (kcal/day; continuous).

[b] HRs were adjusted for age (continuous); total energy intake (continuous); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown); education (<8 years or unknown, 8–11 years, 12 years, some college, college graduate); marital status (married: yes/no); family history of prostate cancer (yes/no); undergoing prostate-specific antigen testing in the past 3 years (never/ever/missing data); history of diabetes (yes/no); body mass index (weight (kg)/height (m)^2; <18.5, 18.5–<25, 25–<30, 30–<35, or ≥35); smoking history (detailed variable derived from smoking status (never, former, current), time since quitting for former smokers, and smoking dose); frequency of vigorous physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, or ≥5 times/week); and intakes of alcohol (0, <5, 5–<15, 15–<30, or ≥30 g/day); calcium (quintiles), tomatoes (quintiles), α-linolenic acid (quintiles), vitamin E (quintiles), zinc (quintiles), and selenium (quintiles).

every organ and tissue, where it can catalyze oxidative reactions, causing damage to lipids, proteins, DNA, and other nucleic acids. The level of free radical damage caused by heme-catalyzed oxidation can be of a magnitude similar to that resulting from ionizing radiation (52).

Another mechanism related to red and processed meat is the formation of NOCs, which are known carcinogens in multiple species (53). Exposure to NOCs occurs from endogenous formation, which is directly related to red meat intake, as well as exogenous exposure from nitrite-preserved meats (28, 46). Heme iron is thought to be the component of red meat that leads to increased endogenous formation of NOCs (27, 31, 32). Human exposure to NOCs and subsequent cancer risk has not been studied extensively. In this report, we present an indirect measure of NOC intake by estimating exposure to various factors (i.e., red and processed meat, heme iron, and nitrate/nitrite) known to increase production of NOCs.

Meat doneness is a surrogate measure of many compounds that are formed during the cooking process (46, 54). We did not find an association between meat doneness levels and prostate cancer in this study. In contrast, in 2 other cohort studies, investigators did observe positive associations with meat doneness. In the Agricultural Health Study, Koutros et al. (11) found an increased risk of prostate cancer associated with intake of well-done/very well-done meat,

Table 4. Hazard Ratios for Relations Between Meat-Cooking Methods, Doneness of Meat, and Intake of Meat Mutagens and Prostate Cancer in the NIH-AARP Diet and Health Study, 1995–2003

Category (Median Intake)	Category 1	2 HR	2 95% CI	3 HR	3 95% CI	4 HR	4 95% CI	5 HR	5 95% CI	*P*-Trend
Meat-Cooking Method										
Grilled/barbequed, g/1,000 kcal	0	2.37		5.93		11.29		22.99		
Total prostate cancer										
No. of cases	2,129	2,141		2,048		1,964		2,031		
Age- and energy-adjusted[a]	1	1.02	0.96, 1.09	1.00	0.94, 1.06	1.00	0.93, 1.06	1.09	1.02, 1.16	0.01
Multivariate[b]	1	1.02	0.96, 1.08	1.00	0.94, 1.07	1.00	0.94, 1.07	1.11	1.03, 1.19	0.003
Advanced prostate cancer										
No. of cases	191	214		223		234		240		
Age- and energy-adjusted	1	1.13	0.93, 1.38	1.20	0.98, 1.46	1.28	1.04, 1.56	1.34	1.09, 1.66	0.004
Multivariate	1	1.14	0.94, 1.39	1.21	0.99, 1.48	1.29	1.05, 1.58	1.36	1.10, 1.69	0.01
Fatal prostate cancer										
No. of cases	93	83		87		84		72		
Age- and energy-adjusted	1	0.90	0.67, 1.22	0.98	0.72, 1.32	0.99	0.72, 1.36	0.93	0.66, 1.30	0.88
Multivariate	1	0.92	0.68, 1.25	0.98	0.72, 1.32	0.99	0.72, 1.36	0.91	0.65, 1.29	0.77
Pan-fried, g/1,000 kcal	0	0.16		2.42						
Total prostate cancer										
No. of cases	3,703	3,174		3,436						
Age- and energy-adjusted	1	0.97	0.92, 1.02	1.00	0.95, 1.05					0.60
Multivariate	1	0.96	0.92, 1.01	1.01	0.96, 1.06					0.26
Advanced prostate cancer										
No. of cases	357	364		381						
Age- and energy-adjusted	1	1.10	0.95, 1.29	1.14	0.98, 1.32					0.26
Multivariate	1	1.10	0.94, 1.28	1.13	0.96, 1.32					0.34
Fatal prostate cancer										
No. of cases	146	134		139						
Age- and energy-adjusted	1	1.08	0.84, 1.38	1.02	0.80, 1.31					0.91
Multivariate	1	1.05	0.82, 1.35	0.88	0.68, 1.13					0.16
Microwaved, g/1,000 kcal	0	0.44		4.94						
Total prostate cancer										
No. of cases	5,167	1,690		3,456						
Age- and energy-adjusted	1	1.02	0.96, 1.08	1.00	0.95, 1.05					1.00
Multivariate	1	1.01	0.96, 1.07	1.00	0.95, 1.04					0.94
Advanced prostate cancer										
No. of cases	567	171		364						
Age- and energy-adjusted	1	1.00	0.83, 1.19	1.01	0.88, 1.17					0.96
Multivariate	1	0.99	0.83, 1.19	1.01	0.87, 1.16					0.95
Fatal prostate cancer										
No. of cases	201	70		148						
Age- and energy-adjusted	1	1.06	0.80, 1.42	1.05	0.83, 1.32					0.81
Multivariate	1	1.03	0.77, 1.38	1.03	0.82, 1.30					0.86
Broiled, g/1,000 kcal	0	0.77		6.52						
Total prostate cancer										
No. of cases	5,933	778		3,602						
Age- and energy-adjusted	1	1.00	0.93, 1.08	1.05	1.01, 1.10					0.01
Multivariate	1	1.00	0.93, 1.08	1.04	1.00, 1.09					0.03
Advanced prostate cancer										
No. of cases	664	78		360						
Age- and energy-adjusted	1	0.96	0.76, 1.22	1.01	0.88, 1.17					1.00
Multivariate	1	0.95	0.75, 1.21	1.00	0.87, 1.15					0.82
Fatal prostate cancer										
No. of cases	241	32		146						
Age- and energy-adjusted	1	0.98	0.67, 1.42	1.01	0.80, 1.26					0.98
Multivariate	1	0.95	0.65, 1.38	0.97	0.77, 1.22					0.81

Table continues

Table 4. Continued

Category (Median Intake)	Category 1	2 HR	2 95% CI	3 HR	3 95% CI	4 HR	4 95% CI	5 HR	5 95% CI	*P*-Trend
Doneness of Meat										
Rare/medium, g/1,000 kcal	0	1.18		4.53		10.23		22.50		
Total prostate cancer										
No. of cases	2,682	1,489		2,054		2,056		2,032		
Age- and energy-adjusted	1	1.00	0.94, 1.07	1.00	0.94, 1.06	1.02	0.96, 1.08	1.05	0.98, 1.12	0.07
Multivariate	1	1.00	0.94, 1.07	1.00	0.94, 1.06	1.02	0.96, 1.09	1.06	0.99, 1.14	0.03
Advanced prostate cancer										
No. of cases	257	158		233		240		214		
Age- and energy-adjusted	1	1.15	0.94, 1.41	1.23	1.02, 1.48	1.27	1.05, 1.54	1.14	0.93, 1.41	0.33
Multivariate	1	1.16	0.95, 1.42	1.23	1.02, 1.48	1.27	1.04, 1.54	1.14	0.92, 1.41	0.41
Fatal prostate cancer										
No. of cases	113	62		90		85		69		
Age- and energy-adjusted	1	0.97	0.71, 1.33	0.99	0.74, 1.32	0.90	0.67, 1.23	0.74	0.53, 1.04	0.13
Multivariate	1	1.01	0.74, 1.39	1.01	0.75, 1.35	0.90	0.66, 1.24	0.72	0.51, 1.03	0.10
Well-done/very well-done, g/1,000 kcal	0.09	2.15		5.63		10.70		21.37		
Total prostate cancer										
No. of cases	2,050	2,061		2,129		2,004		2,069		
Age- and energy-adjusted	1	0.98	0.93, 1.05	1.02	0.96, 1.09	0.98	0.91, 1.04	1.04	0.97, 1.11	0.17
Multivariate	1	1.00	0.94, 1.06	1.03	0.97, 1.10	0.98	0.92, 1.05	1.06	0.99, 1.14	0.06
Advanced prostate cancer										
No. of cases	237	197		208		233		227		
Age- and energy-adjusted	1	0.82	0.68, 1.00	0.89	0.73, 1.08	1.02	0.84, 1.24	1.04	0.85, 1.27	0.32
Multivariate	1	0.82	0.68, 1.00	0.88	0.73, 1.07	1.01	0.83, 1.23	1.04	0.84, 1.28	0.33
Fatal prostate cancer										
No. of cases	96	75		89		80		79		
Age- and energy-adjusted	1	0.70	0.52, 0.96	0.81	0.59, 1.09	0.72	0.52, 0.99	0.74	0.53, 1.03	0.26
Multivariate	1	0.67	0.49, 0.91	0.75	0.55, 1.03	0.68	0.49, 0.94	0.68	0.48, 0.97	0.16
Intake of Meat Mutagens										
MeIQx, ng/1,000 kcal	0.65	2.86		6.03		11.45		26.55		
Total prostate cancer										
No. of cases	2,105	2,135		2,097		2,014		1,962		
Age- and energy-adjusted	1	1.02	0.95, 1.09	0.98	0.91, 1.05	0.94	0.86, 1.02	0.95	0.87, 1.03	0.26
Multivariate	1	1.02	0.95, 1.09	0.98	0.91, 1.06	0.95	0.87, 1.03	0.98	0.90, 1.08	0.85
Advanced prostate cancer										
No. of cases	214	212		237		231		208		
Age- and energy-adjusted	1	0.95	0.77, 1.18	0.99	0.78, 1.24	0.92	0.72, 1.19	0.87	0.66, 1.15	0.43
Multivariate	1	0.94	0.76, 1.16	0.98	0.77, 1.23	0.91	0.70, 1.17	0.86	0.65, 1.14	0.38
Fatal prostate cancer										
No. of cases	96	70		91		80		82		
Age- and energy-adjusted	1	0.81	0.57, 1.14	1.03	0.72, 1.47	0.90	0.60, 1.34	1.11	0.72, 1.71	0.21
Multivariate	1	0.76	0.54, 1.07	0.90	0.63, 1.30	0.76	0.51, 1.15	0.87	0.55, 1.35	0.91
DiMeIQx, ng/1,000 kcal	0	0.05		0.22		0.65		1.85		
Total prostate cancer										
No. of cases	3,643	489		2,144		2,086		1,951		
Age- and energy-adjusted	1	0.97	0.88, 1.06	1.01	0.96, 1.07	1.04	0.97, 1.11	1.00	0.93, 1.08	0.70
Multivariate	1	0.96	0.87, 1.05	1.01	0.95, 1.07	1.04	0.97, 1.11	1.00	0.93, 1.08	0.71
Advanced prostate cancer										
No. of cases	378	57		214		239		214		
Age- and energy-adjusted	1	1.10	0.83, 1.46	0.99	0.83, 1.19	1.14	0.93, 1.38	1.11	0.89, 1.40	0.39
Multivariate	1	1.10	0.83, 1.46	1.00	0.83, 1.20	1.15	0.94, 1.39	1.13	0.89, 1.42	0.34

Table continues

Table 4. Continued

Category (Median Intake)	Category									P-Trend
	1	2		3		4		5		
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
Fatal prostate cancer										
No. of cases	159	16		72		100		72		
Age- and energy-adjusted	1	0.71	0.43, 1.20	0.82	0.61, 1.10	1.16	0.85, 1.58	0.84	0.57, 1.23	0.44
Multivariate	1	0.73	0.44, 1.23	0.84	0.62, 1.13	1.20	0.88, 1.64	0.88	0.60, 1.29	0.61
PhIP, ng/1,000 kcal	3.69	14.59		29.80		55.88		131.95		
Total prostate cancer										
No. of cases	2,069	2,154		2,050		2,062		1,978		
Age- and energy-adjusted	1	1.07	1.01, 1.14	1.02	0.96, 1.10	1.04	0.97, 1.12	1.02	0.94, 1.11	0.87
Multivariate	1	1.07	1.00, 1.14	1.02	0.95, 1.09	1.03	0.96, 1.11	1.00	0.92, 1.09	0.50
Advanced prostate cancer										
No. of cases	203	230		232		237		200		
Age- and energy-adjusted	1	1.13	0.93, 1.38	1.11	0.90, 1.37	1.07	0.86, 1.34	0.88	0.67, 1.14	0.04
Multivariate	1	1.12	0.92, 1.37	1.09	0.88, 1.35	1.05	0.83, 1.31	0.85	0.66, 1.11	0.03
Fatal prostate cancer										
No. of cases	87	96		82		85		69		
Age- and energy-adjusted	1	1.21	0.89, 1.64	1.04	0.74, 1.46	1.15	0.81, 1.64	1.00	0.66, 1.53	0.58
Multivariate	1	1.17	0.86, 1.59	1.00	0.71, 1.41	1.11	0.78, 1.58	0.98	0.64, 1.49	0.59
Benzo[*a*]pyrene, ng/1,000 kcal	0.28	2.11		8.57		20.86		50.53		
Total prostate cancer										
No. of cases	2,106	2,154		1,965		2,066		2,022		
Age- and energy-adjusted	1	1.03	0.97, 1.10	0.94	0.88, 1.00	1.03	0.95, 1.10	1.08	1.00, 1.17	0.04
Multivariate	1	1.02	0.96, 1.09	0.93	0.87, 1.00	1.02	0.95, 1.10	1.09	1.00, 1.18	0.03
Advanced prostate cancer										
No. of cases	217	203		215		229		238		
Age- and energy-adjusted	1	0.93	0.76, 1.13	0.98	0.80, 1.20	1.06	0.85, 1.33	1.27	0.99, 1.62	0.002
Multivariate	1	0.93	0.76, 1.13	0.99	0.81, 1.21	1.08	0.86, 1.35	1.28	1.00, 1.65	0.002
Fatal prostate cancer										
No. of cases	109	80		74		88		68		
Age- and energy-adjusted	1	0.76	0.56, 1.02	0.71	0.52, 0.98	0.89	0.64, 1.25	0.72	0.49, 1.08	0.44
Multivariate	1	0.78	0.58, 1.05	0.78	0.57, 1.07	0.99	0.71, 1.39	0.80	0.54, 1.20	0.65

Abbreviations: CI, confidence interval; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; HR, hazard ratio; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; NIH, National Institutes of Health; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine.

[a] HRs were adjusted for age (years; continuous) and total energy intake (kcal/day; continuous).

[b] HRs were adjusted for age (continuous); total energy intake (continuous); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown); education (<8 years or unknown, 8–11 years, 12 years, some college, college graduate); marital status (married: yes/no); family history of prostate cancer (yes/no); undergoing prostate-specific antigen testing in the past 3 years (never/ever/missing data); history of diabetes (yes/no); body mass index (weight (kg)/height (m)^2; <18.5, 18.5–<25, 25–<30, 30–<35, or ≥35); smoking history (detailed variable derived from smoking status (never, former, current), time since quitting for former smokers, and smoking dose); frequency of vigorous physical activity (never/rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, or ≥5 times/week); and intakes of alcohol (0, <5, 5–<15, 15–<30, or ≥30 g/day); calcium (quintiles), tomatoes (quintiles), α-linolenic acid (quintiles), vitamin E (quintiles), zinc (quintiles), and selenium (quintiles).

and in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, Cross et al. (10) reported a 1.7-fold increased risk of incident disease for consuming more than 10 g/day of very well-done meat.

Heterocyclic amines are formed from the reaction between creatine or creatinine (found in muscle meats), amino acids, and sugars (55). Over 20 individual heterocyclic amines have been identified; heterocyclic amines most abundant in the human diet are PhIP, MeIQx, and DiMeIQx (56). Most heterocyclic amines are potent bacterial mutagens, and at least 10 have been found to induce multisite tumors in laboratory animals (24, 57–59). PhIP, specifically, has been associated with an increased risk of prostate tumors in rats (24, 60). In the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (10), men in the highest quintile of PhIP had a 1.3-fold increased risk of incident disease. However, we did not observe an association between PhIP intake and prostate cancer in this study. Our results for PhIP intake are consistent with the null associations observed in a case-control study ($n = 317$ cases) in New Zealand (61) and the Agricultural Health Study (11). Other cohort studies collecting detailed data on meat-cooking are ongoing.

We observed an increased risk of prostate cancer with intake of grilled/barbecued meat and B[*a*]P. PAHs are mutagenic compounds formed in foods prepared by smoking or grilling/barbecuing (16). Cooking meat over a flame results in fat/meat juices' dripping onto the hot fire, which yields flames containing a number of PAHs that coat the surface of the food. B[*a*]P is one of the most potent PAHs in animal studies and can induce leukemia as well as gastric, pulmonary, fore-stomach, esophageal, and tongue tumors in rodents (62). Grilled and well-done steak, hamburgers, and chicken contain the highest levels of B[*a*]P—up to 4 ng per gram of cooked meat (16). Depending on individual factors, total PAH intake may vary between 25 μg/day and 300 μg/day. However, there is little evidence for an association of dietary PAHs with prostate cancer in published studies. The positive association we observed in this study needs to be investigated further in other cohort studies.

For fatal prostate cancer, we observed a suggestive increased risk with red meat intake, similar to our results for total and advanced prostate cancer. Even though the risk magnitudes were similar, we had fewer cases of fatal cancer, with limited power to reach statistical significance. For the other types of meat and meat-related compounds, our results for advanced prostate cancer more resembled those for total prostate cancer; this implies that they may influence the initiation and early progression of the disease rather than terminal progression. It could also be the case that a sizable number of the fatal prostate cancer cases were diagnosed at an earlier stage; this could have attenuated the association.

The principal strength of this study was the prospective design, the large size of the cohort, and the wide range of intakes. The questionnaire included details on meat-cooking practices, which allowed us to investigate various mechanisms by which meat may exert its effect in the etiology of prostate cancer. However, we were not able to disentangle the effects of each of the measurable meat-related compounds, since they were highly correlated. Our study also collected information on nondietary variables, such as PSA screening and prostate tumor characteristics, which enabled us to evaluate relations by tumor aggressiveness. Specifically, we evaluated associations with advanced prostate cancer—an endpoint that is considered more relevant for disease progression, since the majority of prostate tumors do not progress, and is less likely to be influenced by medical screening practices. Detection bias due to more frequent PSA screening among men with low meat intakes would tend to produce underestimation of a true positive association between red meat intake and total or early-stage prostate cancer. Although studying fatal prostate cancer cases clearly reflects the tumors that do progress, our study had a limited number of fatal cases and therefore lower statistical power for this endpoint.

The issues of measurement error in this study are similar to those of any nutritional epidemiology study in which estimates are based on memory and participants' ability to recall their usual intake over a given period. We adjusted our models for reported energy intake to try and decrease the degree of measurement error somewhat. Estimated intakes of compounds related to the various mechanisms by which meat may exert its deleterious effect were based on the best databases available to date. However, these databases are small and need further refining. The problem of residual confounding is always an issue; even after careful adjustment with known confounders, it may still be important and could explain the relatively small associations found. For example, other combinations of dietary factors or certain dietary patterns could be related to both a higher consumption of red and processed meat and prostate cancer risk, thereby confounding the associations we observed. However, adjustment for a range of potential dietary confounders (e.g., alcohol, calcium, tomatoes, α-linolenic acid, vitamin E, zinc, selenium) did not meaningfully change the associations.

In conclusion, we found that consumption of red and processed meat was associated with increased risks of total and advanced prostate cancer. Further study of heme iron, nitrite/nitrate, grilled/barbecued meat, and B[*a*]P may provide insights into possible mechanisms underlying these associations. These novel findings should be investigated in other studies with detailed questionnaires, databases, and biomarkers.

ACKNOWLEDGMENTS

Author affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Rashmi Sinha, Yikyung Park, Barry I. Graubard, Arthur Schatzkin, Amanda J. Cross); Institute of Epidemiology and Preventive Medicine, University of Regensburg, Regensburg, Germany (Michael F. Leitzmann); and AARP, Washington, DC (Albert Hollenbeck).

Cancer incidence data from the Atlanta, Georgia, metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit, Michigan, metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract with the Department of Health. (The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the Florida Department of Health.) Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health. (The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.) Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, and the Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas

Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, Nevada Department of Health and Human Services.

The authors thank Sigurd Hermansen and Kerry Grace Morrissey of Westat, Inc. (Rockville, Maryland) for ascertainment of study outcomes and management and Michael Spriggs, Adam Risch, and Leslie Carroll of Information Management Services (Silver Spring, Maryland) for data support and analysis.

Conflict of interest: none declared.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures 2008*. Atlanta, GA: American Cancer Society; 2008. (http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf). (Accessed November 5, 2008).
2. Cook LS, Goldoft M, Schwartz SM, et al. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. *J Urol*. 1999;161(1):152–155.
3. Kolonel LN, Hankin JH, Nomura AM. Multiethnic studies of diet, nutrition, and cancer in Hawaii. *Princess Takamatsu Symp*. 1985;16:29–40.
4. Shimizu H, Ross RK, Bernstein L, et al. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer*. 1991;63(6):963–966.
5. 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.
6. Deneo-Pellegrini H, De Stefani E, Ronco A, et al. Foods, nutrients and prostate cancer: a case-control study in Uruguay. *Br J Cancer*. 1999;80(3-4):591–597.
7. Ewings P, Bowie C. A case-control study of cancer of the prostate in Somerset and East Devon. *Br J Cancer*. 1996;74(4):661–666.
8. Dagnelie PC, Schuurman AG, Goldbohm RA, et al. Diet, anthropometric measures and prostate cancer risk: a review of prospective cohort and intervention studies. *BJU Int*. 2004;93(8):1139–1150.
9. Kolonel LN. Fat, meat, and prostate cancer. *Epidemiol Rev*. 2001;23(1):72–81.
10. Cross AJ, Peters U, Kirsh VA, et al. A prospective study of meat and meat mutagens and prostate cancer risk. *Cancer Res*. 2005;65(24):11779–11784.
11. Koutros S, Cross AJ, Sandler DP, et al. Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev*. 2008;17(1):80–87.
12. Rohrmann S, Platz EA, Kavanaugh CJ, et al. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control*. 2007;18(1):41–50.
13. Tseng M, Breslow RA, DeVellis RF, et al. Dietary patterns and prostate cancer risk in the National Health and Nutrition Examination Survey Epidemiological Follow-up Study cohort. *Cancer Epidemiol Biomarkers Prev*. 2004;13(1):71–77.
14. Michaud DS, Augustsson K, Rimm EB, et al. A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control*. 2001;12(6):557–567.
15. Schuurman AG, van den Brandt PA, Dorant E, et al. Animal products, calcium and protein and prostate cancer risk in the Netherlands Cohort Study. *Br J Cancer*. 1999;80(7):1107–1113.
16. Kazerouni N, Sinha R, Hsu CH, et al. Analysis of 200 food items for benzo[*a*]pyrene and estimation of its intake in an epidemiologic study. *Food Chem Toxicol*. 2001;39(5):423–436.
17. Knize MG, Sinha R, Brown ED, et al. Heterocyclic amine content in restaurant-cooked hamburgers, steaks, ribs and chicken. *J Agric Food Chem*. 1998;46(11):4648–4651.
18. Knize MG, Sinha R, Rothman N, et al. Heterocyclic amine content in fast-food meat products. *Food Chem Toxicol*. 1995;33:545–551.
19. Knize MG, Sinha R, Salmon CP, et al. Formation of heterocyclic amine mutagens/carcinogens during cooking of muscle meat. *J Muscle Foods*. 1996;7(3):271–279.
20. Sinha R, Gustafson DR, Kulldorff M, et al. 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine, a carcinogen in high-temperature-cooked meat, and breast cancer risk. *J Natl Cancer Inst*. 2000;92(16):1352–1354.
21. Sinha R, Knize MG, Salmon CP, et al. Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. *Food Chem Toxicol*. 1998;36(4):289–297.
22. Sinha R, Rothman N, Salmon CP, et al. Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem Toxicol*. 1998;36(4):279–287.
23. Ito N, Hasegawa R, Imaida K, et al. Carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in the rat. *Mutat Res*. 1997;376(1-2):107–114.
24. Shirai T, Sano M, Tamano S, et al. The prostate: a target for carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) derived from cooked foods. *Cancer Res*. 1997;57(2):195–198.
25. Sugimura T. Overview of carcinogenic heterocyclic amines. *Mutat Res*. 1997;376(1-2):211–219.
26. Adamson RH. Sixth international conference on carcinogenic/mutagenic *N*-substituted aryl compounds: conclusions and perspectives. *Mutat Res*. 1997;376(1-2):3–6.
27. Cross AJ, Pollock JRA, Bingham SA. Increased endogenous *N*-nitrosation in the human colon: a response to red and white meat? [abstract]. *Br J Cancer*. 2000;83:81.
28. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen*. 2004;44(1):44–55.
29. Hughes R, Cross AJ, Pollock JR, et al. Dose-dependent effect of dietary meat on endogenous colonic *N*-nitrosation. *Carcinogenesis*. 2001;22(1):199–202.
30. Cross AJ, Gunter MJ, Wood RJ, et al. Iron and colorectal cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Int J Cancer*. 2006;118(12):3147–3152.
31. Cross AJ, Pollock JR, Bingham SA. Red meat and colorectal cancer risk: the effect of dietary iron and haem on endogenous *N*-nitrosation. *IARC Sci Publ*. 2002;156:205–206.
32. Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal *N*-nitrosation arising from red meat. *Cancer Res*. 2003;63(10):2358–2360.
33. Lewin MH, Bailey N, Bandaletova T, et al. Red meat enhances the colonic formation of the DNA adduct O^6-carboxymethyl guanine: implications for colorectal cancer risk. *Cancer Res*. 2006;66(3):1859–1865.
34. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake

distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001;154(12):1119–1125.
35. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Registry Manag*. 2005;32:70–77.
36. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 5th ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997.
37. Applied Research Program, National Cancer Institute. *Diet History Questionnaire, Version 1.0*. Bethesda, MD: National Cancer Institute; 2007. (http://riskfactor.cancer.gov/DHQ/forms/files/shared/dhq1.2002.sample.pdf). (Accessed November 5, 2008).
38. Cross AJ, Leitzmann MF, Gail MH, et al. A prospective study of red and processed meat intake in relation to cancer risk [electronic article]. *PLoS Med*. 2007;4(12e325.
39. Thompson FE, Kipnis V, Midthune D, et al. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr.* 2008;11(2):183–195.
40. Kabat GC, Cross AJ, Park Y, et al. Meat intake and meat preparation in relation to risk of postmenopausal breast cancer in the NIH-AARP Diet and Health Study. *Int J Cancer.* 2008; 124(10):2430–2435.
41. 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;43:1824–1827.
42. Kongkachuichai R, Napatthalung P, Charoensiri R. Heme and non-heme iron content of animal products commonly consumed in Thailand. *J Food Comp Anal*. 2002;15(4):389–398.
43. Lombardi-Boccia G, Martinez-Dominguez B, Aguzzi A. Total heme and non-heme iron in raw and cooked meats. *J Food Sci.* 2002;67(5):1738–1741.
44. Monsen ER, Balintfy JL. Calculating dietary iron bioavailability: refinement and computerization. *J Am Diet Assoc.* 1982;80(4):307–311.
45. Balder HF, Vogel J, Jansen MC, et al. Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev.* 2006;15(4): 717–725.
46. Sinha R, Cross A, Curtin J, et al. Development of a food frequency questionnaire module and databases for compounds in cooked and processed meats. *Mol Nutr Food Res.* 2005; 49(7):648–655.
47. Park Y, Mitrou PN, Kipnis V, et al. Calcium, dairy foods, and risk of incident and fatal prostate cancer: the NIH-AARP Diet and Health Study. *Am J Epidemiol*. 2007;166(11):1270–1279.
48. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124(1):17–27.
49. Park SY, Murphy SP, Wilkens LR, et al. Fat and meat intake and prostate cancer risk: the Multiethnic Cohort Study. *Int J Cancer*. 2007;121(6):1339–1345.
50. Allen NE, Key TJ, Appleby PN, et al. Animal foods, protein, calcium and prostate cancer risk: the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer*. 2008; 98(9):1574–1581.
51. Rodriguez C, McCullough ML, Mondul AM, et al. Meat consumption among black and white men and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2006;15(2): 211–216.
52. Tappel A. Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. *Med Hypotheses*. 2007;68(3):562–564.
53. Lijinsky W. *Chemistry and Biology of* N*-Nitroso Compounds*. Cambridge, United Kingdom: Cambridge University Press; 1992.
54. Sinha R. An epidemiologic approach to studying heterocyclic amines. *Mutat Res.* 2002;506-507:197–204.
55. Knize MG, Salmon CP, Pais P, et al. Food heating and the formation of heterocyclic aromatic amine and polycyclic aromatic hydrocarbon mutagens/carcinogens. *Adv Exp Med Biol.* 1999;459:179–193.
56. Sugimura T. Mutagens, carcinogens, and tumor promoters in our daily food. *Cancer.* 1970;49(10):1970–1981.
57. Adamson RH, Thorgeirsson UP, Snyderwine EG, et al. Carcinogenicity of 2-amino-3-methylimidazo[4,5-*f*]quinoline in nonhuman primates: induction of tumors in three macaques. *Jpn J Cancer Res.* 1990;81(1):10–14.
58. Kato T, Ohgaki H, Hasegawa H, et al. Carcinogenicity in rats of a mutagenic compound, 2-amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline. *Carcinogenesis.* 1988;9(1):71–73.
59. Ohgaki H, Hasegawa H, Kato T, et al. Carcinogenicities in mice and rats of IQ, MeIQ, and MeIQx. *Princess Takamatsu Symp*. 1985;16:97–105.
60. Shirai T, Cui L, Takahashi S, et al. Carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in the rat prostate and induction of invasive carcinomas by subsequent treatment with testosterone propionate. *Cancer Lett.* 1999;143(2):217–221.
61. Norrish AE, Ferguson LR, Knize MG, et al. Heterocyclic amine content of cooked meat and risk of prostate cancer. *J Natl Cancer Inst*. 1999;91(23):2038–2044.
62. Culp SJ, Gaylor DW, Sheldon WG, et al. A comparison of the tumors induced by coal tar and benzo[*a*]pyrene in a 2-year bioassay. *Carcinogenesis*. 1998;19(1):117–124.