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Meat consumption, Cooking Practices, Meat Mutagens and Risk of Prostate Cancer

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Abstract

Consumption of red meat, particularly well done meat, has been associated with increased prostate cancer risk. High temperature cooking methods such as grilling and barbequeing may produce heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) which are known carcinogens. We assessed the association with meat consumption and estimated HCA and PAH exposure in a population-based case-control study of prostate cancer. Newly diagnosed cases aged 40–79 years (531 advanced cases, 195 localized cases) and 527 controls were asked about dietary intake, including usual meat cooking methods and doneness levels. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate logistic regression. For advanced prostate cancer, but not localized disease, increased risks were associated with higher consumption of hamburgers (OR=1.79, CI=1.10–2.92), processed meat (OR=1.57, CI=1.04, 2.36), grilled red meat (OR=1.63, CI=0.99–2.68), and well done red meat (OR=1.52, CI=0.93–2.46), and intermediate intake of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) (quartile 2 vs. 1: OR=1.41, CI=0.98–2.01; quartile 3 vs. 1: OR=1.42, CI=0.98–2.04), but not for higher intake. White meat consumption was not associated with prostate cancer. These findings provide further evidence that consumption of processed meat and red meat cooked at high temperature is associated with increased risk of advanced, but not localized prostate cancer.

Keywords

Cooking methods; heterocyclic amines; processed meat; prostate cancer; red meat

INTRODUCTION

High consumption of meat, particularly red meat (1–8) and processed meat (8–13), has been associated with increased prostate cancer risk, although the epidemiologic evidence is not consistent (14). It has been hypothesized that the increased risks may be due to the high fat content of red meat and processed meat, formation of N-nitroso compounds from meat curing or endogenous formation, or exposure to heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) formed when cooking meat at high temperature.

The relation between fat intake and prostate cancer risk has been widely investigated and many, but not all studies reported positive associations (14–16). An increased risk associated with high red meat intake has been found in the absence of an association with fat intake (4), therefore suggesting that the high fat content of red meat does not fully explain the association between red meat consumption and prostate cancer risk. At least three carcinogens are known to accumulate in cooked and/or processed meats. N-nitroso compounds can be formed in meats preserved with nitrates or nitrites (e.g., cured meats or sausages) (17), and can also be endogenously produced by the reaction of amines and amides from red meat with nitrosating agents in the intestines (18). Depending on type of meat, cooking method, and preferred level of browning or doneness, red and white meats cooked at high temperature (i.e., grilling, barbequeing, broiling, pan-frying) may have high levels of meat mutagens, including HCAs, such as 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), 2-amino-3,8-dimethylimidazo-[4,5-*b*]quinoxaline (MeIQx), and 2-amino-3,4,8-trimethylimidazo-[4,5-*f*]quinoxaline (DiMeIQx), or PAHs, such as benzo(*a*)pyrene (BaP) (9, 19–21). It has been shown that the prostate gland can metabolize these chemicals into activated carcinogens (22) which in turn can induce DNA damage, thereby contributing to prostate cancer carcinogenesis. Exposure of laboratory rats to PhIP, one of the most abundant HCAs accounting for about 70% of dietary intake of HCAs in the U.S. (23), has been shown to induce mutations (24) and tumors (24, 25) in prostate tissue, even after short-term exposure. Furthermore, it has been proposed that in the prostate, PhIP might contribute to carcinogenesis by inducing mutations and inflammation, thus acting both as a tumor initiator and promoter (24).

Exposure to meat mutagens has been linked to increased risks of several cancers (9), though for prostate cancer the epidemiologic evidence is limited (2, 3, 5, 8, 26, 27). Increased risk has been associated with high consumption of grilled or barbecued meat (8) and well done meat (2, 3, 5, 26), with a possibly stronger association for advanced prostate cancer (3, 8). Studies that estimated HCA intake from cooked meat (2, 3, 5, 8, 27) found elevated risks associated with high PhIP intake (2). Consumption of grilled red meat has been associated with higher levels of PhIP-DNA adducts in prostate tumor cells of men who underwent radical prostatectomy (28), and PhIP intake from cooked meat has been associated with elevated PSA levels in African-American men (29).

Since few risk factors for prostate cancer have been identified, the investigation of potentially modifiable lifestyle factors such as diet or cooking methods is relevant for prevention efforts. We examined associations with the consumption of different types of meat, taking into account cooking methods and doneness levels, and estimated levels of meat mutagens in a population-based case-control study that included a large proportion of advanced prostate cancer cases.

MATERIALS AND METHODS

Study Design and Population

Study participants are from a population-based case-control study of prostate cancer described elsewhere (30). Non-Hispanic White and African-American men newly diagnosed with localized or advanced prostate cancer (cases) were identified through the cancer registry of the Greater San Francisco Bay Area. Men without a history of prostate cancer (controls) were identified through random-digit dialing (RDD) and random selections from the rosters of beneficiaries of the Health Care Financing Administration (HCFA). Controls were frequency matched to advanced cases on race/ethnicity and 5-year age group.

Eligible cases aged 40–79 years were non-Hispanic White and African-American men with a first primary localized prostate cancer diagnosed between October 1, 1997 and September

30, 1998; non-Hispanic White men with a first primary advanced prostate cancer diagnosed between July 1, 1997 and February 29, 2000; and African-American men with a first primary advanced prostate cancer diagnosed between July 1, 1997 and December 31, 2000. Localized prostate cancer was defined as a tumor limited to the prostatic capsule; advanced prostate cancer was defined as a tumor invading and extending beyond the prostatic capsule and/or extending into adjacent tissue or involving regional lymph nodes or distant metastatic sites (SEER 1995 clinical and pathologic extent of disease codes 41–85). The study included all African-American and non-Hispanic White cases with advanced prostate cancer, and random samples of localized cases (60% of African Americans, 15% of non-Hispanic Whites). *Localized cases:* Of 319 randomly selected cases, 274 met the eligibility criteria (alive, no physician refusal, residing in the San Francisco Bay area, valid phone number, English speaking), and of these 208 (76%) completed the interview, including 135 non-Hispanic Whites, and 73 African Americans. *Advanced cases:* Of 1,015 advanced prostate cancer cases ascertained, 788 met the above eligibility criteria, 568 (72%) completed the interview, including 450 non-Hispanic Whites and 118 African Americans. Of 1,081 controls (717 RDD controls and 364 HCFA controls) selected into the study, 868 met the eligibility criteria and 545 (63%) completed the interview, including 455 non-Hispanic Whites and 90 African Americans.

The study was approved by the Institutional Review Board of the Cancer Prevention Institute of California. Written informed consent was obtained for all study participants.

Data Collection

Trained professional interviewers conducted home visits to administer a structured questionnaire about demographic background, medical history and various lifestyle factors, and to measure anthropometry. Usual dietary intake (during the calendar year prior to diagnosis for cases and prior to selection into the study for controls) was assessed using a 74-item food frequency questionnaire (FFQ) that was adapted from Block's Health History and Habits Questionnaire. Questions on cooking methods and degree of doneness and browning were adapted from a commonly used meat cooking module developed by Sinha et al. (31). For six meat items, including hamburgers, steak, pork chops, poultry, bacon, and sausages, information was obtained on usual method of meat preparation (e.g., fried, oven-broiled, grilled or barbecued). Level of doneness and browning was assessed using a series of color photographs showing increasing degrees of doneness and browning, with four levels of doneness and browning (e.g., rare, just done, well done, very well done) for hamburger and steak, and three levels (e.g., medium done, well done, very well done) for the other meat items.

Exposure Variables

We examined prostate cancer risk in relation to several dietary exposure variables, including fat intake (total fat, saturated fat, total fat from red meat, total fat from other food items), and consumption of total meat (beef, pork, poultry, liver, processed meat) and specific types of meat, such as red meat (all types of beef and pork), hamburgers, steak, white meat (chicken or turkey), and processed meat (sausages made from red or white meat, bacon, and cold cuts). Except for burritos, tacos, tostados, or enchiladas made with beef or chicken, the meat portion in other mixed meat dishes was assessed separately. Prostate cancer risk was also assessed in relation to cooking methods (grilled or barbecued, broiled, pan-fried, baked or roasted), and level of doneness and browning (well done, very well done; assessed for grilled, barbecued, broiled or pan-fried meat only) for selected types of red meat (steak, hamburgers, pork chops), white meat (chicken), and processed meats (bacon, hotdogs, sausages). Based on frequency and serving size of consumption of specific meats (hamburgers, steak, pork chops, poultry, bacon, and sausages), cooking method, and level of

doneness and browning, exposure to three HCAs (PhIP, MeIQ_x, and DiMeIQ_x), BaP as a marker of total PAH exposure, and meat-derived mutagenicity (measured as revertant colonies per day) was estimated using the CHARRED database (<http://www.charred.cancer.gov>) which was developed based on measurements in meat samples prepared using different cooking methods and temperatures (31).

Statistical Analysis

Unconditional logistic regression modeling was used to calculate odds ratios (OR) and 95% confidence intervals (CI) as an estimate of the relative risk associated with the various exposure measures. The main exposures variables (meat consumption, meat mutagens) were categorized according to the quartile distribution among controls. To adjust for energy intake, we used the multivariate nutrient density method (32). Meat variables, as well as other dietary variables were expressed as grams per 1,000 kcal, and total energy intake was adjusted for in all analyses. In multivariate model 1, analyses were adjusted for age (continuous), race (non-Hispanic white, African American), socioeconomic status (SES, 1–3, 4, 5), family history of prostate cancer in first-degree relatives (yes, no), and body mass index (BMI <25, 25.0–29.9, ≥30). In multivariate model 2, we additionally adjusted for three dietary variables: intake of total fat (gm/1000 kcal, continuous), fruits (gm/1000 kcal, continuous), and vegetables (gm/1000 kcal, continuous). Adjustment for smoking, a source of PAH and HCA exposure, did not change the OR estimates, and was therefore not retained in the final multivariate model. A measure of SES was derived using 2000 US census data at the census block group level. A 5-level SES variable was assigned to each address at diagnosis (cases) or selection into the study (controls), based on quintiles of education, income, and occupation (33). BMI as a measure of overall adiposity was calculated as weight (kg) / height² (m) and was based on height measured at interview and self-reported weight in the reference year, or self-reported adult height when measured height was not available (9.2% of cases, 7.4% of controls) and measured weight when self-reported weight in the reference year was not available (1 case, 1 control). Given epidemiologic evidence that risk factors may differ for localized and advanced prostate cancer (34), we performed separate analyses for localized and advanced cases. After excluding 68 (5%) individuals with dietary data considered unreliable (i.e., daily energy intake <600 kcal or > 5000 kcal), the analyses were based on 195 localized cases, 531 advanced cases, and 527 controls.

RESULTS

Characteristics of cases and controls are shown in Table 1. Advanced cases were diagnosed at a younger age than localized cases. Compared to controls, both localized and advanced prostate cancer cases were more likely to have a family history of prostate cancer and to be of higher SES, and less likely to be obese (BMI ≥30). Localized and advanced cases and controls were similar with regard to education, history of benign prostatic hyperplasia, height, alcohol consumption, tobacco use, and consumption of fruits and vegetables. Average daily caloric intake was similar for localized cases (2,496 kcal/d), advanced cases (2,569 kcal/d), and controls (2,481 kcal/d).

High total fat intake was associated with increased risk of advanced prostate cancer, with an odds ratio (OR) of 1.75 (95% CI=1.20–2.54, $p_{\text{trend}}=0.01$) for the highest vs. lowest quartile of intake (Table 2). A similar significant trend was observed for saturated fat intake. Further adjustment for total meat or red meat intake changed the OR estimates for total fat and saturated fat only minimally (data not shown). The association with fat intake was limited to fat from foods other than meat (highest vs. lowest quartile of intake: OR=1.58, 95% CI=1.09–2.29, $p_{\text{trend}}=0.02$). Risk of localized prostate cancer was not associated with total or saturated fat intake.

For both advanced and localized prostate cancer, total meat (red meat, white meat, and processed meat) and white meat (chicken and turkey) consumption were not associated with risk (Table 2). There were no associations of red meat and processed meat consumption with localized prostate cancer risk; positive associations were found for advanced prostate cancer only. In multivariate models without adjustment for dietary variables (fat, fruit, and vegetable consumption), risk of advanced prostate cancer increased with increasing consumption of total red meat, hamburgers, steak, and processed meat, with ORs ranging from 1.61 to 1.96 for high consumption (tertile 3 vs. no consumption). Significantly increased risks of advanced prostate cancer were also found for high consumption of bacon, sausage, and homemade gravy, with ORs ranging from 1.39 to 1.63. Additional adjustment for dietary variables attenuated these associations somewhat; significant trends and/or elevated ORs for high consumption remained for red meat (OR=1.53, 95% CI=0.93–2.49, $p_{\text{trend}}=0.02$), hamburger (OR=1.79, 95% CI=1.10–2.92, $p_{\text{trend}}=0.005$), steak (OR=1.45 (95% CI=0.89–2.35, $p_{\text{trend}}=0.05$), and processed meat (OR=1.57, 95% CI=1.04–2.36, $p_{\text{trend}}=0.05$).

For red meat, risk varied by cooking method and doneness level (Table 3). In multivariate models without adjustment for dietary variables, risk of advanced prostate cancer was highest for men with a high consumption (above the median vs. no red meat consumption) of grilled or barbecued red meat (OR=1.81, 95% CI=1.11–2.93), and slightly attenuated after adjustment for dietary variables (OR=1.63, 95% CI=0.99–2.68). Risk did not vary by other cooking methods such as broiling, pan-frying, oven-baking or roasting. Risk of advanced prostate cancer was also elevated for high consumption of well or very well done red meat (OR=1.68, 95% CI=1.05–2.68), though slightly lower after adjustment for dietary variables (OR=1.52, 95% CI=0.93–2.46). For specific red meats, such as hamburger and steak, risk did not vary by doneness level. For processed meat, there was no evidence of higher risks being associated with high consumption of broiled, pan-fried and well or very well done meat (data not shown). Consumption of white meat was not associated with advanced or localized prostate cancer, and risk did not vary by cooking methods (data not shown).

Compared to controls, both advanced and localized cases had higher average exposure to MeIQx and mutagenic activity, and localized cases had lower BaP exposure, although the differences were not statistically significant (Table 4). Compared to non-Hispanic White controls, African American controls had significantly higher intakes of MeIQx and DiMeIQx and nearly two-fold higher exposure to mutagenic activity, whereas their intake of BaP was significantly lower. For both localized and advanced prostate cancer, there was no evidence of association with estimated MeIQx, DiMeIQx, or BaP exposure, or mutagenic activity (Table 5). For PhIP, significantly increased risks of advanced disease were associated with intermediate intake (quartile 2 vs. 1: OR=1.48, 95% CI=1.04–2.11; quartile 3 vs. 1: OR=1.53, 95% CI=1.08–2.19), but not with high intake (quartile 4 vs. 1). Additional adjustment for dietary variables slightly attenuated the associations with intermediate intake (OR=1.41, 95% CI=0.98–2.01 and OR=1.42, 95% CI=0.98–2.04, respectively).

DISCUSSION

In this population-based case-control study, advanced prostate cancer, but not localized disease, was associated with higher consumption of red meat and processed meat. Although increased risk was associated with grilled or well done red meat, we found no consistent associations with estimated HCA and BaP exposure. Total meat and white meat consumption were not associated with either type of prostate cancer.

Our findings for red and processed meat are consistent with other studies that reported positive associations with red (1, 35–37) and processed (1, 2, 8, 13, 36) meat for advanced or metastatic disease only, or stronger associations with red (7, 8) and processed (8, 10–12)

meat for advanced disease than total prostate cancer. The epidemiologic evidence, however, is mixed (9, 14), with a number of studies not finding any association with consumption of red (2, 3, 10, 12, 13, 36, 38, 39) or processed (3, 5, 39–42) meat. However, not all studies presented results separately for advanced disease (9, 14). Although in the present study fat intake was associated with increased risk of advanced prostate cancer, there was no association with fat from meat, suggesting that the association between diets high in red meat and cancer is not driven by fat content.

We and others assessed cooking methods and meat doneness level by questionnaire as surrogate measures of potential HCA or PAH exposure (43, 44). Previous studies have reported increased risks associated with higher consumption of grilled or barbecued total meat (8), or well done total meat (2, 3, 5, 26), with total meat usually including red meat and processed meats and in some instances also white meat. In our study we found increased risks for high consumption of grilled or barbecued red meat and well done red meat, but no associations for processed or white meat, regardless of cooking method or doneness level. In agreement with our findings, other studies reported associations with consumption of very well done beef steak (5) and well done red and processed meat (26). In contrast, some studies found little variation in risk by meat cooking methods (2, 3) or doneness level (45).

Our findings for grilled and well done red meat don't appear to be in agreement with those for estimated exposure to specific HCAs and BaP. We found no associations with HCA exposure, except for a possible association of advanced disease with PhIP exposure, although increased risks were limited to exposure quartiles 2 and 3. Similarly, other studies have produced inconclusive results (2, 3, 5, 8, 27). PhIP exposure has been associated with incident, but not advanced prostate cancer in one study (2), whereas another study found no association with PhIP intake, but suggestive associations of incident prostate cancer with MeIQx and DiMeIQx intake (3), two mutagens that are much less abundant than PhIP, but more potent (46). In both of these studies, the increases in risk were small (less than 30%). Other studies did not find any significant associations with total or individual HCAs (5, 8, 27), with the exception of an association of borderline significance with 2-amino-1,6-dimethylfuro[3,2-*e*]imidazo[4,5-*b*]pyridine (IFP) (5).

Results are sparse and inconsistent for BaP, which is formed when fat from meats being grilled or smoked drips onto the flames (47). We and others (2, 3) found no evidence of increased risk with BaP, whereas one study reported a small increased risk (8). Whereas BaP is the most abundant PAH formed in meats cooked over flames, we cannot exclude the possibility that other PAHs formed during this process may underlie the observed association between grilled red meat and prostate cancer risk.

The finding in several studies (1, 8), including ours, of associations with fat intake and consumption of red meat, grilled red meat, or well done red meat for advanced but not localized prostate cancer or stronger associations for advanced disease than total prostate cancer suggests that intake of fat, red meat, and HCAs presumed to be present in grilled and well-done red meat, may affect disease progression. In rodents, PhIP has been shown to induce inflammation in areas of the prostate where tumors develop, thus suggesting a potential role for meat mutagens as both tumor initiators and promoters (24, 48). If this were true, it would be plausible that diets high in red meat cooked at high temperatures might play a relevant role in contributing to inflammation in the prostate and thus contribute to progression of existing tumors that otherwise might remain localized.

The reasons for the discrepant findings on the relation with meat consumption, cooking methods, meat doneness level, and estimated exposure to meat mutagens are not obvious. Several studies (2, 3, 8), including ours, used the same validated method (49) to assess meat

consumption and estimate HCA and BaP intake, except for our use of color photographs showing several levels of doneness and browning which may have reduced reporting error of meat doneness level. The timing of exposure assessment differed between these studies; the cohort studies (2, 3, 8) assessed usual dietary intake at baseline without assessment of dietary changes over the follow-up period, whereas the present case-control study assessed recent dietary intake. If HCAs play a role in disease progression, then recent dietary intake may be more relevant than diet many years before diagnosis (1). Thus, cohort studies with longer follow-up times may not be able to detect strong associations with meat intake patterns.

Several limitations need to be considered when interpreting the present results. Although the questionnaire-based method to assess meat cooking methods and doneness level and the use of the CHARRED database to estimate HCA and BaP intake has been validated (49) and used in other studies that found associations with several types of cancer (50–52), we cannot exclude the possibility of measurement error in assessing dietary intake and cooking practices using a food frequency questionnaire or in estimating HCA and BaP exposure. When we collected the interview data, there was no widespread knowledge that consumption of certain types of meat or certain cooking methods may be associated with prostate cancer risk. Furthermore, the associations we found were specific for advanced, but not localized disease. These observations minimize the possibility that the associations found in the present study are solely due to differential dietary recall by cases and controls. Nevertheless, we cannot exclude the possibility of non-differential inaccuracies in dietary recall leading to exposure misclassification, which may have biased the odds ratio estimates towards the null. It has also been shown that HCA and BaP formation is affected not only by type of meat, cooking temperature and duration, but also by other factors, such as marinating of meat (53), which we did not assess in the present study. It is possible that the lack of information on marinating practices may have contributed to exposure misclassification, potentially biasing the results towards the null. Although this study over-sampled advanced prostate cancer cases, the sample size for specific exposure categories (e.g., high intake of grilled red meat) was limited. It is therefore possible that we missed associations present in certain subgroups only. There is some evidence that associations of meat-derived HCA exposure with prostate cancer risk may be modified by variants in genes involved in HCA metabolism (54), although another study found no support for this effect modification (45). Studies with large sample sizes will be needed to address this possibility.

Compared to non-Hispanic White control men, African Americans had a higher intake of well done meat (33.4 g/d vs. 18.4 g/d, $p=0.001$), pan-fried meat (22.3 g/d vs. 13.3 g/d, $p=0.02$), and broiled meat (15.4 g/d vs. 9.6 g/d, $p=0.06$). Similarly, other studies reported higher consumption of well done (45, 50) or pan-fried (23) meat and higher intake of PhIP (23, 29) in African Americans. Future studies that include a larger number of African American men will increase the range of exposure and thereby the likelihood of detecting associations with high exposure to specific meat mutagens, if such associations truly exist. The number of African Americans included in the present study was too small for separate analyses.

In conclusion, our findings from a population-based study add to the epidemiologic evidence that higher consumption of red meat and processed meat may increase the risk of advanced prostate cancer. Weekly consumption of three or more servings of red meat, 1.5 or more servings of processed meat, 1 or more servings of grilled red meat, and 1 or more servings of well done red meat were each associated with an approximately 50% increased risk of developing advanced prostate cancer, but not localized disease. Further investigation is warranted of this potentially modifiable lifestyle factor and the underlying mechanisms by which red meat cooked at high temperature increases risk.

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Abbreviations

CI	confidence interval
OR	odds ratio
HCA	heterocycline amine
PAH	polycyclic aromatic hydrocarbon
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5- <i>b</i>]pyridine
MeIQx	2-amino-3,8-dimethylimidazo-[4,5- <i>b</i>]quinoxaline
DiMeIQx	2-amino-3,4,8-trimethylimidazo-[4,5- <i>f</i>]quinoxaline
BaP	benzo(<i>a</i>)pyrene

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TABLE 1
 Characteristics of cases and controls: The San Francisco Bay Area Prostate Cancer Study

	Controls N=527		Localized cases N=195		Advanced cases N=531	
	N	%	N	%	N	%
Age						
40-49	14	3	7	4	19	4
50-59	138	26	39	20	152	29
60-69	236	45	65	33	223	42
70-79	139	26	84	43	137	26
Race						
Non-Hispanic White	448	85	134	69	433	82
African-American	79	15	61	31	98	18
Education						
High school graduate or less	114	22	61	31	135	25
Some college/vocational school	159	30	50	26	139	26
College graduate	254	48	84	43	257	48
Socio-economic status						
1-3 (low)	128	24	54	28	112	21
4	154	29	34	17	121	23
5 (high)	245	47	107	55	298	56
Family history of prostate cancer						
No	464	88	155	80	428	81
Yes	63	12	40	20	103	19
History of benign prostatic hyperplasia (BPH)						
No	402	78	149	76	398	75
Yes	117	23	38	20	112	21
Don't know	8		8	4	21	4
Height (cm)						
<170	131	25	38	19	119	22
170-174.9	131	25	54	28	140	26
175-179.9	132	25	41	21	139	26

	Controls N=527		Localized cases N=195		Advanced cases N=531	
	N	%	N	%	N	%
180	133	25	62	32	133	25
Body mass index (BMI)						
<25	134	25	60	31	152	29
25.0–29.9	245	47	101	52	259	49
30	148	28	34	17	120	22
Alcohol consumption (g/day)						
0	155	29	60	31	157	30
0.1–4.9	95	18	29	15	96	18
5.0–9.9	55	10	19	9	50	9
10–19.9	83	16	25	13	79	15
20	139	26	62	32	149	28
Tobacco use						
Never	150	28	49	25	146	28
Former	289	55	112	57	277	52
Current	88	17	34	17	108	20
Caloric intake (kcal/day)						
<1800	131	25	48	25	125	23
1800–2399	132	25	48	25	122	23
2400–3060	132	25	44	23	132	25
3061	132	25	55	28	152	29
Fruit consumption (g/day)						
<6.5	131	25%	50	26%	118	22%
6.5–20.6	132	25%	47	24%	139	26%
20.7–78.8	133	25%	59	30%	153	29%
78.8	131	25%	39	20%	121	23%
Vegetable consumption (g/day)						
<29.3	132	25%	40	21%	133	25%
29.3–70.2	132	25%	40	21%	106	20%
70.3–141.0	131	25%	64	33%	162	31%
141.1	132	25%	51	26%	130	24%

TABLE 2
Associations between fat intake, meat consumption, and prostate 0cancer risk by cancer subtype

	Controls N=527		Localized cases N=195		Advanced cases N=531		
	n	OR, 95% CI ¹ Model 1	n	OR, 95% CI ¹ Model 2	n	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2
Total fat (g/1000 kcal/day)							
Quartile 1	132	51	1.0	1.0	100	1.0	1.0
Quartile 2	131	58	1.22 0.76–1.95	1.13 0.70–1.83	138	1.47 1.03–2.11	1.48 1.03–2.13
Quartile 3	132	47	0.94 0.57–1.55	0.92 0.55–1.53	135	1.43 0.99–2.06	1.47 1.02–2.14
Quartile 4	132	39	0.76 0.45–1.29	0.74 0.43–1.26	158	1.69 1.17–2.44	1.75 1.20–2.54
			P _{trend} =0.21	P _{trend} =0.19		P _{trend} =0.01	P _{trend} =0.01
Saturated fat intake (g/1000 kcal/day)							
Quartile 1	132	59	1.0	1.0	104	1.0	1.0
Quartile 2	131	47	0.81 0.50–1.31	0.77 0.47–1.24	134	1.37 0.95–1.96	1.39 0.96–1.99
Quartile 3	132	57	1.00 0.62–1.59	0.98 0.61–1.59	137	1.41 0.98–2.03	1.45 1.00–2.10
Quartile 4	132	32	0.56 0.33–0.95	0.55 0.32–0.95	156	1.61 1.12–2.32	1.66 1.15–2.41
			P _{trend} =0.09	P _{trend} =0.09		P _{trend} =0.01	P _{trend} =0.01
Total fat from meat (g/1000 kcal/day)							
Quartile 1	132	50	1.0	1.0	124	1.0	1.0
Quartile 2	131	47	1.01 0.62–1.65	1.09 0.66–1.80	143	1.24 0.87–1.75	1.25 0.88–1.79
Quartile 3	133	53	1.05 0.65–1.70	1.13 0.69–1.84	131	1.12 0.79–1.60	1.14 0.80–1.63
Quartile 4	131	45	0.94 0.57–1.54	0.97 0.58–1.62	133	1.20 0.84–1.72	1.23 0.85–1.77
			P _{trend} =0.86	P _{trend} =0.96		P _{trend} =0.43	P _{trend} =0.38
Total fat from foods other than meat (g/1000 kcal/day)							
Quartile 1	132	55	1.0	1.0	108	1.0	1.0
Quartile 2	132	51	1.04 0.64–1.67	0.96 0.59–1.55	133	1.31 0.91–1.87	1.31 0.92–1.88
Quartile 3	132	45	0.83 0.50–1.36	0.79 0.48–1.33	132	1.27 0.89–1.83	1.31 0.90–1.88
Quartile 4	131	44	0.78 0.47–1.31	0.74 0.44–1.23	158	1.54 1.07–2.22	1.58 1.09–2.29
			P _{trend} =0.26	P _{trend} =0.22		P _{trend} =0.03	P _{trend} =0.02
Total meat (g/1000 kcal/day)							
Quartile 1	131	48	1.0	1.0	119	1.0	1.0

	Controls N=527		Localized cases N=195			Advanced cases N=531		
	n	n	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2	n	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2	n
Quartile 2	133	54	1.20 0.74–1.94	1.30 0.80–2.13	161	1.39 0.98–1.96	1.36 0.96–1.93	
Quartile 3	131	64	1.53 0.95–2.47	1.71 1.04–2.80	130	1.12 0.79–1.61	1.06 0.73–1.53	
Quartile 4	132	29	0.59 0.33–1.03	0.66 0.37–1.18	121	1.06 0.73–1.53	0.94 0.64–1.38	
			P _{trend} = 0.27	P _{trend} = 0.50		P _{trend} = 0.90	P _{trend} = 0.44	
White meat (g/1000 kcal/day) ³								
Quartile 1	132	41	1.0	1.0	131	1.0	1.0	
Quartile 2	132	63	1.62 0.99–2.65	1.57 0.96–2.58	159	1.20 0.85–1.69	1.20 0.85–1.69	
Quartile 3	132	47	1.15 0.69–1.92	1.15 0.70–1.93	134	0.93 0.65–1.31	0.95 0.67–1.35	
Quartile 4	131	44	1.18 0.70–1.99	1.15 0.68–1.95	107	0.80 0.55–1.15	0.82 0.56–1.18	
			P _{trend} = 0.95	P _{trend} = 0.98		P _{trend} = 0.11	P _{trend} = 0.15	
Red meat (g/1000 kcal/day) ⁴								
No red meat consumed	58	30	1.0	1.0	42	1.0	1.0	
Tertile 1	156	49	0.65 0.36–1.16	0.71 0.39–1.27	128	1.15 0.71–1.84	1.10 0.68–1.79	
Tertile 2	157	66	0.98 0.56–1.72	1.12 0.63–2.01	190	1.77 1.11–2.81	1.65 1.02–2.65	
Tertile 3	156	50	0.76 0.42–1.35	0.91 0.49–1.69	171	1.69 1.06–2.69	1.53 0.93–2.49	
			P _{trend} = 0.91	P _{trend} = 0.62		P _{trend} = 0.003	P _{trend} = 0.02	
Hamburger (g/1000 kcal/day)								
No red meat consumed	58	30	1.0	1.0	42	1.0	1.0	
Tertile 1	157	47	0.58 0.32–1.05	0.65 0.35–1.18	144	1.27 0.79–2.04	1.21 0.75–1.95	
Tertile 2	156	56	0.80 0.45–1.40	0.93 0.52–1.68	150	1.41 0.88–2.25	1.33 0.82–2.14	
Tertile 3	156	62	1.03 0.59–1.82	1.28 0.70–2.34	195	1.96 1.23–3.12	1.79 1.10–2.92	
			P _{trend} = 0.24	P _{trend} = 0.06		P _{trend} = 0.001	P _{trend} = 0.005	
			P _{trend} = 0.02 ⁷	P _{trend} = 0.01 ⁷		P _{trend} = 0.01 ⁷	P _{trend} = 0.02 ⁷	
Steak (g/1000 kcal/day)								
No red meat consumed	58	30	1.0	1.0	42	1.0	1.0	
Tertile 1	157	53	0.70 0.40–1.25	0.76 0.42–1.38	134	1.20 0.74–1.92	1.12 0.69–1.82	
Tertile 2	155	70	1.05b 0.61–1.83	1.19 0.67–2.12	189	1.78 1.12–2.83	1.64 1.02–2.65	
Tertile 3	157	42	0.62 0.34–1.12	0.70 0.38–1.30	166	1.61 1.01–2.57	1.45 0.89–2.35	

	Controls N=527		Localized cases N=195		Advanced cases N=531	
	n	OR, 95% CI ¹ Model 1	n	OR, 95% CI ¹ Model 2	n	OR, 95% CI ¹ Model 2
Processed Meat (g/1000 kcal/day) ⁵						
No processed meat consumed	112		46	1.0	88	1.0
Tertile 1	139		46	0.97 0.59–1.62	135	1.28 0.88–1.87
Tertile 2	138		44	0.81 0.48–1.36	129	1.22 0.83–1.79
Tertile 3	139		59	0.99 0.60–1.64	179	1.74 1.19–2.53
Bacon (g/1000 kcal/day)						
No processed meat consumed	112		46	1.0	88	1.0
No bacon	141		64	1.23 0.76–1.99	151	1.43 0.99–2.08
Below median	137		29	0.62 0.35–1.08	124	1.18 0.80–1.73
Above median	137		56	0.88 0.53–1.46	168	1.63 1.11–2.40
Sausage (g/1000 kcal/day)						
No processed meat consumed	112		46	1.0	88	1.0
No sausage consumed	124		37	0.88 0.52–1.49	134	1.44 0.98–2.11
Below median	146		53	1.02 0.62–1.69	139	1.24 0.84–1.84
Above median	145		59	0.88 0.53–1.46	170	1.52 1.04–2.22
Homemade gravy (g/1000 kcal/day) ⁶						
No gravy consumed	358		130	1.0	337	1.0
Below median	85		36	1.20 0.74–1.54	86	1.09 0.76–1.55
Above median	84		29	0.87 0.53–1.43	108	1.39 1.00–1.94

¹Odds ratio (OR) and 95% confidence interval (CI). Model 1 adjusted for age, race, SES, family history of prostate cancer, BMI, and caloric intake.

²Model 2 also adjusted for intake of fat, fruits, and vegetables.

³White meat includes chicken and turkey.

⁴Red meat includes beef and pork.

⁵Processed meat includes sausage, bacon, hot dogs, lunch meats (e.g., cold cuts, ham, bologna).

⁶Made from meat or chicken drippings.

⁷Trend among consumers of red meat only.

⁸Trend among consumers of processed meat only.

TABLE 3

Associations between red meat intake, cooking method, and level of doneness and prostate cancer risk by cancer subtype

	Controls N=527		Localized cases N=195		Advanced cases N=531	
	n	n	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2
Grilled or barbecued red meat (g/1000 kcal/day)						
No red meat consumed	58	30	1.0	1.0	1.0	1.0
No grilled red meat consumed	238	92	0.85 0.50–1.46	0.95 0.55–1.66	1.49 0.95–2.33	1.36 0.86–2.16
Below median	116	32	0.60 0.32–1.12	0.65 0.35–1.24	1.37 0.84–2.23	1.26 0.76–2.07
Above median	115	41	0.87 0.48–1.59	1.02 0.54–1.90	1.81 1.11–2.93	1.63 0.99–2.68
			P _{trend} =0.49 ⁴	P _{trend} =0.76 ⁴	P _{trend} =0.05 ⁴	P _{trend} =0.12 ⁴
			P _{trend} =0.85 ⁵	P _{trend} =0.94 ⁵	P _{trend} =0.28 ⁵	P _{trend} =0.33 ⁵
Broiled red meat (g/1000 kcal/day)						
No red meat consumed	58	30	1.0	1.0	1.0	1.0
No broiled red meat consumed	298	98	0.75 0.44–1.26	0.83 0.48–1.44	1.51 0.97–2.35	1.38 0.88–2.16
Below median	86	34	0.88 0.47–1.65	1.01 0.53–1.94	1.54 0.92 2.56	1.42 0.84–2.39
Above median	85	33	0.88 0.47–1.64	0.95 0.50–1.83	1.58 0.95–2.62	1.41 0.83–2.37
			P _{trend} =0.93 ⁴	P _{trend} =0.76 ⁴	P _{trend} =0.22 ⁴	P _{trend} =0.38 ⁴
			P _{trend} =0.42 ⁵	P _{trend} =0.46 ⁵	P _{trend} =0.83 ⁵	P _{trend} =0.91 ⁵
Pan-fried red meat (g/1000 kcal/day)						
No red meat consumed	58	30	1.0	1.0	1.0	1.0
No pan-fried red meat consumed	229	86	0.85 0.45–1.44	0.91 0.53–1.58	1.43 0.91–2.25	1.32 0.83–2.09
Below median	120	43	0.79 0.43–1.44	0.91 0.49–1.71	1.65 1.02–2.68	1.52 0.93–2.49
Above median	120	36	0.69 0.38–1.27	0.80 0.42–1.51	1.60 0.99–2.59	1.42 0.86–2.34
			P _{trend} =0.23 ⁴	P _{trend} =0.50 ⁴	P _{trend} =0.09 ⁴	P _{trend} =0.21 ⁴
			P _{trend} =0.40 ⁵	P _{trend} =0.57 ⁵	P _{trend} =0.42 ⁵	P _{trend} =0.58 ⁵
Oven baked or roasted red meat (g/1000 kcal/day)						
No red meat consumed	58	30	1.0	1.0	1.0	1.0
No oven cooked red meat consumed	422	153	0.82 0.49–1.36	0.92 0.54–1.57	1.54 1.00–2.36	1.40 0.90–2.18
Below median	23	6	0.56 0.19–1.66	0.64 0.21–1.92	1.56 0.75–3.22	1.38 0.66–2.90

	Controls N=527		Localized cases N=195		Advanced cases N=531		
	n	OR, 95% CI ¹ Model 1	n	OR, 95% CI ² Model 2	n	OR, 95% CI ¹ Model 1	OR, 95% CI ² Model 2
Above median	24	6	0.53 0.19–1.51 P _{trend} =0.16 ⁴	0.55 0.19–1.58 P _{trend} =0.23 ⁴	22	1.38 0.68–2.83 P _{trend} =0.36 ⁴	1.25 0.60–2.58 P _{trend} =0.57 ⁴
			P _{trend} =0.27 ⁵	P _{trend} =0.23 ⁵		P _{trend} =0.80 ⁵	P _{trend} =0.76 ⁵
Well or very well done red meat ³ (g/1000 kcal)							
No red meat consumed	58	30	1.0	1.0	42	1.0	1.0
No well done/very well done red meat	168	60	0.88 0.50–1.56	0.95 0.53–1.70	170	1.48 0.93–2.36	1.35 0.84–2.18
Below median	150	43	0.62 0.34–1.13	0.70 0.38–1.30	148	1.41 0.88–2.27	1.31 0.81–2.13
Above median	151	62	0.84 0.48–1.48 P _{trend} =0.44 ⁴	0.98 0.54–1.75 P _{trend} =0.82 ⁴	171	1.68 1.05–2.68 P _{trend} =0.08 ⁴	1.52 0.93–2.46 P _{trend} =0.17 ⁴
			P _{trend} =0.83 ⁵	P _{trend} =0.91 ⁵		P _{trend} =0.44 ⁵	P _{trend} =0.51 ⁵
Doneness of hamburgers among consumers of hamburgers							
Rare	47	17	1.0	1.0	42	1.0	1.0
Medium	121	52	1.40 0.71–2.74	1.40 0.71–2.76	171	1.64 1.01–2.68	1.64 1.00–2.68
Well done	176	57	0.91 0.47–1.76	0.92 0.47–1.79	162	1.08 0.67–1.75	1.09 0.67–1.76
Very well done	45	19	1.00 0.43–2.30 P _{trend} =0.39 ⁵	0.98 0.42–2.25 P _{trend} =0.39 ⁵	44	1.12 0.60–2.07 P _{trend} =0.34 ⁵	1.12 0.60–2.09 P _{trend} =0.37 ⁵
Doneness of steak among consumers of steak							
Rare	50	17	1.0	1.0	57	1.0	1.0
Medium	195	53	0.96 0.50–1.86	1.01 0.52–1.96	198	0.92 0.59–1.42	0.91 0.59–1.42
Well done	85	43	1.35 0.67–2.71	1.47 0.73–2.98	107	1.12 0.69–1.84	1.09 0.66–1.80
Very well done	21	10	1.14 0.41–3.12 P _{trend} =0.38 ⁵	1.22 0.44–3.36 P _{trend} =0.29 ⁵	24	1.03 0.50–2.11 P _{trend} =0.56 ⁵	1.04 0.50–2.16 P _{trend} =0.60 ⁵

¹ Odds ratio (OR) and 95% confidence interval (CI). Model 1 adjusted for age, race, SES, family history of prostate cancer, BMI, and caloric intake.

² Model 2 also adjusted for intake of fat, fruits, and vegetables.

³ Includes only grilled or barbecued, broiled or pan-fried meat.

⁴ Overall trend.

5. Trend for consumers of red meat only.

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TABLE 4

Mean HCA and BaP exposure, by case-control status and by race

	Localized cases N=195	Advanced cases N=531	Controls N=527	Non-Hispanic white controls N=448	African-American controls N=79	p-value [*]
PhIP &	146.6	134.1	140.8	133.9	179.8	0.19
MeIQx &	54.0	51.0	43.9	37.5	80.0	0.0004
DiMeIQx &	3.5	3.0	2.7	2.3	4.7	0.003
Benzo(a)pyrene &	27.0	35.3	36.3	38.8	21.9	0.04
Actual mutagenic activity #	8134	7327	6650	5788	11539	0.0003

^{*} p-value based on t-test, comparing non-Hispanic white vs. African-American controls

& ng/1,000 kcal/day

per 1,000 revertant colonies

TABLE 5

Associations between HCA, BaP and prostate cancer risk by cancer subtype

Controls N=527		Localized cases N=195			Advanced cases N=531		
n	n	OR, 95% CI ¹ Model 1	OR, 95% CI ¹ Model 2	n	OR, 95% CI ¹ Model 1	OR, 95% CI ¹ Model 2	
PhIP (ng/1000 kcal/day)							
132	46	1.0	1.0	107	1.0	1.0	
132	48	1.18 0.72–1.94	1.26 0.76–2.07	154	1.48 1.04–2.11	1.41 0.98–2.01	
131	51	1.26 0.77–2.05	1.37 0.83–2.26	152	1.53 1.08–2.19	1.42 0.98–2.04	
132	50	1.14 0.70–1.88	1.27 0.76–2.10	118	1.16 0.81–1.67	1.05 0.73–1.53	
		P _{trend} =0.56	P _{trend} =0.33		P _{trend} =0.44	P _{trend} =0.86	
MeIQx (ng/1000 kcal/day)							
131	55	1.0	1.0	131	1.0	1.0	
133	45	0.81 0.50–1.32	0.89 0.54–1.46	129	0.96 0.68–1.36	0.92 0.64–1.31	
132	41	0.79 0.48–1.31	0.91 0.54–1.53	134	1.03 0.72–1.46	0.96 0.67–1.38	
131	54	0.84 0.52–1.37	1.03 0.61–1.74	137	1.07 0.75–1.52	0.93 0.64–1.35	
		P _{trend} =0.49	P _{trend} =0.92		P _{trend} =0.66	P _{trend} =0.78	
DiMeIQx (ng/1000 kcal/day)							
141	61	1.0	1.0	146	1.0	1.0	
129	41	0.87 0.54–1.42	0.91 0.55–1.49	123	0.96 0.68–1.36	0.92 0.65–1.31	
128	46	0.91 0.56–1.46	1.04 0.63–1.69	134	1.04 0.74–1.47	0.97 0.69–1.38	
129	47	0.77 0.48–1.23	0.85 0.52–1.39	128	0.97 0.68–1.36	0.88 0.61–1.25	
		P _{trend} =0.31	P _{trend} =0.64		P _{trend} =0.97	P _{trend} =0.55	
Benzo(a)pyrene (ng/1000 kcal)							
131	52	1.0	1.0	131	1.0	1.0	
133	56	0.98 0.61–1.57	1.03 0.63–1.67	135	0.99 0.70–1.40	0.91 0.63–1.29	
131	45	0.86 0.53–1.42	0.94 0.56–1.58	126	0.98 0.69–1.39	0.90 0.63–1.29	
132	42	0.98 0.59–1.60	1.09 0.65–1.82	139	1.14 0.80–1.61	1.02 0.72–1.47	
		P _{trend} =0.78	P _{trend} =0.86		P _{trend} =0.51	P _{trend} =0.89	
Actual mutagenic activity (per 1,000 revertant colonies)							
132	49	1.0	1.0	122	1.0	1.0	

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Controls N=527		Localized cases N=195				Advanced cases N=531			
n	n	OR, 95% CI ¹ Model 1	OR, 95% CI ¹ Model 2	n	n	OR, 95% CI ¹ Model 1	OR, 95% CI ¹ Model 2	n	n
131	42	0.86 0.52–1.42	0.95 0.57–1.59	149	149	1.24 0.88–1.75	1.17 0.82–1.66		
133	58	1.25 0.78–2.00	1.51 0.91–2.50	118	118	1.00 0.70–1.42	0.89 0.61–1.29		
131	46	0.79 0.47–1.32	0.93 0.54–1.57	142	142	1.20 0.84–1.70	1.06 0.74–1.53		
		P _{trend} =0.73				P _{trend} =0.59			
						P _{trend} =0.78			
								P _{trend} =0.89	

¹ Odds ratio (OR) and 95% confidence interval (CI). Model 1 adjusted for age, race, SES, family history of prostate cancer, BMI, and caloric intake.

² Model 2 also adjusted for intake of fat, fruits, and vegetables.