

Egg, Red Meat, and Poultry Intake and Risk of Lethal Prostate Cancer in the Prostate-Specific Antigen-Era: Incidence and Survival

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Abstract

Red and processed meat may increase risk of advanced prostate cancer. Data on postdiagnostic diet and prostate cancer are sparse, but postdiagnostic intake of poultry with skin and eggs may increase risk of disease progression. Therefore, we prospectively examined total, unprocessed, and processed red meat, poultry, and eggs in relation to risk of lethal prostate cancer (e.g., men without cancer at baseline who developed distant organ metastases or died from prostate cancer during follow-up) among 27,607 men followed from 1994 to 2008. We also conducted a case-only survival analysis to examine postdiagnostic consumption of these foods and risk of lethal prostate cancer among the 3,127 men initially diagnosed with nonmetastatic prostate cancer during follow-up. In the incidence analysis, we observed 199 events during 306,715 person-years. Men who consumed 2.5 or more eggs per week had an 81% increased risk of lethal prostate cancer compared with men who consumed less than 0.5 eggs per week (HR: 1.81; 95% CI: 1.13–2.89; P_{trend} : 0.01). In the case-only survival analysis, we observed 123 events during 19,354 person-years. There were suggestive, but not statistically significant, positive associations between postdiagnostic poultry (HR ≥ 3.5 vs. <1.5 servings per week: 1.69; 95% CI: 0.96–2.99; P_{trend} : 0.07) and postdiagnostic processed red meat (HR ≥ 3 vs. <0.5 servings per week: 1.45; 95% CI: 0.73–2.87; P_{trend} : 0.08) and risk of progression of localized prostate cancer to lethal disease. In conclusion, consumption of eggs may increase risk of developing a lethal form of prostate cancer among healthy men. *Cancer Prev Res*; 4(12); 2110–21. ©2011 AACR.

Introduction

Prostate cancer is the most common nonskin cancer among men in the United States, with over 217,000 new cases diagnosed in 2010 (1). We previously reported in the Health Professionals Follow-up Study (HPFS) that red meat intake was associated with increased risk of metastatic prostate cancer based on follow-up from 1986 to 1996 (2). We also reported that postdiagnostic red meat intake was not associated with risk of prostate cancer progression using data from men diagnosed with prostate cancer in HPFS during the same time period (3). Many of the cases in these previous analyses were diagnosed before prostate-specific antigen (PSA) testing was commonly used. Conse-

quently, the results may not be applicable to contemporary prostate cancer cases that are diagnosed and followed through PSA testing.

The high incidence rate and relatively long-life expectancy of men diagnosed with prostate cancer in the PSA-era (e.g., 1994 to current) underscores the importance of examining the role of diet after diagnosis. Few studies have examined the impact of postdiagnostic diet on prostate cancer progression. Meyer and colleagues reported an association between higher saturated fat intake after diagnosis and risk of prostate cancer-specific survival in a small population of men with prostate cancer, 23% of whom had advanced disease at diagnosis (4). In the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), we reported no association between red meat intake after diagnosis and risk of prostate cancer progression among men diagnosed with localized disease and followed from 2004 to 2009, similar to our findings in HPFS (5). However, we observed statistically significant positive associations between poultry with skin and egg intakes after diagnosis and risk of prostate cancer progression—foods that had not been examined in the previous HPFS study.

In this study, we examined intake of red meat, poultry, and eggs in relation to risk of lethal prostate cancer among men free of diagnosed cancer as of 1994 (e.g., men without cancer at baseline in 1994 who developed prostate cancer

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metastases or died from prostate cancer during follow-up). We also conducted a case-only survival analysis in which we examined postdiagnostic consumption of these foods and risk of progression to lethal prostate cancer among men initially diagnosed with clinically localized or regional disease after 1994. On the basis of previous studies, we hypothesized that red meat intake would be associated with increased risk of lethal prostate cancer (2, 6), and postdiagnostic intakes of eggs and poultry with skin would be associated with increased risk of lethal disease among men initially diagnosed with clinically localized or regional prostate cancer (5).

Subjects and Methods

Study population

The HPFS is an on-going prospective cohort study initiated in 1986 among 51,529 U.S. male health professionals, 40 to 75 years at baseline. Participants completed a baseline questionnaire on medical diagnoses, physical activity, weight, medications, and smoking, as well as a semiquantitative food frequency questionnaire (FFQ; ref. 7). Information on medical diagnoses, physical activity, weight, medications, and smoking is updated every 2 years, and dietary information is updated every 4 years. The average questionnaire response rate exceeds 94%.

The base population for the incidence analysis included HPFS participants who were free of diagnosed cancer, except nonmelanoma skin cancer, as of 1994. To define a PSA-screened study population, we began follow-up in 1994 and required eligible men to report having had a PSA test. The Federal Drug Administration approved PSA testing for use as a screening tool for prostate cancer in 1994. Men who reported their first PSA test and a diagnosis of prostate cancer on the same questionnaire were not eligible. We did not require the PSA concentration to be below a particular value because PSA can be elevated for reasons other than prostate cancer. The base population for the case-only survival analyses included participants initially diagnosed with clinically localized or regional prostate cancer after 1994. The Institutional Review Board at the Harvard School of Public Health approved this study.

Dietary assessment

Participants in HPFS completed a semiquantitative FFQ in 1986 and updated their dietary intake every 4 years. A common serving size was specified for approximately 148 foods and beverages (e.g., 1 egg including yolk) and participants were asked to report their average frequency of intake over the past year using 9 frequency options ranging from less than once per month to 6 or more times per day.

Exposures of interest for this analysis included: processed red meat [salami, bologna, or other processed meat sandwiches; other processed meats (e.g., sausage, kielbasa, etc.); bacon; hot dogs], unprocessed red meat [regular hamburger; lean or extra-lean hamburger; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); beef or lamb as a main dish (e.g., steak, roast, ham, etc.);

pork as a main dish (e.g., ham or chops)], total red meat (the sum of processed and unprocessed red meat), total poultry (chicken or turkey with or without skin; chicken or turkey hot dogs; chicken or turkey sandwiches), eggs (including yolk), and individual red meat and poultry items. We combined items when necessary for consistency across questionnaires, for example "hamburger" included regular and lean or extra-lean hamburger and "sausage/salami/bologna" included salami, bologna, or other processed meat sandwiches and other processed meats.

The FFQ was validated in 1986 among 127 HPFS participants living near Boston, MA. Correlation coefficients comparing the FFQ with the average of two 1-week-food diaries for exposures of interest were: eggs = 0.76; chicken or turkey without skin = 0.56; chicken or turkey with skin = 0.49; sausage/salami/bologna = 0.83; bacon = 0.77; hot dogs = 0.30; hamburger = 0.63; and beef, pork, lamb = 0.66 (8).

Outcome assessment and follow-up

We asked participants biennially if they had been diagnosed with prostate cancer during the previous 2 years and, after a report of prostate cancer diagnosis, we requested permission to obtain medical records to confirm the diagnosis. Approximately 83% of self-reported cases were confirmed via medical record review. The remaining cases were pending review at the time of analysis (14%), or the medical records were unavailable or lacked sufficient information to confirm the diagnosis (4%). We included unconfirmed cases in our analysis due to the high concordance between self-reported diagnoses and actual diagnoses based on the available medical records. We abstracted date of diagnosis, clinical TNM stage, Gleason sum, PSA at diagnosis, and treatment information from the medical records. In addition, we mailed biennial follow-up questionnaires to participants with confirmed prostate cancer to update information on treatments and disease progression. Deaths were identified by mail, telephone, and review of the National Death Index; we ascertain more than 98% of deaths using these methods (9). Four study physicians determined cause of death from death certificates and medical records.

Our primary outcome was lethal prostate cancer, defined as distant organ metastases due to prostate cancer (TNM stage: M1) or prostate cancer death that occurred during the follow-up period of 1994 to 2008.

Inclusion/exclusion criteria

We excluded men who: (i) did not adequately complete the baseline FFQ in 1986 (e.g., reported <800 or >4,200 kcal/d and/or had >70 food items missing), (ii) were diagnosed with cancer (except nonmelanoma skin cancer) before 1994, and (iii) did not report having had a PSA test, leaving 27,607 men eligible for the incidence analysis. For the case-only survival analyses, in addition to the criteria listed above, we excluded men with extra-prostatic prostate cancer at diagnosis (clinical stage T3b+) and men with unknown clinical stage or primary treatment, leaving 3,127

men diagnosed with prostate cancer between 1994 and 2008 eligible for follow-up for lethal outcomes.

Statistical analysis

Incidence of lethal prostate cancer. We used Cox proportional hazards regression to examine the associations between red meat, poultry, and eggs and risk of lethal prostate cancer. Person-time was calculated from the date of the 1994 questionnaire for men who reported having had a PSA test prior to 1994 or date of the questionnaire when the participant first reported having had a PSA test, until date of prostate cancer diagnosis, death from another cause, or end of follow-up (January 31, 2008), whichever occurred first. We used calendar time in 2-year intervals as the time scale and stratified by age in months.

Cumulative average intakes of the exposures of interest were calculated from 1986 to date of prostate cancer diagnosis, death from another cause, or end of follow-up (e.g., the average of the 1986, 1990, and 1994 FFQs was applied to person-time accrued between 1994 and 1998; the average of the 1986, 1990, 1994, and 1998 FFQs was applied to person-time accrued between 1998 and 2002, etc.; ref. 10). We only used data from FFQs that were adequately completed (i.e., had an estimated daily energy intake of 800–4200 kcal/d); therefore if a participant was missing data on an individual food item, we assumed he did not consume that item. We categorized exposures based on the distribution of intakes in the study population, modeled the categories using indicator variables, and conducted tests of trend by modeling the median of each category as a continuous term.

Model 1 was adjusted for age (mo.; continuous), time period (2-year intervals; continuous), and energy (kcal/d; quartiles). Model 2 was additionally adjusted for body mass index (BMI; <25, 25–29.9, ≥ 30 kg/m²), smoking (current, former, not current with unknown history, never smoker), vigorous physical activity (metabolic equivalent task (MET)-h/wk; quartiles) and lycopene intake (quartiles). In addition, all red meat and poultry categories were adjusted for eggs; total processed red meat and total unprocessed red meat were adjusted for each other; individual processed red meat items were adjusted for each other; individual unprocessed red meat items were adjusted for each other; and individual poultry items were adjusted for each other. We also considered the following variables as potential confounders: race, family history of prostate cancer, history of diabetes, frequency of PSA screening, use of cholesterol-lowering drugs, and quartile intakes of dairy, fish, tomato sauce, fresh tomato products, cruciferous vegetables, calcium, and coffee, but the point estimates changed less than 10% and therefore these variables were omitted from the final model. These variables were chosen because they were previously reported to be associated with prostate cancer risk or survival (3, 11–17).

We examined whether BMI (<25 vs. ≥ 25 kg/m²), smoking (ever vs. never), or age (continuous) modified the associations between total, unprocessed, or processed red meat, total poultry, or eggs and risk of lethal prostate cancer

using likelihood ratio tests. In addition, the clinical distinction of "pre-" and "post-" diagnostic diet may not capture the most biologically relevant exposure if dietary factors affect prostate cancer throughout its natural history. Therefore, we conducted a sensitivity analysis in which we followed men until date of lethal event (e.g., first bone scan indicating metastasis), death from another cause, or January 31, 2008. We calculated cumulative average dietary intake, updating until the end of the new follow-up period, and applied a 2 to 6 years lag out of concern that reverse causation could influence these results since men with metastatic prostate cancer may change their diet due to their illness (e.g., cumulative average dietary intake from the 1986, 1990, 1994 FFQs was applied to follow-up accrued from 1996 to 2000). Lastly, to examine the impact of assuming food items with missing data were not consumed, we conducted a sensitivity analysis excluding men missing data on any food item of interest.

Case-only survival analyses

We used Cox proportional hazards regression to examine the relation between postdiagnostic consumption of red meat, poultry, and eggs and risk of progression to lethal prostate cancer. Person-time was calculated from the date of prostate cancer diagnosis to lethal event, death from another cause, or January 31, 2008, whichever occurred first. We used calendar time in 2-year intervals as the time scale and stratified by years since diagnosis.

Cumulative average postdiagnostic intakes were calculated from the FFQ immediately preceding diagnosis until end of follow-up. The FFQ immediately preceding diagnosis was used to estimate participants' exposure from date of diagnosis until the next available FFQ because that FFQ reflects diet around the time of diagnosis and men diagnosed with prostate cancer did not change their diet after diagnosis any more or less on average compared with men in HPFS who were not diagnosed with prostate cancer during the same time period. For consistency, we used the cut-points determined for the incidence analyses and modeled the categories using indicator variables. We conducted tests of trend by modeling the median of each category as a continuous term.

Model 1 was adjusted for age at diagnosis (y; continuous), time period (2-year intervals; continuous), time since diagnosis (y; continuous), and energy (kcal/d; quartiles). Model 2 was additionally adjusted for Gleason sum at diagnosis (<7, 7, >7), clinical T-stage at diagnosis (T1, T2, T3), primary treatment (radical prostatectomy, radiation, hormone therapy, active surveillance/other), BMI (<25, 25–29.9, ≥ 30 kg/m²), vigorous physical activity (MET-h/wk; quartiles), smoking status (current, not current with unknown history, former, never), and prediagnostic intakes of the exposures of interest based on the 1986 questionnaire (except for chicken or turkey hot dogs and sandwiches which were first queried in 1994 and 1998, respectively). Total unprocessed and total processed red meat were adjusted for each other; individual processed red meat items were adjusted for each other; individual unprocessed red meat items were adjusted for each other; and individual poultry items were

adjusted for each other. In addition to the risk factors for lethal prostate cancer mentioned above (see statistical analysis: Incidence of lethal prostate cancer), we considered adjustment for PSA at diagnosis, but no additional covariate changed the effect estimates more than 10% and therefore they were omitted from the final model.

We examined whether the associations between post-diagnostic categories of red meat, poultry, or eggs and risk of progression to lethal prostate cancer were modified by smoking status (ever vs. never), BMI (<25 vs. ≥ 25 kg/m²), age at diagnosis (continuous), Gleason sum (<7 vs. ≥ 7), and time since diagnosis (continuous) using likelihood ratio tests. In addition, we conducted a sensitivity analysis excluding men with missing data on any food items of interest.

SAS version 9.2 was used for all statistical analyses, and 2-sided $P \leq 0.05$ were considered statistically significant.

Results

Incidence of lethal prostate cancer

We observed 199 events of lethal prostate cancer among 27,607 men during 306,715 person-years. Men who consumed more red meat and eggs had a higher average BMI; engaged in less vigorous activity; were more likely to be current smokers, have a history of type II diabetes, and have a family history of prostate cancer; and tended to eat less poultry and fish and more dairy compared with men who consumed the least red meat or eggs (Table 1). In contrast, men who consumed more poultry engaged in more vigorous activity, were less likely to be current smokers, and tended to eat less red meat, dairy, and coffee, and more fish compared with men who consumed the least poultry.

We observed a statistically significant positive association between intake of eggs and risk of lethal prostate cancer (Table 2). Men who consumed 2.5 or more eggs per week had a 81% increased risk of lethal prostate cancer compared with men who consumed less than half an egg per week (HR: 1.81; 95% CI: 1.13–2.89; P_{trend} : 0.01). In addition, contrary to our hypothesis and the previous report from this cohort, we observed a suggestion of an inverse association between total unprocessed red meat and risk of lethal prostate cancer, but none of the point estimates were statistically significant (HR ≥ 5 vs. <2 servings/wk: 0.64; 95% CI: 0.38–1.06; P_{trend} : 0.03). No other meat group (Table 2) or individual meat or poultry item (data not shown in tables) was statistically significantly associated with risk of lethal prostate cancer after multivariate adjustment.

We observed no evidence of effect modification by smoking, BMI, or age (data not shown). In addition, the results were similar when we followed men to date of lethal event, death from another cause, or January 31, 2008 (updating diet until the end of the new follow-up period with a 2–6 years lag). However, the association for eggs was slightly attenuated and not statistically significant (HR ≥ 2.5 vs. <0.5 eggs/wk: 1.50; 95% CI: 0.90–2.48; P_{trend} : 0.14). Lastly, our results were unchanged when excluding men with

missing data on any of the food items of interest (HR comparing ≥ 2.5 vs. <0.5 eggs/wk: 1.81; 95% CI: 1.13–2.91; P_{trend} : 0.009).

Case-only survival analyses

We observed 123 events of lethal prostate cancer during 19,354 person-years among 3,127 men initially diagnosed with clinically localized or regional prostate cancer after 1994. Lifestyle and dietary factors varied in a similar pattern in men with prostate cancer as compared with the entire cohort, and clinical factors varied only modestly across categories of red meat, poultry, and egg intake (Table 3).

Intake of total red meat (unprocessed or processed), total poultry, and eggs after diagnosis were not statistically significantly associated with risk of progression to lethal prostate cancer (Table 4). There was a positive linear association between total processed red meat intake after diagnosis and risk of lethal prostate cancer in the age- and calorie-adjusted model (HR ≥ 3 vs. <0.5 servings/wk: 1.40; 95% CI: 0.81–2.44; P_{trend} : 0.04), which was somewhat attenuated after multivariate adjustment. In addition, men who consumed 3.5 or more servings per week of poultry after diagnosis had a 69% increased risk of lethal prostate cancer compared with men who consumed less than 1.5 servings/wk (HR: 1.69; 95% CI: 0.96–2.99; P_{trend} : 0.07). This suggestive association seemed to be driven by sources of poultry other than skinless poultry (e.g., chicken or turkey with skin, chicken or turkey hot dogs, chicken or turkey sandwiches), but we had limited power to examine individual poultry items due to low consumption of these foods in our study population (Table 5).

In addition, although total, total unprocessed, and total processed red meat intakes after diagnosis were not statistically significantly associated with risk of progression to lethal prostate cancer (Table 4), intake of 1.5 or more servings/wk of beef, lamb, or pork in a sandwich or mixed dish after diagnosis was associated with a greater than 2-fold increased risk of lethal prostate cancer compared to less than 0.5 serving/wk (HR: 2.21; 95% CI: 1.12–4.36; P_{trend} : 0.14; Table 5). Intake of 1.5 or more servings/wk of sausage/salami/bologna after diagnosis was also associated with an increased risk of lethal prostate cancer compared with no intake in the age- and calorie-adjusted model (HR: 1.76; 95% CI: 1.02–3.05; P_{trend} : 0.06; Table 5), but this association was not statistically significant after multivariate adjustment (HR: 1.60; 95% CI: 0.83–3.06; P_{trend} : 0.23). No other individual red meat item after diagnosis was associated with risk of progression to lethal prostate cancer.

We did not observe any statistically significant interactions between postdiagnostic consumption of red meat, poultry, or eggs with age at diagnosis, Gleason sum, BMI, smoking, or time since diagnosis (data not shown). In addition, when we excluded men with missing data on any of the food items of interest, the observed associations were unchanged or strengthened. For example, consuming 3.5 or more servings/wk of poultry was associated with an 82% increased risk of lethal prostate cancer compared with consuming less than 1.5 servings/wk (HR: 1.82; 95% CI:

Table 1. Baseline age-standardized characteristics of 27,607 healthy male health professionals according to their red meat, poultry, and egg intake

	Total red meat ^a		Total poultry ^b		Eggs ^c	
Servings/wk	<3	≥8	<1.5	≥3.5	<0.5	≥2.5
Age, mean (SD), y	61.8 (9.1)	60.2 (8.7)	62.7 (8.9)	59.2 (8.7)	60.7 (8.9)	61.5 (8.8)
BMI, mean (SD), kg/m ²	25.0 (3.0)	26.7 (3.9)	25.8 (3.5)	26.0 (3.5)	25.2 (3.1)	26.5 (4.0)
Vigorous MET-h/wk, mean (SD)	20.7 (30.2)	10.5 (20.5)	12.6 (23.5)	17.0 (30.1)	18.6 (31.9)	12.1 (21.8)
White, (%)	90.8	93.6	92.6	91.5	91.0	92.9
Current smokers, (%)	1.9	8.3	7.2	3.3	2.8	7.4
History of diabetes mellitus, (%)	2.9	5.6	3.9	4.4	3.2	4.9
Family history of prostate cancer, (%)	12.7	15.2	14.5	13.9	12.4	14.7
Dietary intakes, mean (SD), servings/wk ^d						
Red meat	1.8 (1.6)	9.2 (3.7)	6.1 (4.3)	4.6 (3.4)	3.5 (3.3)	7.1 (4.0)
Eggs	0.8 (1.7)	2.0 (2.4)	1.6 (2.2)	1.2 (1.9)	0.1 (0.3)	3.5 (3.0)
Poultry	3.5 (2.6)	2.5 (1.7)	1.1 (0.8)	4.6 (2.5)	3.4 (2.6)	2.7 (1.9)
Fish	3.4 (2.7)	1.7 (1.4)	1.8 (1.8)	2.9 (2.3)	3.1 (2.6)	2.1 (1.7)
Dairy ^e	13.2 (9.4)	14.2 (9.1)	15.9 (10.8)	12.6 (8.3)	12.5 (8.9)	15.4 (9.9)
Tomato sauce	1.4 (1.5)	0.9 (0.9)	1.0 (1.2)	1.2 (1.3)	1.3 (1.4)	1.0 (1.0)
Coffee	14.1 (15.3)	13.8 (12.5)	16.0 (16.3)	13.0 (12.9)	13.4 (15.1)	14.6 (13.3)

^aOne serving of total red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.); 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^bOne serving of total poultry = 1 chicken or turkey hot dog; chicken or turkey sandwich; 85 g of other chicken or turkey, with skin; or 85 g of other chicken or turkey, without skin.

^cOne serving of eggs = 1 egg with yolk.

^dStandardized to 2,000 kcal/d.

^eDairy includes: skim milk; 1 or 2% milk; whole milk; cream; frozen yogurt, sherbet, or low-fat ice cream; regular ice cream; yogurt; butter; cottage or ricotta cheese; cream cheese; and other cheese.

0.93–3.57; P_{trend} : 0.03), and consuming 3 or more servings/wk of total processed red meat was suggestively associated with a 60% increased risk of lethal prostate cancer compared with consuming less than 0.5 servings/wk (HR: 1.60; 95% CI: 0.71–3.59; P_{trend} : 0.08).

Discussion

In this prospective study of red meat, poultry, and egg consumption and risk of lethal prostate cancer in the PSA-era, we observed a statistically significant positive association between intake of eggs and risk of lethal prostate cancer. In addition, among men initially diagnosed with clinically localized or regional prostate cancer, we observed suggestive positive associations between total poultry and total processed red meat intake and progression to lethal prostate cancer, but these relations were of borderline statistical significance.

Eggs

Only 3 prior studies have prospectively examined egg consumption in relation to risk of advanced or fatal prostate cancer (18–20). Snowden and colleagues reported a 60% increased risk of fatal prostate cancer among men eating 3 or

more eggs per week compared with less than 1 egg per week (HR: 1.60; 95% CI: 0.9–2.8; ref. 18). In contrast, there was no difference in prostate cancer death comparing men eating 7 eggs per week (21–38/mo) to 1 or fewer eggs per week in the Lutheran Brotherhood Cohort Study (HR: 0.90; 95% CI: 0.5–1.5; ref. 19), and a 20 g increase in egg intake per day (approximately half an egg) was associated with a 30% reduction in risk of advanced prostate cancer (HR: 0.70; 95% CI: 0.53–0.93) in the Netherlands Cohort Study (20). Although the limited data available are inconsistent, our results are similar to those of Snowden and colleagues and highly suggestive of an association; therefore additional research on egg consumption and risk of lethal prostate cancer is warranted.

Support for an association between egg consumption and risk of lethal prostate cancer comes from our previous report of a 2-fold increased risk of prostate cancer progression (mainly PSA rise) associated with high egg intake after diagnosis among men initially diagnosed with localized disease (HR comparing extreme quartiles: 2.02; 95% CI: 1.10–3.72; P_{trend} : 0.05) (5). Prediagnostic diet was not available in CaPSURE, and it is possible that the increased risk of prostate cancer progression we observed in that study population was a reflection of egg intake prior to diagnosis.

Table 2. Relative hazard of lethal prostate cancer among 27,607 male health professionals by red meat, poultry, and egg intake (1994–2008)

	Servings/wk				P ^a
Total red meat^b	< 3	3–4.9	5–7.9	≥ 8	
Events	46	50	54	49	
Model 1 HR (95% CI) ^c	1.0	1.38 (0.91–2.08)	1.26 (0.83–1.90)	1.31 (0.83–2.06)	0.35
Model 2 HR (95% CI) ^d	1.0	1.27 (0.84–1.93)	1.10 (0.72–1.70)	1.07 (0.66–1.75)	0.99
Total unprocessed red meat^e	< 2	2–3.4	3.5–4.9	≥ 5	
Events	50	63	44	42	
Model 1 HR (95% CI) ^c	1.0	1.35 (0.92–1.98)	1.26 (0.82–1.93)	0.85 (0.54–1.34)	0.34
Model 2 HR (95% CI) ^d	1.0	1.18 (0.78–1.78)	1.02 (0.63–1.62)	0.64 (0.38–1.06)	0.03
Total processed red meat^f	< 0.5	0.5–1.4	1.5–2.9	≥ 3	
Events	34	63	51	51	
Model 1 HR (95% CI) ^c	1.0	1.31 (0.86–2.01)	1.18 (0.75–1.85)	1.56 (0.98–2.48)	0.11
Model 2 HR (95% CI) ^d	1.0	1.29 (0.82–2.02)	1.09 (0.66–1.80)	1.52 (0.89–2.61)	0.20
Total poultry^g	< 1.5	1.5–2.4	2.5–3.4	≥ 3.5	
Events	39	70	37	53	
Model 1 HR (95% CI) ^c	1.0	1.09 (0.73–1.63)	0.74 (0.47–1.17)	1.06 (0.68–1.63)	0.82
Model 2 HR (95% CI) ^d	1.0	1.14 (0.76–1.71)	0.79 (0.49–1.25)	1.15 (0.74–1.78)	0.89
Eggs^h	< 0.5	0.5–1.4	1.5–2.4	≥ 2.5	
Events	30	64	50	55	
Model 1 HR (95% CI) ^c	1.0	1.35 (0.87–2.09)	1.50 (0.94–2.39)	1.87 (1.17–2.96)	0.009
Model 2 HR (95% CI) ^d	1.0	1.33 (0.85–2.07)	1.49 (0.93–2.37)	1.81 (1.13–2.89)	0.01

^aCalculated using the median of each category as a continuous term.

^bOne serving of total red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.); 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^cAdjusted for age (continuous) and energy (quartiles, kcal/d).

^dAdjusted for age (continuous), energy (quartiles, kcal/d), BMI (<25, 25–29.9, ≥30 kg/m²), smoking (never, not current with unknown history, former, current), vigorous activity (MET-h/wk; quartiles), and lycopene intake (quartiles). All red meat categories and poultry were adjusted for eggs. Unprocessed and processed red meat were adjusted for each other.

^eOne serving of total unprocessed red meat = 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^fOne serving of total processed red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.).

^gOne serving of total poultry = 1 chicken or turkey hot dog; chicken or turkey sandwich; 85 g of other chicken or turkey, with skin; or 85 g of other chicken or turkey, without skin.

^hOne serving of eggs = 1 egg with yolk.

Our observation of no association between postdiagnostic egg intake and risk of progression to lethal prostate cancer, as well as the attenuation of the association in the incidence analysis when following men to date of lethal event, suggests egg intake affects risk of lethal prostate cancer early in the natural history of the disease.

Eggs are particularly rich dietary sources of choline and cholesterol, which are highly concentrated in prostate cancer cells, and blood concentrations of both nutrients have been positively associated with risk of advanced prostate cancer (21, 22). Epidemiologic evidence for choline and prostate cancer is limited; however, a nested case-control study reported that men in the highest quartile of plasma choline had a 48% increased risk of prostate cancer com-

pared with men in the lowest quartile (OR: 1.48; 95% CI: 1.07–2.04; ref. 21). Choline is essential for a variety of cell functions involved in cancer growth and progression (23), and malignant prostate cells have greater uptake of choline and overexpress choline kinase compared with normal cells (24–26).

The high cholesterol content of eggs may also explain the observed positive association between eggs and risk of lethal prostate cancer. Cholesterol homeostasis is disrupted in aging and malignant cells, leading to accumulation of cholesterol, which in turn may act as a precursor for androgen production and alter signaling pathways to promote cancer progression (27, 28). However, although inhibition of dietary cholesterol

Table 3. Baseline age-standardized characteristics of 3,127 male health professionals diagnosed with clinically localized or regional prostate cancer according to their red meat, egg, and poultry intake after diagnosis

	Red meat ^a		Poultry ^b		Eggs ^c	
Servings/wk	<3	≥8	<1.5	≥3.5	<0.5	≥2.5
Age at diagnosis, mean (SD), y	69.2 (7.5)	69.0 (7.1)	70.0 (7.1)	68.2 (7.6)	68.6 (7.2)	69.5 (7.2)
BMI, mean (SD), kg/m ²	25.1 (3.1)	26.4 (3.3)	25.8 (3.5)	25.6 (3.1)	25.1 (2.9)	26.3 (3.5)
Vigorous activity, mean (SD), MET-h/wk	18.2 (29.6)	9.8 (22.4)	12.1 (22.8)	15.3 (27.8)	16.4 (26.2)	11.8 (24.4)
White, (%)	90.5	92.9	90.1	92.8	92.4	93.0
Current smokers, (%)	0.9	8.2	4.7	3.4	2.0	5.9
History of diabetes mellitus, (%)	4.3	5.5	4.8	3.8	4.0	5.4
Family history of prostate cancer, (%)	19.5	20.1	21.3	20.2	20.8	20.6
Clinical T-stage, (%) ^d						
T1	66.1	61.4	65.8	66.0	66.7	62.3
T2	31.4	36.5	30.7	31.9	31.2	35.5
T3a	2.6	2.2	3.6	2.1	2.0	2.2
Gleason sum, (%) ^d						
≤6	54.5	51.6	53.6	53.9	54.4	52.8
7	33.5	35.9	34.4	32.6	33.3	35.5
≥8	9.0	9.4	9.4	10.8	8.5	9.6
Missing	3.0	3.2	2.6	2.7	3.7	2.1
PSA at diagnosis, (%) ^d						
<4 ng/mL	11.9	11.0	12.0	10.8	12.0	11.6
4–9.9 ng/mL	61.3	57.5	60.4	62.4	59.9	59.5
10–19.9 ng/mL	17.4	19.2	16.4	17.8	16.9	19.7
≥20 ng/mL	6.6	8.6	8.3	6.8	7.5	7.1
Missing	2.7	3.8	2.9	2.3	3.8	2.2
Treatment, (%) ^d						
Radical prostatectomy	46.4	47.4	45.0	47.6	49.4	43.8
Radiation therapy	39.7	35.2	38.7	37.9	37.5	42.4
Hormonal therapy	3.4	6.4	3.9	5.2	3.8	4.3
Other/active surveillance	10.4	10.9	12.4	9.2	9.3	9.6
Dietary intakes, mean (SD), servings/wk ^e						
Red meat	2.4 (2.3)	9.1 (4.0)	5.8 (4.2)	5.1 (3.7)	3.5 (3.4)	6.9 (4.1)
Eggs	0.9 (1.5)	1.9 (2.6)	1.6 (2.4)	1.2 (1.9)	0.3 (0.8)	3.0 (3.2)
Poultry	3.4 (2.6)	2.4 (1.6)	1.4 (1.3)	3.9 (2.4)	3.3 (2.5)	2.7 (1.9)
Fish	3.1 (2.5)	1.8 (1.4)	2.0 (1.9)	2.8 (2.1)	2.9 (2.4)	2.1 (1.7)
Dairy ^f	13.6 (9.0)	14.0 (9.5)	16.2 (10.9)	12.9 (8.0)	13.0 (8.8)	14.9 (9.8)
Tomato sauce	1.2 (1.3)	0.8 (0.9)	1.0 (1.1)	1.1 (1.1)	1.2 (1.2)	0.9 (0.9)
Coffee	12.8 (13.7)	14.0 (13.2)	15.0 (15.7)	13.2 (12.7)	12.1 (13.7)	14.3 (13.4)

^aOne serving of total red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.); 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^bOne serving of total poultry = 1 chicken or turkey hot dog; chicken or turkey sandwich; 85 g of other chicken or turkey, with skin; or 85 g of other chicken or turkey, without skin.

^cOne serving of eggs = 1 egg with yolk.

^dPercentages may not add to 100% due to rounding.

^eStandardized to a 2,000 kcal/d diet.

^fDairy includes: skim milk; 1 or 2% milk; whole milk; cream; frozen yogurt, sherbet, or low-fat ice cream; regular ice cream; yogurt; butter; cottage or ricotta cheese; cream cheese; and other cheese.

absorption leads to regression of prostate tumors in rodents and dogs (27), dietary cholesterol has only a modest effect on plasma cholesterol in humans and Park

and colleagues reported no association between dietary cholesterol and prostate cancer in the Multiethnic Cohort Study (29).

Table 4. Postdiagnostic consumption of red meat, poultry, and eggs and relative hazard of lethal prostate cancer among 3,127 men diagnosed with clinically localized or regional prostate cancer (1994–2008)

	Servings/wk				P ^a
Total red meat^b	<3	3–4.9	5–7.9	≥8	
Events	33	23	35	32	
Model 1 HR (95% CI) ^c	1.0	1.03 (0.60–1.77)	1.32 (0.80–2.18)	1.38 (0.81–2.37)	0.19
Model 2 HR (95% CI) ^d	1.0	0.97 (0.55–1.70)	1.20 (0.69–2.10)	1.13 (0.60–2.10)	0.66
Total unprocessed red meat^e	<2	2–3.4	3.5–4.9	≥5	
Events	38	29	22	34	
Model 1 HR (95% CI) ^c	1.0	0.96 (0.58–1.56)	1.08 (0.62–1.88)	1.34 (0.80–2.26)	0.22
Model 2 HR (95% CI) ^d	1.0	0.74 (0.43–1.27)	0.84 (0.45–1.55)	0.94 (0.52–1.70)	0.88
Total processed red meat^f	<0.5	0.5–1.4	1.5–2.9	≥3	
Events	23	24	42	34	
Model 1 HR (95% CI) ^c	1.0	0.76 (0.43–1.35)	1.41 (0.84–2.37)	1.40 (0.81–2.44)	0.04
Model 2 HR (95% CI) ^d	1.0	0.78 (0.42–1.44)	1.47 (0.80–2.70)	1.45 (0.73–2.87)	0.08
Total poultry^g	<1.5	1.5–2.4	2.5–3.4	≥3.5	
Events	20	32	20	51	
Model 1 HR (95% CI) ^c	1.0	1.09 (0.62–1.93)	1.22 (0.65–2.30)	1.45 (0.85–2.49)	0.12
Model 2 HR (95% CI) ^d	1.0	1.28 (0.72–2.28)	1.55 (0.81–2.97)	1.69 (0.96–2.99)	0.07
Eggs^h	<0.5	0.5–1.4	1.5–2.4	≥2.5	
Events	26	34	28	35	
Model 1 HR (95% CI) ^c	1.0	0.76 (0.46–1.28)	1.29 (0.74–2.23)	1.14 (0.68–1.92)	0.17
Model 2 HR (95% CI) ^d	1.0	0.74 (0.44–1.25)	1.06 (0.60–1.88)	0.95 (0.55–1.64)	0.62

^aCalculated using the median of each category as a continuous term.

^bOne serving of total red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.); 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^cModel 1 adjusted for age at diagnosis (continuous, y), time since diagnosis (continuous, y), and energy (quartiles, kcal/d).

^dModel 2 adjusted for covariates in Model 1 plus Gleason sum (<7, 7, ≥7), clinical T-stage (T1, T2, T3), primary treatment (radical prostatectomy, radiation, active surveillance/other, androgen deprivation therapy), BMI (<25, 25–29.9, ≥30 kg/m²), smoking (current, former, not current with unknown history, never), vigorous activity (quartiles, MET-h/wk), and prediagnostic intake of the exposure of interest (quartiles). Unprocessed red meat was adjusted for processed red meat.

^eOne serving of total unprocessed red meat = 1 hamburger patty; beef, pork, or lamb as a sandwich or mixed dish (e.g., stew, casserole, lasagna, etc.); 113 to 170 g of pork as a main dish (e.g., ham or chops); or 113 to 170 g of beef or lamb as a main dish (e.g., steak, roast).

^fOne serving of total processed red meat = 1 beef or pork hot dog; 2 slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or 2 links of other processed meats (e.g., sausage, kielbasa, etc.).

^gOne serving of total poultry = 1 chicken or turkey hot dog; chicken or turkey sandwich; 85 g of other chicken or turkey, with skin; or 85 g of other chicken or turkey, without skin.

^hOne serving of eggs = 1 egg with yolk.

Poultry

In this study, we observed a suggestive positive association between total poultry intake after prostate cancer diagnosis and risk of progression to lethal disease. This association seemed to be driven by sources of poultry other than skinless poultry, but our data were sparse and the results for the individual poultry items were not statistically significant. The relation between consumption of poultry with skin after diagnosis and clinical outcomes in men with prostate cancer has been examined in 1 prior study. In CaPSURE, men in the highest tertile of poultry with skin intake after diagnosis had a 2.26-fold increased risk of prostate cancer progression compared with men in the first

tertile (HR: 2.26; 95% CI: 1.36–3.76; P_{trend} : 0.003; ref. 5). Poultry hot dogs or poultry in sandwiches were not examined in CaPSURE.

Exposure to heterocyclic amines (HCA), compounds formed when meat is cooked at high temperatures, may account for a positive association between intake of poultry after diagnosis and risk of lethal prostate cancer. HCA form DNA adducts in multiple human tissues and increase the occurrence of numerous cancers, including prostate cancer, in animal studies (30). Chicken is the primary source of HCAs in the United States diet (31), and pan-fried, oven broiled, and grilled chicken have particularly high amounts of HCAs (32). In particular, chicken with skin has higher

mutagenicity measured by the Ames test compared with skinless chicken or chicken cooked with the skin but the skin discarded. For example, according to the National Cancer Institute's Charred Database, the actual mutagenicity of broiled, well-done chicken cooked with skin on and the skin consumed is approximately 3-fold greater than chicken cooked the same way but with the skin discarded (33). However, epidemiologic studies on HCAs and pros-

tate cancer are limited and inconsistent, perhaps due to the difficulty in accurately quantifying HCA exposure in large population-based studies and variability in metabolism of HCAs across individuals (6, 34–38).

Unprocessed and processed red meat

An international panel concluded there was limited evidence suggesting processed meat increases risk of prostate

Table 5. Postdiagnostic consumption of individual red meat and poultry items and relative hazard of lethal prostate cancer among 3,127 men diagnosed with clinically localized or regional prostate cancer (1994–2008)

	Servings/wk				P ^a
Unprocessed red meat items					
Hamburger ^b	<0.5	0.5–0.9	1–1.4	≥1.5	
Events	22	39	32	30	
Model 1 HR (95% CI) ^c	1.0	1.02 (0.60–1.72)	1.18 (0.68–2.05)	1.01 (0.57–1.80)	0.95
Model 2 HR (95% CI) ^d	1.0	0.92 (0.52–1.63)	0.97 (0.52–1.81)	0.76 (0.38–1.52)	0.41
Beef, lamb, pork (sandwich or mixed dish) ^e	<0.5	0.5–0.9	1–1.4	≥1.5	
Events	24	50	20	29	
Model 1 HR (95% CI) ^c	1.0	1.81 (1.10–2.98)	1.44 (0.77–2.66)	1.94 (1.09–3.47)	0.09
Model 2 HR (95% CI) ^d	1.0	2.08 (1.20–3.59)	1.74 (0.87–3.50)	2.21 (1.12–4.36)	0.14
Beef, lamb, pork (main dish) ^f	<1	1–1.4	1.5–2.4	≥2.5	
Events	42	20	32	29	
Model 1 HR (95% CI) ^c	1.0	0.60 (0.35–1.03)	0.81 (0.50–1.31)	1.18 (0.71–1.97)	0.23
Model 2 HR (95% CI) ^d	1.0	0.51 (0.29–0.92)	0.60 (0.34–1.04)	0.79 (0.43–1.46)	0.88
Processed red meat items					
Sausage/salami/bologna ^g	0	0.1–0.5	0.6–1.5	>1.5	
Events	25	35	32	31	
Model 1 HR (95% CI) ^c	1.0	1.33 (0.79–2.24)	1.77 (1.03–3.05)	1.76 (1.02–3.05)	0.06
Model 2 HR (95% CI) ^d	1.0	1.27 (0.72–2.22)	1.55 (0.84–2.88)	1.60 (0.83–3.06)	0.23
Bacon ^h	0	0.1–0.5	>0.5		
Events	39	36	48		
Model 1 HR (95% CI) ^c	1.0	1.06 (0.67–1.68)	1.50 (0.97–2.32)		0.07
Model 2 HR (95% CI) ^d	1.0	0.97 (0.58–1.60)	1.13 (0.66–1.93)		0.62
Hot dogs ⁱ	0	0.1–0.5	>0.5		
Events	41	49	33		
Model 1 HR (95% CI) ^c	1.0	1.11 (0.73–1.70)	1.39 (0.86–2.24)		0.19
Model 2 HR (95% CI) ^d	1.0	1.01 (0.64–1.62)	1.17 (0.68–2.02)		0.57
Poultry items					
Chicken or turkey without skin ^j	<1	1–1.4	1.5–2.4	≥2.5	
Events	55	13	28	27	
Model 1 HR (95% CI) ^c	1.0	0.54 (0.30–1.00)	0.94 (0.59–1.50)	0.90 (0.56–1.45)	0.97
Model 2 HR (95% CI) ^d	1.0	0.60 (0.32–1.12)	1.10 (0.67–1.82)	0.96 (0.57–1.62)	0.75
Chicken or turkey with skin ^k	0	0.1–0.5	0.6–1	>1	
Events	48	34	19	22	
Model 1 HR (95% CI) ^c	1.0	1.19 (0.76–1.86)	1.18 (0.69–2.02)	1.52 (0.91–2.55)	0.12
Model 2 HR (95% CI) ^d	1.0	1.16 (0.72–1.85)	1.29 (0.72–2.30)	1.36 (0.77–2.40)	0.27
Chicken or turkey sandwiches ^l	<0.5	0.5–0.9	1–1.4	≥1.5	
Events	22	36	23	30	
Model 1 HR (95% CI) ^c	1.0	1.18 (0.69–2.01)	1.44 (0.79–2.62)	1.31 (0.74–2.30)	0.45
Model 2 HR (95% CI) ^d	1.0	1.22 (0.70–2.10)	1.52 (0.81–2.84)	1.55 (0.85–2.85)	0.20

(Continued on the following page)

Table 5. Postdiagnostic consumption of individual red meat and poultry items and relative hazard of lethal prostate cancer among 3,127 men diagnosed with clinically localized or regional prostate cancer (1994–2008) (Cont'd)

	Servings/wk		P ^a
Chicken or turkey hot dogs ^m	0	>0	
Events	70	53	
Model 1 HR (95% CI) ^c	1.0	1.21 (0.84–1.75)	0.30
Model 2 HR (95% CI) ^d	1.0	1.22 (0.84–1.78)	0.30

^aCalculated using the median of each category as a continuous term.

^bOne serving = 1 hamburger patty.

^cModel 1 adjusted for age at diagnosis (continuous, y), time since diagnosis (continuous, y), and energy (quartiles, kcal/d).

^dModel 2 adjusted for covariates in Model 1 plus Gleason sum (<7, 7, ≥7), clinical T-stage (T1, T2, T3), primary treatment (radical prostatectomy, radiation, active surveillance/other, androgen deprivation therapy), BMI (<25, 25–29.9, ≥30 kg/m²), smoking (current, former, not current with unknown history, never), vigorous activity (quartiles, MET-h/wk), and quartile ranks of prediagnostic intake of the exposure of interest (except for chicken or turkey sandwiches). All unprocessed red meat items were adjusted for each other; all processed red meat items were adjusted for each other; and poultry items were adjusted for each other.

^eOne serving = 1 beef, pork, or lamb sandwich or 1 serving of a mixed dish (e.g., stew, casserole, lasagna, etc.).

^fOne serving = 113 to 170 g of beef, pork, or lamb as a main dish (e.g., ham, chops, steak, roast).

^gOne serving = 1 salami, bologna, or other processed meat sandwich or 57 g (approx. 2 links) of other processed meats (e.g., sausage, kielbasa, etc.).

^hOne serving = 2 slices of bacon.

ⁱOne serving = 1 beef or pork hot dog.

^jOne serving = 85 g of other chicken or turkey, without skin.

^kOne serving = 85 g of other chicken or turkey, with skin.

^lOne serving = 1 chicken or turkey sandwich. Chicken or turkey sandwiches were first asked about on the 1998 questionnaire; therefore, follow-up for this item started in 1998 (events = 111; 10,379 person-y) and we were unable to adjust for prediagnostic intake.

^mOne chicken or turkey hot dog. Chicken or turkey hot dogs were first asked about on the 1994 questionnaire; therefore, prediagnostic intake was estimated using data from the 1994 questionnaire.

cancer (39). Since that review, Sinha and colleagues reported approximately 30% increases in risk of advanced prostate cancer associated with high intakes of red and processed meat (6). Similar to our findings however, there was no statistically significant association with fatal prostate cancer (events = 419). A recent population-based case-control study also reported an increased risk of advanced, but not localized, prostate cancer associated with greater intake of hamburgers, processed meat, grilled red meat, and well-done red meat (40). However, a meta-analysis of prospective studies reported no association between red or processed meat and risk of advanced prostate cancer (41). These mixed results, combined with our findings, suggest that unprocessed red meat is not associated with an increased risk of lethal prostate cancer, and if any association exists between processed red meat and risk of lethal prostate cancer, it is likely modest.

Only 2 prior studies have examined red meat intake after prostate cancer diagnosis and risk of prostate cancer progression, including the previous report from this cohort. In CaPSURE, there was no statistically significant association between unprocessed or processed red meat intake after diagnosis and prostate cancer progression (5). Our findings support the conclusion of no association between total unprocessed red meat intake after diagnosis and risk of

lethal prostate cancer. However, we observed a positive association between postdiagnostic consumption of beef, pork, or lamb as sandwiches or mixed dishes, and a suggestive relation between sausage/salami/bologna after diagnosis, with risk of progression to lethal prostate cancer. The inconsistency in the findings for beef, pork, or lamb as sandwiches or mixed dishes compared with beef, pork, or lamb as main dishes suggests this finding may be due to chance. Alternatively, it is possible that participants incorrectly reported processed lunchmeats made from red meat as "beef pork or lamb as sandwiches or mixed dishes," and thus some misclassification of processed red meat intake may have occurred.

Processed red meats contain preformed *N*-nitroso compounds (NOC; ref. 42), as well as nitrites, nitrates, and heme iron (43), which can lead to endogenous formation of NOCs. NOC and heme iron cause oxidative damage to tissues (43), and NOCs are carcinogens in animal models (42). Moreover, Sinha and colleagues reported that heme iron and nitrate consumption were each associated with increased risk of advanced prostate cancer (6). However, the lack of consistency in our results for the total meat categories and the individual meat items suggests these findings may not be robust and caution is warranted in their interpretation.

Limitations

Limitations of this study include the small number of events of lethal prostate cancer in the PSA-era, particularly in the case-only survival analysis, and the low consumption of foods of interest in this study population. In general, the men in our study population consumed low amounts of the foods of interest for this analysis, which limited our statistical power to examine these exposures. Nonetheless, given our findings and those of CaPSURE, as well as the recommendations to limit intake of processed meats and poultry with skin for cardiovascular health, it may be prudent for men with prostate cancer to limit intake of these foods pending more definitive results. In addition, our study population was predominately Caucasian, and therefore our findings may not be generalizable to populations with different racial distributions. Strengths of our study include our detailed covariate information, completeness and duration of follow-up, and 6 repeated measures of diet using a validated questionnaire, all of which contribute to the internal validity of our results.

In conclusion, we observed a nearly 2-fold increased risk of lethal prostate among men who consumed higher amounts of eggs. Although our results are novel and addi-

tional large prospective studies are needed, caution in egg intake may be warranted for adult men.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

- Prostate. SEER stat fact sheets. 2010 November 2009 [cited 2011 March 14]. Available from: <http://seer.cancer.gov/statfacts/html/prost.html>.
- Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E. A prospective study on intake of animal products and risk of prostate cancer. *Cancer Causes Control* 2001;12:557-67.
- Chan JM, Holick CN, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, et al. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). *Cancer Causes Control* 2006;17:199-208.
- Meyer F, Bairati I, Shadmani R, Fradet Y, Moore L. Dietary fat and prostate cancer survival. *Cancer Causes Control* 1999;10:245-51.
- Richman EL, Stampfer MJ, Paciorek A, Broering JM, Carroll PR, Chan JM. Intakes of meat, fish, poultry, and eggs and risk of prostate cancer progression. *Am J Clin Nutr* 2010;91:712-21.
- Sinha R, Park Y, Graubard BI, Leitzmann MF, Hollenbeck A, Schatzkin A, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. *Am J Epidemiol* 2009;170:1165-77.
- Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology* 1996;7:81-6.
- Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc* 1993;93:790-6.
- Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. *Am J Epidemiol* 1984;119:837-9.
- Willett WC. *Nutritional epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
- Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. *Int J Cancer* 2007;121:1571-8.
- Kasper JS, Liu Y, Giovannucci E. Diabetes mellitus and risk of prostate cancer in the health professionals follow-up study. *Int J Cancer* 2009;124:1398-403.
- Rohrmann S, Platz EA, Kavanaugh CJ, Thuita L, Hoffman SC, Helzlsouer KJ. Meat and dairy consumption and subsequent risk of prostate cancer in a US cohort study. *Cancer Causes Control* 2007;18:41-50.
- Wilson KM, Kasperzyk JL, Rider JR, Kenfield S, van Dam RM, Stampfer MJ, et al. Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. *J Natl Cancer Inst* 2011;103:876-84.
- Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. *JAMA* 2011;305:2548-55.
- Murtola TJ, Tammela TL, Maattanen L, Huhtala H, Platz EA, Ala-Opas M, et al. Prostate cancer and PSA among statin users in the finnish prostate cancer screening trial. *Int J Cancer* 2010;127:1650-9.
- Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. *J Clin Oncol* 2005;23:8152-60.
- Snowdon DA, Phillips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. *Am J Epidemiol* 1984;120:244-50.
- Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, et al. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. *Cancer Res* 1990;50:6836-40.
- Schuerman AG, van den Brandt PA, Dorant E, Goldbohm RA. Animal products, calcium and protein and prostate cancer risk in The Netherlands Cohort Study. *Br J Cancer* 1999;80:1107-13.
- Johansson M, Van Guelpen B, Vollset SE, Hultdin J, Bergh A, Key T, et al. One-carbon metabolism and prostate cancer risk: prospective investigation of seven circulating B vitamins and metabolites. *Cancer Epidemiol Biomarkers Prev* 2009;18:1538-43.
- Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. *Int J Cancer* 2008;123:1693-8.
- Zeisel SH. Choline and brain development. In: Bowman BA, Russell RM, editors. *Present knowledge in nutrition*. 9th ed. Washington, DC: International Life Sciences Institute; 2006. p. 352-60.
- Apolo AB, Pandit-Taskar N, Morris MJ. Novel tracers and their development for the imaging of metastatic prostate cancer. *J Nucl Med* 2008;49:2031-41.

25. Glunde K, Ackerstaff E, Mori N, Jacobs MA, Bhujwala ZM. Choline phospholipid metabolism in cancer: consequences for molecular pharmaceutical interventions. *Mol Pharm* 2006;3:496–506.
26. Glunde K, Bhujwala ZM. Choline kinase alpha in cancer prognosis and treatment. *Lancet Oncol* 2007;8:855–7.
27. Freeman MR, Solomon KR. Cholesterol and prostate cancer. *J Cell Biochem* 2004;91:54–69.
28. Dillard PR, Lin MF, Khan SA. Androgen-independent prostate cancer cells acquire the complete steroidogenic potential of synthesizing testosterone from cholesterol. *Mol Cell Endocrinol* 2008;295:115–20.
29. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Fat and meat intake and prostate cancer risk: the multiethnic cohort study. *Int J Cancer* 2007;121:1339–45.
30. Zheng W, Lee SA. Well-done meat intake, heterocyclic amine exposure, and cancer risk. *Nutr Cancer* 2009;61:437–46.
31. Bogen KT, Keating GA. U.S. dietary exposures to heterocyclic amines. *J Expo Anal Environ Epidemiol* 2001;11:155–68.
32. Sinha R, Rothman N, Brown ED, Salmon CP, Knize MG, Swanson CA, et al. High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. *Cancer Res* 1995;55:4516–9.
33. National Cancer Institute. CHARRED: Computerized heterocyclic amines resource for research in epidemiology of disease. 2006 [cited 2011 March 2]. Available from: <http://dceg.cancer.gov/neb/tools/charred>.
34. Koutros S, Cross AJ, Sandler DP, Hoppin JA, Ma X, Zheng T, et al. Meat and meat mutagens and risk of prostate cancer in the Agricultural Health Study. *Cancer Epidemiol Biomarkers Prev* 2008;17:80–7.
35. Cross AJ, Peters U, Kirsh VA, Andriole GL, Reding D, Hayes RB, et al. A prospective study of meat and meat mutagens and prostate cancer risk. *Cancer Res* 2005;65:11779–84.
36. Sander A, Linseisen J, Rohrmann S. Intake of heterocyclic aromatic amines and the risk of prostate cancer in the EPIC-Heidelberg cohort. *Cancer Causes Control* 2011;22:109–14.
37. Sharma S, Cao X, Wilkens LR, Yamamoto J, Lum-Jones A, Henderson BE, et al. Well-done meat consumption, NAT1 and NAT2 acetylase genotypes and prostate cancer risk: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;19:1866–70.
38. Koutros S, Berndt SI, Sinha R, Ma X, Chatterjee N, Alavanja MC, et al. Xenobiotic metabolizing gene variants, dietary heterocyclic amine intake, and risk of prostate cancer. *Cancer Res* 2009;69:1877–84.
39. AICR/WCRF. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research/World Cancer Research Fund; 2007.
40. John EM, Stern MC, Sinha R, Koo J. Meat consumption, cooking practices, meat mutagens, and risk of prostate cancer. *Nutr Cancer* 2011;63:525–37.
41. Alexander DD, Mink PJ, Cushing CA, Scurman B. A review and meta-analysis of prospective studies of red and processed meat intake and prostate cancer. *Nutr J* 2010;9:50.
42. Lijinsky W. N-Nitroso compounds in the diet. *Mutat Res* 1999;443:129–38.
43. 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;68:562–4.