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Research Article

Cancer Prevention Research

Meat, Fish, Poultry, and Egg Intake at Diagnosis and Risk of Prostate Cancer Progression

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Abstract

Little information exists on diet and prostate cancer progression. We examined the association between intakes of total red meat, processed and unprocessed red meat, poultry, fish, and eggs and prostate cancer recurrence. We conducted a prospective study of 971 men treated with radical prostatectomy for prostate cancer between 2003 and 2010. Men completed a food frequency questionnaire at diagnosis. We used logistic regression to study the association between diet and high-grade or advanced-stage disease. We used Cox models to study the risk of progression [$N = 94$ events, mainly prostate-specific antigen (PSA) recurrence]. Total red meat intake was marginally associated with risk of high-grade disease [Gleason $\geq$ 4+3; adjusted OR top vs. bottom quartile: 1.66; 95% confidence interval (CI), 0.93–2.97; $P_{trend} = 0.05$], as was very high intake of eggs (OR top decile vs. bottom quartile: 1.98; 95% CI, 1.08–3.63, $P_{trend} = 0.08$). Well-done red meat was associated with advanced disease ($\geq$pT3; OR top vs. bottom quartile: 1.74, 95% CI, 1.05–2.90; $P_{trend} = 0.01$). Intakes of red meat, fish, and eggs were not associated with progression. Very high poultry intake was inversely associated with progression (HR top decile vs. bottom quartile: 0.19; 95% CI, 0.06–0.63; $P_{trend} = 0.02$). Substituting 30 g/d of poultry or fish for total or unprocessed red meat was associated with significantly lower risk of recurrence. Lower intakes of red meat and well-done red meat and higher intakes of poultry and fish are associated with lower risk of high grade and advanced prostate cancer and reduced recurrence risk, independent of stage and grade. *Cancer Prev Res; 9(12); 933–41. ©2016 AACR.*

Introduction

Patients with prostate cancer wonder whether lifestyle factors may alter their clinical course, yet there is little evidence to guide patients on the association between diet and the risk of prostate cancer progression after prostate cancer treatment. This is a critical question given that more than 2.7 million men currently live with prostate cancer in the United States, and approximately 181,000 new cases are expected to be diagnosed in 2016 (1, 2).

Studies of diet and risk of prostate cancer have been mixed, with few consistently identified risk factors. However, prediagnosis intake of processed or cured meat and lower intake of fish have both been associated with the incidence of more aggressive prostate cancer, suggesting that meat intake may play a role in the disease (3–10). Intake of these dietary factors and the risk of progression after cancer treatment have been examined in only a few studies. In a cohort of 1,294 men with localized prostate cancer, higher intakes at diagnosis of eggs and poultry with skin were associated with an increased risk of cancer progression, primarily defined as prostate-specific antigen (PSA) recurrence (11). A study in the Health Professionals Follow-up Study (HPFS) found greater fish intake *after* diagnosis was associated with lower risk of PSA recurrence (12). A later study in the same population found suggestive but not statistically significant associations between higher postdiagnosis intakes of poultry and processed red meat and cancer-specific survival (13).

Because of these suggestive but inconclusive results, we examined the association between intake of total red meat, processed (cured) and unprocessed (uncured) red meat, poultry, fish, and eggs with prostate cancer recurrence in a cohort of nearly 1,000 men with treated with radical prostatectomy for localized prostate cancer between 2003 and 2010.

Materials and Methods

Study population

Men in this study were participants in the Washington University Genetics Study, a cohort of men with biopsy-diagnosed prostate cancer treated at the Washington University School of Medicine in St. Louis between 2003 and 2010 (14). Men were invited to participate in the study at the time of prostate cancer diagnosis. Clinical details on diagnosis, initial treatment, and follow-up visits were collected from medical records. Upon enrollment in the study, after diagnosis, and prior to treatment, men completed a questionnaire with demographic, smoking, and health information along with a food frequency questionnaire (FFQ) initially developed for the National Cancer Institute-Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. This FFQ was modeled on

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3 commonly used and validated FFQs: the Block FFQ, the Willett FFQ, and the National Cancer Institute Diet History Questionnaire; however, the PLCO FFQ was not itself validated in the PLCO study (15–17).

Of 1,208 men enrolled in the study, 977 were treated with prostatectomy for clinical stage T1 or T2 disease and adequately completed the FFQ. Among these, we excluded 3 men missing pathologic stage, 2 men missing Gleason score, and 1 man with no follow-up after surgery, resulting in a population of 971 men for analysis of tumor stage and grade. For the survival analysis, we further focused the analysis on men with pathologic stage T3N0M0 or lower disease, resulting in a population of 940 men. This study was approved by the Institutional Review Boards at the Washington University School of Medicine and the Dana-Farber/Harvard Cancer Center (Boston, MA).

Dietary assessment

The FFQ assessed frequency of consumption of 137 individual food items, 77 with questions on usual portion size and frequency, over the year prior to diagnosis. Additional questions asked about cooking methods, including frequency of fried food consumption and doneness preferences for meats.

We assessed intake of 7 food groups: total red meat, unprocessed red meat, processed red meat (hot dogs, bacon, deli meats), fish, seafood (fish + shellfish), poultry, and eggs. Intake of each group was estimated in grams per day and included intake from mixed dishes. We further divided poultry and fish intake into grams per day of fried and non-fried poultry or fish. We also studied consumption specifically of rare/medium rare red meat and well/very well-done red meat.

Assessment of prostate cancer recurrence

Men were followed for disease progression through clinical records, either from continued care at Washington University, or through follow-up phone calls or mailings for men who opted for local care after their treatment. To assess biochemically recurrence, patients' charts were reviewed annually to determine whether patients experienced a PSA increase and/or received additional therapy. If patients did not return to Washington University, they were contacted by phone or mail annually, and relevant medical records were obtained from the patient's medical provider. Patients agreed to this ongoing monitoring as part of the initial study consent, and follow-up was 98% complete. Incorrect addresses were searched for each year, and a National Death Index search was done each year to check for deaths.

Disease recurrence was defined as the first occurrence of: 2 or more successive PSA values of 0.2 ng/mL or more, initiation of non-adjuvant treatment, or diagnosis of metastatic disease.

Statistical analysis

We calculated ORs and 95% confidence intervals (CI) using logistic regression models to assess the cross-sectional association between quartile of dietary intake and risk of high-grade disease or advanced-stage disease. High-grade disease was defined as pathologic Gleason grade of 4+3 or higher. Advanced-stage disease was defined as pathologic stage T3 or higher. Analysis of high-grade and advanced-stage disease includes men who were diagnosed with node-positive disease at surgery, even though these patients are not included in the recurrence analysis. "Age-adjusted models" are adjusted for age at diagnosis and energy intake. "Covariate-adjusted models" also included race, family history of prostate cancer, body mass index (BMI) at diagnosis (<25, 25–<27.5, 27.5–<30, 30–<35, ≥35 kg/m^2), smoking at diagnosis (never/former/current), vigorous physical activity (none, <1, 1, 2, 3, ≥4 h/wk), and intakes of total calcium (from foods plus supplements, quartiles), cooked tomato products (sum of tomato/vegetable soup, canned tomatoes, tomato/vegetable juice, tomato sauce, quartiles), and coffee (none, <1, 1, 2–3, ≥4 cups/d). These covariates were included because they have been associated with risk of fatal or advanced prostate cancer or with prostate cancer survival in the literature (18, 19). We also considered adjustment for several other dietary factors: supplemental calcium, supplemental selenium (from multivitamins), lycopene, saturated fat, monounsaturated fat, and polyunsaturated fat; these were not included in the final models, as they were not associated with the outcomes of interest and had no effect on the estimates for meat/poultry/fish/eggs. In addition, covariate-adjusted models are adjusted for clinical stage at diagnosis (T1 or T2); however, results were qualitatively similar for models with and without adjustment for clinical stage. Models for rare/medium rare and well/very well-done red meat intake are also adjusted for total red meat intake to simulate the effect of substituting red meat of one level of doneness for the other, holding total red meat intake constant.

We used Cox proportional hazards models to assess the association between quartile of dietary intake and risk of prostate cancer progression, presented as HRs and 95% CIs. Follow-up began on the date of surgery and ended at the time of disease recurrence or the date of the last follow-up visit. Models for recurrence were all adjusted for age at diagnosis and energy intake. "Covariate-adjusted models" are adjusted for the same variables as the advanced-stage and high-grade models. We also present results further adjusted for clinical characteristics: pathologic stage (T2, T3a, T3b), Gleason grade (6, 3+4, 4+3, 8–10), and PSA at diagnosis (0–4.0, 4.1–10.0, >10.0 units). Models for rare/medium and well/very well-done red meat were also adjusted for total red meat intake.

The modeling approach above estimates the effects of increasing intake of a given food group while holding total energy intake constant; thus it is the effect of substituting the food group in question for an equal number of calories from a nonspecified mix of other foods. To understand the effects of explicitly replacing one source of meat/protein with another, we estimated the impact of substituting 30 g/d (~1 ounce) of poultry or fish for 30 grams of red meat or eggs by including all food groups as continuous variables in the same multivariable Cox proportional hazards or logistic regression models (also adjusted for other confounders, including total energy intake). The difference in beta coefficients between the 2 food groups of interest was used to estimate the substitution associations, and the variances and covariance of the betas were used to estimate the 95% CIs.

Statistical tests were 2-sided with a significance level of 0.05. SAS (version 9.3) was used for all analyses.

Results

Characteristics of the full study population (N = 971) at diagnosis are shown in Table 1. Mean PSA at diagnosis was 5.9 ng/mL. The majority of men were diagnosed with clinical stage T1 disease (81%), with 19% of men cT2. Pathologic stage

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Table 1. Age-adjusted characteristics of the study population at diagnosis overall and by lowest and highest quartiles of food intakes

		Red meat		Processed meat		Poultry		Fish		Eggs	
	Full cohort	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**	**Q1**	**Q4**
N	971	242	243	242	243	232	250	236	244	175	357
Age at diagnosis, y	61	63	60	61	60	62	59	61	61	61	61
Follow-up time, y	3.1	3.0	2.9	3.1	2.9	2.9	3.0	3.0	3.0	3.2	2.8
White race, %	96	95	98	96	95	96	96	96	95	95	94
Current smokers, %	10	6	14	5	14	15	9	12	11	8	13
BMI, kg/m^2	28.7	27.5	29.8	27.4	29.2	28.6	29.1	28.6	28.7	27.5	29.3
BMI < 25, %	18	26	12	26	16	16	20	18	19	26	12
BMI 35+, %	8	6	11	5	8	7	12	7	10	3	9
Vigorous physical activity											
None, %	14%	10%	15%	9%	19%	19%	10%	20%	11%	11%	14%
≥4 h/wk, %	25%	33%	21%	31%	21%	24%	29%	21%	27%	29%	25%
Family history PCa, %	31	32	31	31	28	32	30	33	30	28	31
Dietary intakes (servings/wk except as noted)											
Red meat	4.1	1.8	6.8	2.7	5.3	3.5	4.5	4.1	4.0	3.4	4.5
Processed meat	2.8	1.3	4.4	1.1	5.1	2.7	2.8	3.2	2.7	1.6	3.7
Poultry	1.7	1.8	1.8	2.1	1.7	0.4	3.4	1.4	2.2	1.8	1.8
Fish	1.3	1.5	1.3	1.5	1.2	1.1	1.7	0.4	2.7	1.3	1.4
Eggs	1.6	1.3	2.2	1.3	1.8	1.3	1.8	1.6	1.8	0.2	3.2
Total calcium, mg/d	1077	973	1230	1006	1214	984	1239	1017	1212	932	1151
Tomatoes,[a] g/d	89	89	101	99	87	77	110	72	121	82	94
Coffee, cups/d	1.6	1.6	1.6	1.5	1.6	1.8	1.6	1.6	1.8	1.7	1.7
Disease characteristics											
PSA	6.2	6.4	6.4	6.2	6.4	6.4	6.0	6.5	6.1	5.6	6.4
Gleason grade, %											
8–10	8	5	11	5	12	7	8	7	7	4	8
4+3	11	13	15	12	9	13	12	12	12	9	12
3+4	41	40	37	36	37	38	39	42	43	38	41
6	40	42	37	47	43	43	40	39	38	48	39
Clinical stage, %											
T1	80	79	79	81	79	81	82	78	75	81	82
T2	20	21	21	19	21	19	18	22	25	19	18
Pathologic stage, %											
T2	75	76	72	75	75	75	76	73	79	80	73
T3a	16	15	17	16	15	18	14	19	14	16	18
T3b	5	6	8	5	6	4	7	5	4	2	7
T4/N1	4	3	3	4	4	3	3	3	3	2	2

NOTE: Values shown are means or percentages. All variables except age at diagnosis have been standardized to the age distribution of the entire study population.

Abbreviation: PCa, prostate cancer.

[a]Cooked tomato products: sum of tomato/vegetable soup, canned tomatoes, tomato/vegetable juice, and tomato sauce.

distribution was: 78% T2, 17% T3a, and 6% T3b. Gleason grade from prostatectomy was 8 to 10 in 6% of men, 4+3 in 11%, 3+4 in 42%, and 6 in 41%. Median follow-up time of the cohort was 3.0 years (range, 1 month to 7 years and 8 months). For the analysis of disease recurrence among 940 men (2,933.9 person-years) with stage T3 or lower disease, we identified 94 recurrence events (10%). Of these, 79 were based on PSA increase, 12 on initiation of new treatment, and 3 on diagnosis of metastatic disease. Of those with a recurrence, 13 developed metastatic disease during the follow-up period.

Characteristics of the study population for the lowest and highest quartile of consumers for each food group are also shown in Table 1. Consumption of red meat, processed meat, and eggs was positively correlated. Higher fish consumption was associated with somewhat lower processed meat intake and somewhat higher poultry intake. Higher red meat consumption was associated with greater current smoking. Higher consumption of red meat, processed meat, and eggs were all associated with higher BMI. Higher red and processed meat consumption was associated with lower levels of vigorous physical activity, whereas poultry and fish consumption was associated with higher activity. Energy intake and total calcium intake was positively associated with consumption of all food groups. Higher poultry, fish, and egg consumption was associated with greater intake of cooked tomato products. Men who consumed more poultry and fish had somewhat lower PSA levels at diagnosis, whereas men who consumed more eggs had somewhat higher levels. (Table 1) Men with higher red meat, processed meat, and egg intakes were more likely to be diagnosed with high grade (Gleason 8–10) disease. In addition, men with higher egg intake were more likely to have pathologic stage T3 disease and less likely to have T2 disease.

Associations between food groups and risk of high-grade prostate cancer (Gleason 4+3 and higher) are presented in Table 2. Higher intake of total red meat was marginally associated with greater risk of high-grade disease. This association was due mainly to intakes of unprocessed red meat and not to processed red meat. In addition, intake of well and very well-done meat was marginally associated with greater risk of high-grade disease, given a constant intake of total red meat. There was a suggestion of an increased risk for high-grade disease in the highest quartile of egg intake. When the top 10% of egg consumption was compared to the bottom quartile, the OR for high-grade disease was significantly elevated, although

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Table 2. Risk of high-grade prostate cancer—Gleason 4+3 and higher—(ORs and 95% CIs) by quartile of dietary intake among 971 men in the Washington University Genetics Study

	Quartile of intake				
	Q1	Q2	Q3	Q4	P_{trend}
Total red meat, median, g/d	39	70	109	180	
N events/N participants	44/242	39/243	44/243	57/243	
Age-adjusted	1.00	0.92 (0.57–1.49)	1.13 (0.69–1.85)	1.62 (0.96–2.76)	0.04
Covariate-adjusted	1.00	0.94 (0.57–1.55)	1.14 (0.68–1.93)	1.66 (0.93–2.97)	0.05
Unproc red meat (Median)	26	52	83	142	
N events/N participants	40/242	42/243	48/243	54/243	
Age-adjusted	1.00	1.09 (0.68–1.76)	1.41 (0.86–2.29)	1.65 (0.97–2.78)	0.05
Covariate-adjusted	1.00	1.08 (0.66–1.79)	1.32 (0.79–2.20)	1.60 (0.91–2.83)	0.09
Processed meat (Median)	3	8	17	36	
N events/N participants	43/242	41/243	52/243	48/243	
Age-adjusted	1.00	0.93 (0.58–1.49)	1.22 (0.77–1.93)	1.11 (0.68–1.81)	0.54
Covariate-adjusted	1.00	0.88 (0.53–1.46)	1.24 (0.76–2.02)	1.21 (0.71–2.06)	0.31
Rare/Medium rare red meat	0	10	27	61	
N events/N participants	47/247	38/221	48/268	51/235	
Age-adjusted	1.00	0.90 (0.56–1.45)	0.94 (0.59–1.48)	1.23 (0.73–2.08)	0.37
Covariate-adjusted	1.00	0.81 (0.49–1.34)	0.86 (0.53–1.40)	1.23 (0.70–2.16)	0.35
Well/Very well-done red meat	3	9	18	45	
N events/N participants	33/243	41/242	54/242	56/244	
Age-adjusted	1.00	1.26 (0.76–2.09)	1.78 (1.09–2.91)	1.76 (1.04–2.98)	0.05
Covariate-adjusted	1.00	1.16 (0.68–1.97)	1.73 (1.04–2.90)	1.72 (0.99–3.01)	0.06
Poultry (Median)	5	13	23	49	
N events/N participants	46/232	43/250	45/239	50/250	
Age-adjusted	1.00	0.83 (0.52–1.31)	1.02 (0.64–1.63)	1.07 (0.66–1.73)	0.53
Covariate-adjusted	1.00	0.77 (0.47–1.25)	0.91 (0.55–1.50)	1.00 (0.60–1.66)	0.67
Fried poultry	0	1	6	12	
N events/N participants	22/121	65/363	42/226	55/261	
Age-adjusted	1.00	0.96 (0.56–1.65)	0.99 (0.55–1.76)	1.11 (0.63–1.96)	0.52
Covariate-adjusted	1.00	1.05 (0.60–1.84)	0.91 (0.50–1.68)	1.15 (0.63–2.09)	0.64
Not fried poultry	1	6	11	35	
N events/N participants	34/153	48/327	43/172	59/319	
Age-adjusted	1.00	0.63 (0.38–1.02)	1.27 (0.75–2.15)	0.86 (0.52–1.41)	0.90
Covariate-adjusted	1.00	0.57 (0.34–0.96)	1.09 (0.62–1.92)	0.76 (0.44–1.30)	0.88
Fish (Median)	5	13	25	50	
N events/N participants	42/236	50/248	47/243	45/244	
Age-adjusted	1.00	1.16 (0.73–1.83)	1.07 (0.67–1.71)	0.97 (0.60–1.57)	0.70
Covariate-adjusted	1.00	1.24 (0.77–2.03)	1.11 (0.68–1.82)	0.83 (0.50–1.38)	0.25
Fried fish	0	2	5	17	
N events/N participants	28/186	36/194	69/332	51/259	
Age-adjusted	1.00	1.20 (0.70–2.07)	1.37 (0.84–2.23)	1.21 (0.72–2.04)	0.77
Covariate-adjusted	1.00	1.19 (0.67–2.11)	1.42 (0.85–2.38)	1.12 (0.65–1.94)	0.89
Not fried fish	0	2	4	16	
N events/N participants	40/196	36/178	42/222	66/375	
Age-adjusted	1.00	0.98 (0.59–1.63)	0.95 (0.58–1.54)	0.84 (0.54–1.30)	0.37
Covariate-adjusted	1.00	0.94 (0.55–1.61)	0.93 (0.55–1.57)	0.77 (0.47–1.24)	0.23
Eggs (Median)	3	7	12	39	
N events/N participants	25/175	37/198	47/241	75/357	
Age-adjusted	1.00	1.38 (0.79–2.42)	1.50 (0.87–2.58)	1.53 (0.92–2.55)	0.27
Covariate-adjusted	1.00	1.44 (0.81–2.59)	1.37 (0.78–2.40)	1.53 (0.89–2.63)	0.28

NOTE: Age-adjusted models adjusted for age at diagnosis and total energy intake. Covariate-adjusted models additionally adjusted for: race, family history of prostate cancer, BMI (5 categories), smoking (never/former/current), vigorous physical activity (6 categories), total calcium intake (quartiles), cooked tomato products intake (quartiles), coffee intake (5 categories), and clinical stage (T1, T2). Models for red meat by doneness also adjust for total red meat intake.

the *P* value for the trend across categories was not significant (OR, 1.98; 95% CI, 1.08–3.63, $P_{trend} = 0.08$).

Diagnosis of advanced-stage disease (pT3 and higher, Table 3) was not associated with intake of any of the meat groups. However, higher intake of well/very well-done meat, substituted for rare/medium rare red meat, was associated with a greater risk of advanced disease.

Intake of total red meat, unprocessed red meat, processed red meat, poultry, fish, and eggs was not associated with risk of prostate cancer recurrence. (Table 4) Relative risk estimates were generally similar for the multivariable-adjusted models and the models with additional adjustment for stage, grade, and PSA at diagnosis for red meat, poultry, and fish. However, adjusting for clinical characteristics greatly attenuated the association between higher egg intake and risk of recurrence, reflecting that the highest egg consumers had worse disease characteristics at diagnosis, as suggested by Table 1. While not significant, intake of fried poultry, fried fish, and rare or medium red meat were positively associated with risk of recurrence, and intake of non-fried poultry, non-fried fish, and well-done or very well-done red meat was inversely associated with risk of recurrence.

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Table 3. Risk of advanced stage prostate cancer—pT3 and higher—(ORs and 95% CIs) by quartile of dietary intake among 971 men in the Washington University Genetics Study

	Quartile of intake				
	Q1	Q2	Q3	Q4	P_{trend}
Total red meat, median, g/d	39	70	109	180	
N events/N participants	50/242	54/243	48/243	57/243	
Age-adjusted	1.00	1.14 (0.74–1.77)	1.02 (0.64–1.62)	1.30 (0.78–2.16)	0.38
Covariate-adjusted	1.00	1.10 (0.70–1.73)	0.99 (0.61–1.62)	1.23 (0.71–2.14)	0.51
Unproc red meat (Median)	26	52	83	142	
N events/N participants	44/242	58/243	54/243	53/243	
Age-adjusted	1.00	1.44 (0.93–2.24)	1.38 (0.87–2.20)	1.35 (0.81–2.25)	0.40
Covariate-adjusted	1.00	1.36 (0.86–2.15)	1.31 (0.81–2.13)	1.25 (0.73–2.15)	0.60
Processed meat (Median)	3	8	17	36	
N events/N participants	50/242	54/243	54/243	51/243	
Age-adjusted	1.00	1.09 (0.71–1.69)	1.08 (0.70–1.68)	1.02 (0.64–1.62)	0.95
Covariate-adjusted	1.00	0.97 (0.61–1.53)	1.10 (0.69–1.75)	0.96 (0.58–1.58)	0.91
Rare/Medium rare red meat	0	10	27	61	
N events/N participants	45/247	57/221	57/268	50/235	
Age-adjusted	1.00	1.58 (1.01–2.47)	1.18 (0.75–1.84)	1.11 (0.66–1.87)	0.92
Covariate-adjusted	1.00	1.60 (1.01–2.55)	1.14 (0.72–1.81)	1.06 (0.61–1.84)	0.76
Well/Very well-done red meat	3	9	18	45	
N events/N participants	42/243	46/242	57/242	64/244	
Age-adjusted	1.00	1.12 (0.70–1.80)	1.48 (0.94–2.34)	1.71 (1.05–2.79)	0.02
Covariate-adjusted	1.00	1.00 (0.61–1.63)	1.34 (0.83–2.15)	1.74 (1.05–2.90)	0.01
Poultry (Median)	5	13	23	49	
N events/N participants	51/232	56/250	53/239	49/250	
Age-adjusted	1.00	1.02 (0.66–1.57)	1.05 (0.67–1.65)	0.89 (0.56–1.42)	0.56
Covariate-adjusted	1.00	1.08 (0.69–1.68)	1.08 (0.68–1.72)	0.94 (0.57–1.53)	0.67
Fried Poultry	0	1	6	12	
N events/N participants	25/121	81/363	38/226	65/261	
Age-adjusted	1.00	1.09 (0.66–1.81)	0.77 (0.44–1.35)	1.26 (0.74–2.15)	0.43
Covariate-adjusted	1.00	1.14 (0.68–1.93)	0.72 (0.40–1.29)	1.29 (0.73–2.26)	0.47
Not fried poultry	1	6	11	35	
N events/N participants	34/153	69/327	39/172	67/319	
Age-adjusted	1.00	0.96 (0.60–1.54)	1.08 (0.64–1.83)	0.99 (0.61–1.60)	0.97
Covariate-adjusted	1.00	0.98 (0.60–1.61)	1.09 (0.62–1.90)	1.06 (0.63–1.77)	0.79
Fish (Median)	5	13	25	50	
N events/N participants	55/236	51/248	59/243	44/244	
Age-adjusted	1.00	0.85 (0.55–1.30)	1.04 (0.68–1.58)	0.70 (0.44–1.10)	0.17
Covariate-adjusted	1.00	0.92 (0.59–1.45)	1.04 (0.67–1.63)	0.64 (0.40–1.03)	0.07
Fried fish	0	2	5	17	
N events/N participants	42/186	35/194	73/332	59/259	
Age-adjusted	1.00	0.73 (0.44–1.20)	0.93 (0.60–1.44)	0.96 (0.60–1.52)	0.69
Covariate-adjusted	1.00	0.68 (0.40–1.16)	0.91 (0.58–1.44)	0.87 (0.53–1.41)	0.98
Not fried fish	0	2	4	16	
N events/N participants	47/196	34/178	44/222	84/375	
Age-adjusted	1.00	0.75 (0.45–1.23)	0.80 (0.50–1.28)	0.92 (0.61–1.39)	0.71
Covariate-adjusted	1.00	0.73 (0.43–1.23)	0.77 (0.47–1.26)	0.94 (0.60–1.46)	0.58
Eggs (Median)	3	7	12	39	
N events/N participants	32/175	36/198	54/241	87/357	
Age-adjusted	1.00	1.01 (0.59–1.71)	1.34 (0.81–2.19)	1.45 (0.91–2.32)	0.08
Covariate-adjusted	1.00	0.92 (0.53–1.59)	1.23 (0.74–2.05)	1.32 (0.81–2.14)	0.16

NOTE: Age-adjusted models adjusted for age at diagnosis and total energy intake. Covariate adjusted models additionally adjusted for: race, family history of prostate cancer, BMI (5 categories), smoking (never/former/current), vigorous physical activity (6 categories), total calcium intake (quartiles), cooked tomato products intake (quartiles), coffee intake (5 categories), and clinical stage (T1, T2). Models for red meat by doneness also adjust for total red meat intake.

To assess very high intakes of each food group, we looked at relative risk of recurrence in the top decile compared with the lowest quartile. The top decile of poultry consumers (≥60 g/d) had a significantly lower risk of recurrence in multivariable models (HR, 0.29; 95% CI, 0.10–0.88; $P_{trend} = 0.07$), which was strengthened with adjustment for clinical characteristics (HR, 0.19; 95% CI, 0.06–0.63; $P_{trend} = 0.02$). There was a suggestion of increased risk for the top 10% of egg consumers (≥42 g/d; HR, 1.71; 95% CI, 0.80–3.64; $P_{trend} = 0.11$); however, this was again greatly attenuated with adjusted for clinical characteristics (HR, 0.98; 95% CI, 0.43–2.21; $P_{trend} = 0.43$). Results for the top decile of intake for other food groups were in line with the quartile results and were not statistically significant.

To assess the impact of substituting red meat or eggs in the diet with poultry or fish, we modeled the association of the food groups simultaneously while adjusting for total energy intake. Results are shown in Fig. 1. Replacing 30 g/d of total red meat with 30 grams of poultry or fish was associated with a significantly lower risk of recurrence (HR, 0.79; 95% CI, 0.66–0.94). This association was seen for unprocessed red meat (HR, 0.76; 95% CI, 0.63–0.92) but not for processed red meat (HR, 1.05; 95% CI, 0.67–1.64). Replacing eggs in the diet with poultry

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Table 4. Risk of prostate cancer recurrence (HR and 95% CI) by quartile of dietary intake among 940 men with localized disease in the Washington University Genetics Study

	Quartile of intake				
	Q1	**Q2**	**Q3**	**Q4**	P_{trend}
Total red meat, median, g/d	39	70	109	180	
N events/N participants	23/235	18/238	21/231	32/236	
Age-adjusted	1.00	0.74 (0.40–1.37)	0.80 (0.43–1.48)	1.11 (0.59–2.09)	0.49
Covariate-adjusted	1.00	0.66 (0.35–1.25)	0.69 (0.36–1.33)	0.90 (0.45–1.80)	0.89
+ adjusted for stage, grade, PSA	1.00	0.64 (0.33–1.25)	0.84 (0.43–1.64)	0.89 (0.45–1.76)	0.94
Unprocessed red meat	26	52	83	142	
N events/N participants	17/235	23/237	20/232	34/236	
Age-adjusted	1.00	1.33 (0.71–2.49)	1.10 (0.56–2.14)	1.76 (0.92–3.37)	0.09
Covariate-adjusted	1.00	1.24 (0.65–2.34)	1.02 (0.51–2.03)	1.66 (0.84–3.31)	0.14
+ adjusted for stage, grade, PSA	1.00	1.15 (0.58–2.27)	0.97 (0.48–1.97)	1.63 (0.81–3.27)	0.14
Processed red meat	3	8	17	36	
N events/N participants	23/232	20/236	23/239	28/233	
Age-adjusted	1.00	0.84 (0.46–1.53)	0.86 (0.48–1.55)	1.04 (0.48–1.88)	0.67
Covariate-adjusted	1.00	0.76 (0.41–1.42)	0.78 (0.43–1.44)	0.89 (0.48–1.66)	0.99
+ adjusted for stage, grade, PSA	1.00	0.79 (0.39–1.57)	0.81 (0.43–1.54)	0.86 (0.42–1.73)	0.87
Rare/Medium rare red meat	0	10	27	61	
N events/N participants	15/236	23/217	29/259	27/228	
Age-adjusted	1.00	1.77 (0.92–3.40)	1.72 (0.92–3.21)	1.70 (0.89–3.25)	0.27
Covariate-adjusted	1.00	1.84 (0.94–3.60)	1.59 (0.83–3.06)	1.30 (0.61–2.74)	0.89
+ adjusted for stage, grade, PSA	1.00	1.97 (0.97–4.00)	1.63 (0.83–3.22)	1.52 (0.70–3.27)	0.61
Well/Very well-done red meat	3	9	18	45	
N events/N participants	23/238	18/236	26/232	27/234	
Age-adjusted	1.00	0.75 (0.41–1.40)	1.05 (0.60–1.84)	1.01 (0.57–1.81)	0.67
Covariate-adjusted	1.00	0.65 (0.34–1.24)	0.88 (0.49–1.58)	0.84 (0.45–1.57)	0.97
+ adjusted for stage, grade, PSA	1.00	0.55 (0.29–1.08)	0.55 (0.30–1.04)	0.57 (0.28–1.15)	0.38
Poultry	5	13	23	49	
N events/N participants	22/224	22/243	28/231	22/242	
Age-adjusted	1.00	0.85 (0.47–1.54)	1.14 (0.65–2.03)	0.77 (0.41–1.42)	0.44
Covariate-adjusted	1.00	0.88 (0.48–1.60)	1.23 (0.68–2.23)	0.79 (0.41–1.52)	0.50
+ adjusted for stage, grade, PSA	1.00	0.98 (0.53–1.82)	1.18 (0.63–2.22)	0.80 (0.40–1.59)	0.27
Fried poultry	0	1	6	12	
N events/N participants	10/116	33/356	15/214	36/254	
Age-adjusted	1.00	1.04 (0.51–2.12)	0.71 (0.32–1.58)	1.45 (0.71–2.97)	0.15
Covariate adjusted	1.00	1.00 (0.49–2.07)	0.58 (0.26–1.34)	1.29 (0.61–2.73)	0.28
+ adjusted for stage, grade, PSA	1.00	1.09 (0.51–2.34)	0.67 (0.28–1.61)	1.29 (0.59–2.82)	0.45
Not fried poultry	1	6	11	35	
N events/N participants	16/147	29/316	21/165	28/312	
Age-adjusted	1.00	0.75 (0.41–1.39)	1.10 (0.57–2.13)	0.68 (0.36–1.28)	0.27
Covariate-adjusted	1.00	0.79 (0.42–1.49)	1.22 (0.61–2.45)	0.76 (0.39–1.48)	0.42
+ adjusted for stage, grade, PSA	1.00	0.79 (0.41–1.52)	0.89 (0.43–1.85)	0.71 (0.36–1.40)	0.40
Fish	5	13	25	50	
N events/N participants	22/228	24/241	28/234	20/237	
Age-adjusted	1.00	1.02 (0.57–1.82)	1.18 (0.67–2.06)	0.74 (0.40–1.36)	0.29
Covariate-adjusted	1.00	1.10 (0.61–1.99)	1.38 (0.77–2.46)	0.84 (0.45–1.58)	0.55
+ adjusted for stage, grade, PSA	1.00	0.93 (0.50–1.74)	0.94 (0.51–1.72)	0.83 (0.43–1.63)	0.61
Fried fish	0	2	5	17	
N events/N participants	10/181	19/188	35/322	30/249	
Age-adjusted	1.00	1.90 (0.88–4.08)	1.93 (0.95–3.91)	1.98 (0.96–4.11)	0.26
Covariate-adjusted	1.00	1.73 (0.79–3.79)	1.87 (0.91–3.85)	1.82 (0.87–3.82)	0.37
+ adjusted for stage, grade, PSA	1.00	1.72 (0.76–3.89)	1.59 (0.76–3.35)	1.49 (0.70–3.21)	0.76
Not fried fish	0	2	4	16	
N events/N participants	23/189	17/170	21/216	33/365	
Age-adjusted	1.00	0.75 (0.40–1.41)	0.78 (0.43–1.40)	0.70 (0.41–1.20)	0.34
Covariate-adjusted	1.00	0.77 (0.40–1.46)	0.83 (0.44–1.54)	0.86 (0.48–1.52)	0.90
+ adjusted for stage, grade, PSA	1.00	0.77 (0.39–1.52)	0.68 (0.35–1.29)	0.78 (0.44–1.40)	0.75
Eggs	3	7	12	39	
N events/N participants	11/171	16/188	26/235	41/346	
Age-adjusted	1.00	1.18 (0.55–2.56)	1.59 (0.78–3.23)	1.69 (0.85–3.35)	0.15
Covariate-adjusted	1.00	0.99 (0.45–2.18)	1.37 (0.67–2.84)	1.46 (0.72–2.94)	0.22
+ adjusted for stage, grade, PSA	1.00	0.63 (0.27–1.47)	0.91 (0.43–1.92)	0.96 (0.45–2.03)	0.44

NOTE: Age-adjusted models adjusted for age at diagnosis and daily energy intake. Covariate adjusted models additionally adjusted for: race, family history of prostate cancer, BMI (5 categories), smoking (never/former/current), vigorous physical activity (6 categories), total calcium intake (quartiles), cooked tomato products intake (quartiles), and coffee intake (5 categories). + adjusted for stage, grade, PSA models are covariate adjusted models with additional adjustment for pathologic stage (T2, T3a, T3b), Gleason sum (2–6, 3+4, 4+3, 8–10), and PSA at diagnosis (0–4.0, 4.1–10.0, ≥10.1)

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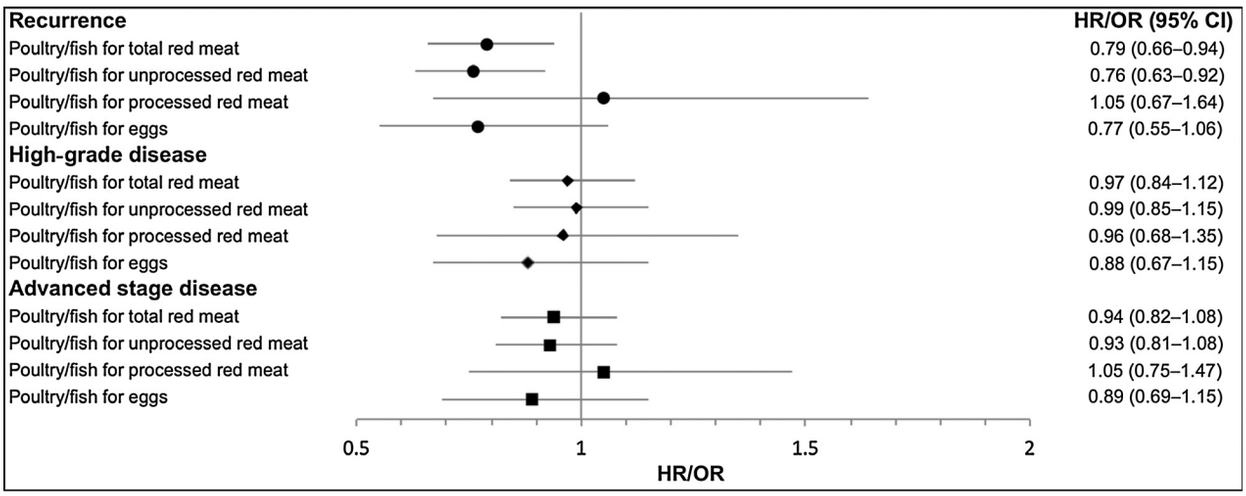

[1]Results for recurrence are adjusted for age, race, family history of prostate cancer, BMI, smoking, vigorous physical activity, intakes of total energy, total calcium, coffee, and cooked tomato products, and pathologic stage, grade, and PSA at diagnosis. Results for high grade and advanced stage disease are adjusted for race, family history of prostate cancer, BMI, smoking, vigorous physical activity, intakes of total energy, total calcium, coffee, and cooked tomato products, and clinical stage.

[2]High-grade disease was defined as pathologic Gleason grade of 4+3 or higher.

[3]Advanced stage disease was defined as pathologic stage T3 or higher.

Figure 1.

HR[1] for recurrence and OR for high-grade[2] or advanced-stage[3] prostate cancer (and 95% CIs) associated with substituting 30 g/d of poultry or fish for 30 g/d of red meat or eggs among men in the Washington University Genetics Study.

or fish was associated with a nonstatistically significant lower risk of recurrence (HR, 0.77; 95% CI, 0.55–1.06). Similar associations were seen for replacing these foods with only poultry, whereas associations were weaker when the foods were replaced only with fish (data not shown). Replacing red meat or eggs with poultry or fish was not associated with risk of high-grade or advanced-stage disease. There was a suggestion of a lower risk of advanced-stage disease when replacing total red meat, unprocessed red meat, or eggs with fish alone (HR, 0.86; 95% CI, 0.70–1.06 for total red meat; HR, 0.86; 95% CI, 0.69–1.06 for unprocessed red meat; HR, 0.82; 95% CI, 0.61–1.11 for eggs).

Discussion

In this study of 971 men diagnosed with prostate cancer and treated with prostatectomy, higher intake of total red meat was marginally associated with greater risk of high-grade disease, mainly due to unprocessed red meat intake. Intake of well/very well-done meat was also associated with high-grade disease and with higher stage at diagnosis. Very high intake of eggs ($\geq$42 g/d; 1 large egg without shell is approximately 50 g) was associated with likelihood of high-grade disease.

Intake of total red meat, unprocessed red meat, processed red meat, fish, and eggs was not associated with risk of prostate cancer recurrence. There was some evidence that very high intakes of poultry—60 or more g/d—were associated with lower risk, and replacing 30 g/d of unprocessed red meat with 30 grams of poultry or fish was associated with a significantly lower risk of recurrence.

Few studies have looked at diet at the time of, or after, diagnosis and risk of prostate cancer recurrence or mortality. The Cancer of the Prostate Strategic Urologic Research Endeavor (CapSURE) found an increased risk of recurrence for higher intakes of eggs and poultry with skin around the time of diagnosis (11). HPFS found a reduced risk of PSA recurrence with higher postdiagnosis intake of fish (12). A more recent HPFS study found a suggestion of increased risk of prostate cancer mortality among patients with prostate cancer with higher postdiagnosis intake of both poultry and processed red meat (13).

We found a suggestive positive association with progression after radical prostatectomy for egg consumption, but it was not independent of stage and grade at diagnosis. We did find that very high egg intake was associated with increased risk of high-grade disease. Differences in the study populations between our cohort and the CapSURE cohort might explain the differences regarding egg intake to some extent. Egg intake in CapSURE was higher, with a mean of 7.9 servings per week in the top quartile of intake compared to 3.2 servings per week in our population. In addition, our population had greater numbers of men with grade 8–10 cancer. It is possible that higher egg intake is differentially associated with PSA screening and lifestyle factors in different parts of the country, so differences in the extent of residual confounding after adjustment for covariates may play a role.

In contrast to CapSURE and HPFS, we did not find evidence of a positive association between poultry intake and risk of recurrence. In fact, we observed a significant inverse association for very high poultry intake, and this finding was supported by the results of our substitution models, which found significantly lower risk of recurrence with substitution of poultry or fish for total red meat, unprocessed red meat, or eggs. The poultry associations in those studies were driven by poultry with skin, with no associations observed for poultry without skin. We did not have data on poultry according to skin, so we

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could not examine this question. We did see a suggestion of a positive association for fried poultry and an inverse association for non-fried poultry and recurrence, possibly indicating that the method of preparing poultry could influence risk of aggressive disease.

Two cohort studies (10, 20) found inverse associations between prediagnosis fish intake and prostate cancer–specific mortality among patients with prostate cancer, and HPFS found an inverse association with PSA recurrence (12). However, CapSURE and this cohort observed no significant associations between fish intake and PSA recurrence. This may be due to differences between populations in the types of fish consumed or in preparation methods; dark fish may have more protective effects than white fish, and frying of fish along with the oils used for frying, may play a role. The FFQ in this study assessed fried versus non-fried fish but did not include detail on type of fish consumed, so we were unable to investigate specifically dark fish intake. In addition, our wide confidence interval for higher fish intakes cannot rule out a notable inverse association.

We found no association between processed red meat and recurrence, which is in line with CapSURE, but in contrast to HPFS. Our observed associations for total red meat with high-grade disease and with recurrence in the substitution models were driven by unprocessed rather than processed red meat intake. We also found a significant positive association between well-done and very well-done red meat and risk of high-grade and advanced-stage disease at diagnosis. This was independent of total red meat intake, suggesting that shifting a given intake of red meat from less done to more done is associated with worse stage and grade.

The findings for well-done and very well-done red meat along with those for fried compared with non-fried chicken support previous work on the doneness of meat and related cooking carcinogens and incidence of prostate cancer (9, 21–26). Heterocyclic amines and polycyclic aromatic hydrocarbons, 2 classes of carcinogenic compounds formed during high-heat cooking of meats, including both red meat and poultry, have been suggested as causes of prostate and other cancers (27, 28). Intake of these compounds is difficult to measure in epidemiologic studies (29), but the hypothesis is supported by various lines of laboratory evidence (28). To our knowledge, doneness of meat has not previously been studied with respect to recurrence among patients with prostate cancer.

Our substitution model results support replacement of red meat and eggs in the diet with poultry or fish. These results are in line with a recent study in the Physicians' Health Study linking a postdiagnosis Western dietary pattern, characterized by higher intake of processed and red meats, high-fat dairy, and refined grains, with higher prostate cancer–specific and total mortality (30). The substitution modeling approach is useful for shaping dietary advice, as the effect of increasing intake of a given food or nutrient can depend on what food or nutrient it replaces (31), and it gives concrete guidance to patients. In addition, it facilitates comparisons between different study populations, as the results of standard models will depend on the typical diet in a population, but the effects of specific substitutions should be comparable even when overall diet composition varies.

Limitations of our study include lack of information on prediagnostic PSA screening, allowing for possible confounding by PSA screening behavior, which is generally associated with more healthy behaviors. We attempted to control for differences in screening to some extent by adjusting for clinical stage T1 versus T2, as most PSA-detected disease with be T1 among men with ongoing screening. However, there is still a possibility of residual confounding by screening.

The use of PSA recurrence as an outcome may also be a limitation. While PSA recurrence is a highly clinically relevant event for men with prostate cancer, many men with PSA recurrence do not experience clinical progression to metastases or prostate cancer–specific death. In this population of men diagnosed with localized disease, only 3 men had progressed to metastatic disease during this follow-up period, so we are unable to study metastatic or fatal disease as an outcome. In addition, we have only a single diet assessment taken at the time of diagnosis, and it is possible that men changed their diet after treatment. The study population is almost entirely white, limiting generalizability. Finally, the follow-up of an average of 3 years is short, and as a result, we had a limited number of PSA recurrence events. Because of this, we had relatively low power to detect associations, which may explain some of our null findings. Strengths of the study include its prospective design, comprehensive FFQ, and availability of clinical and follow-up data from a single treatment center.

In conclusion, our findings support advising men with prostate cancer to replace red meat and eggs in the diet with poultry or fish. This is associated with reduced risk of recurrence independent of stage and grade at diagnosis and is consistent with previous findings on diet and prostate cancer survivorship. While it is unknown if post diagnosis alterations in diet are associated with altered progression, this study raises the possibility that substitution of poultry or fish for red meat and eggs could decrease progression in men surgically treated for prostate cancer. In addition, this is reasonable advice more broadly, given associations between red meat and saturated fat intake and total mortality and heart disease (31–33). Additional studies with longer term follow-up for prostate cancer survival and information on changes in diet after diagnosis are needed to further elucidate the role of diet in prostate cancer progression to inform patients and doctors.

Disclosure of Potential Conflicts of Interest

A.S. Kibel is a consultant/advisory board member of Dendreon, Sanofi Aventis, Profound, and MTG. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.J. Giovannucci, A.S. Kibel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.M. Wilson, L.A. Mucci, B.F. Drake, M.A. Preston, E.J. Giovannucci, A.S. Kibel
Writing, review, and/or revision of the manuscript: K.M. Wilson, L.A. Mucci, B.F. Drake, M.A. Preston, M.J. Stampfer, E.J. Giovannucci, A.S. Kibel
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.S. Kibel
Study supervision: A.S. Kibel

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