Original Investigation

Fat Intake After Diagnosis and Risk of Lethal Prostate Cancer and All-Cause Mortality

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IMPORTANCE Nearly 2.5 million men currently live with prostate cancer in the United States, yet little is known about the association between diet after diagnosis and prostate cancer progression and overall mortality.

OBJECTIVE To examine postdiagnostic fat intake in relation to lethal prostate cancer and all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS Prospective study of 4577 men with nonmetastatic prostate cancer in the Health Professionals Follow-up Study (1986-2010).

EXPOSURES Postdiagnostic intake of saturated, monounsaturated, polyunsaturated, *trans*, animal, and vegetable fat.

MAIN OUTCOMES AND MEASURES Lethal prostate cancer (distant metastases or prostate cancer–specific death) and all-cause mortality.

RESULTS We observed 315 events of lethal prostate cancer and 1064 deaths (median follow-up, 8.4 years). Crude rates per 1000 person-years for lethal prostate cancer were as follows (highest vs lowest quintile of fat intake): 7.6 vs 7.3 for saturated, 6.4 vs 7.2 for monounsaturated, 5.8 vs 8.2 for polyunsaturated, 8.7 vs 6.1 for *trans*, 8.3 vs 5.7 for animal, and 4.7 vs 8.7 for vegetable fat. For all-cause mortality, the rates were 28.4 vs 21.4 for saturated, 20.0 vs 23.7 for monounsaturated, 17.1 vs 29.4 for polyunsaturated, 32.4 vs 17.1 for *trans*, 32.0 vs 17.2 for animal, and 15.4 vs 32.7 for vegetable fat. Replacing 10% of energy intake from carbohydrate with vegetable fat was associated with a lower risk of lethal prostate cancer (hazard ratio [HR], 0.71; 95% CI, 0.51-0.98; $P = .04$) and all-cause mortality (HR, 0.74; 95% CI, 0.61-0.88; $P = .001$). No other fats were associated with lethal prostate cancer. Saturated and *trans* fats after diagnosis (replacing 5% and 1% of energy from carbohydrate, respectively) were associated with higher all-cause mortality (HR, 1.30 [95% CI, 1.05-1.60; $P = .02$] and 1.25 [95% CI, 1.05-1.49; $P = .01$], respectively).

CONCLUSIONS AND RELEVANCE Among men with nonmetastatic prostate cancer, replacing carbohydrates and animal fat with vegetable fat may reduce the risk of all-cause mortality. The potential benefit of vegetable fat for prostate cancer–specific outcomes merits further research.

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Nearly 2.5 million men currently live with prostate cancer in the United States, and more than 241 000 cases were diagnosed in 2012.[1] Dietary fat has been extensively studied in relation to incident prostate cancer, with mixed results.[2-7] Studies of advanced disease have more consistent findings than those examining total prostate cancer, suggesting that fat intake may be relevant to disease progression,[8] but little is known about postdiagnostic fat intake and prostate cancer progression or overall survival.

Three prospective case-only studies have examined fat intake in relation to prostate cancer death. Saturated fats have been associated with higher risk of prostate cancer death, and marine fatty acids and monounsaturated fat have been associated with lower risk.[9-11] However, all these studies had relatively few events, asked men with prostate cancer to recall their diet before diagnosis, and were conducted in unscreened populations.

Thus, we prospectively examined postdiagnostic consumption of saturated, monounsaturated, polyunsaturated, *trans*, animal, and vegetable fats in relation to risk of lethal prostate cancer and all-cause mortality among men with nonmetastatic prostate cancer in the Health Professionals Follow-up Study. Based on prior studies, we hypothesized that saturated fat intake after diagnosis would be associated with higher risk of lethal prostate cancer.

Methods

Study Population

The Health Professionals Follow-up Study was initiated in 1986 among 51 529 male health professionals aged 40 to 75 years. Participants reported medical diagnoses, medication, weight, height, smoking, and physical activity at baseline and every 2 years thereafter; the average questionnaire response rate exceeds 90%. Prostate-specific antigen (PSA) screening practices were added in 1994. Dietary data were collected via food frequency questionnaire at baseline and every 4 years thereafter. The institutional review boards of the Harvard School of Public Health and University of California, San Francisco approved this study.

Dietary Assessment

The food frequency questionnaire (FFQ) asked men to report their usual intake of approximately 130 foods and beverages during the previous year. In addition, they were asked to report fried food consumption, type of cooking fat, and whether visible fat on meat was consumed. To calculate nutrient intake levels, we multiplied the frequency of consumption by the amount of the nutrient in the specified portion of each food and summed across all foods. Nutrient data were obtained from the US Department of Agriculture.

The FFQ was validated among 127 participants in the Health Professionals Follow-up Study. These men completed 2 FFQs 1 year apart and 2 one-week diet records approximately 6 months apart within the same year. The correlation between the FFQ and diet records was 0.75 for saturated, 0.37 for polyunsaturated, and 0.68 for monounsaturated fat.[12] The correlation between the FFQ and composition of subcutaneous fat was 0.18 for saturated, 0.50 for polyunsaturated, 0.14 for monounsaturated, and 0.29 for *trans* fat[13]; low correlations are expected for saturated and monounsaturated fat because of endogenous synthesis.

Outcome Assessment and Follow-up

Men were asked every 2 years whether prostate cancer had been diagnosed. After a report of prostate cancer, we obtained medical records to verify the diagnosis and to abstract information on the date of diagnosis, clinical and pathologic stage, PSA values, Gleason sum, treatments, and metastases. We also sent prostate cancer–specific biennial questionnaires to participants and their physicians to obtain information on PSA values, treatments, and metastases.

Our primary outcomes were lethal prostate cancer, defined as distant metastases or death due to prostate cancer, and all-cause mortality. The occurrence of metastases, including location and date of detection, was determined by review of medical records, physician and patient questionnaires, and death certificates. Study physicians confirmed cause of death through medical records and death certificates. A death was attributed to prostate cancer if prostate cancer metastases were present and no more-plausible cause of death was mentioned. We identified more than 98% of the deaths that occurred during follow-up.[14]

Inclusion and Exclusion Criteria

To be included in this analysis, men had to be free of cancer (except nonmelanoma skin cancer) at baseline and have a diagnosis of nonmetastatic prostate cancer between 1986 and 2010. We excluded men who reported consuming less than 800 or more than 4200 kcal/d, were missing more than 70 items on the baseline FFQ, or were missing clinical stage or treatment data, leaving 4577 men for analysis.

Statistical Analysis

We used Cox proportional hazards regression to examine postdiagnostic saturated, monounsaturated, polyunsaturated, *trans*, animal, and vegetable fat intake levels in relation to risk of lethal prostate cancer and all-cause mortality. For analyses of lethal prostate cancer, person-time was contributed from diagnosis to distant metastases or death due to prostate cancer, death from other causes, or the end of follow-up (January 31, 2010), whichever came first. For all-cause mortality, men were followed up from diagnosis until death or the end of follow-up. We used calendar time in 2-year intervals as our time scale and stratified by the number of years since diagnosis.

We calculated cumulative average postdiagnostic intake from the FFQ preceding diagnosis until the end of follow-up.[15] The FFQ preceding diagnosis was used to classify person-time from diagnosis until the next available FFQ under the assumption that disease was present at that time and because men with prostate cancer diagnoses, on average, did not change their diet more or less than men without such diagnoses during the same period. For example, for a man with prostate cancer diagnosed in 1992, we applied the 1990 FFQ to person-time contributed between 1992 and 1994, the average of the

1990 and 1994 FFQs to person-time contributed between 1994 and 1998, and so forth. On average, participants completed 2.6 FFQs in the postdiagnostic period.

We used the multivariate nutrient-density model[16] and modeled replacing carbohydrates with the fat of interest. We also modeled replacing animal fat with vegetable fat and saturated with monounsaturated or polyunsaturated fats. To do so, we included all macronutrients in the model except the macronutrient we were "replacing."[16] We examined the fats continuously and categorically and modeled the median of each quintile as a continuous term to test for linear trend. In the continuous models, we modeled replacing conventional proportions of energy intake from carbohydrates with the fats of interest: 5% for the major fats, 1% for *trans* fats, and 10% for animal and vegetable fats. These values approximate the differences in medians between the highest and lowest quintiles.

Our basic model was adjusted for age at diagnosis (in years) and energy (in kilocalories per day). For analyses of lethal prostate cancer, our multivariate model was additionally adjusted for treatment (radical prostatectomy, radiotherapy, hormone therapy, or other), Gleason sum (<7, 7, or >7), clinical stage (T1, T2, or T3), diagnostic PSA (4-level ordinal score based on category medians), number of PSA screening tests before diagnosis (continuous), body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]; <25, 25-29.9, or ≥30), vigorous activity (3-level ordinal score based on category medians), smoking (current smoker with ≥40 pack-years, current smoker with <40 pack-years, quit <10 years ago, quit ≥10 years ago, or never smoked), calcium (5-level ordinal score based on category medians), alcohol (percentage of energy intake), protein (percentage of energy intake), the other fats (percentage of energy intake) (ie, saturated fat was adjusted for monounsaturated, polyunsaturated, and *trans* fats, and vegetable fat was adjusted for animal and *trans* fats), and prediagnostic intake of the exposure of interest based on the baseline FFQ (5-level ordinal score based on category medians). For all-cause mortality, our multivariate model included all the above plus the following (yes or no): parental history of myocardial infarction before age 60 years, high blood pressure at diagnosis, diabetes mellitus at diagnosis, elevated cholesterol at diagnosis, and presence of comorbid conditions (myocardial infarction, angina, coronary artery bypass or angioplasty, stroke, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, or Parkinson disease). For lethal prostate cancer, we also considered adjustment for intake of coffee, phosphorous, zinc, vitamin D, vitamin E, choline, and lycopene; type 2 diabetes mellitus; walking pace; height; and use of cholesterol-lowering medication, aspirin, secondary treatments, and adjuvant therapies. The estimates remained essentially the same, however, and we present results from models omitting these variables.

We performed several secondary and sensitivity analyses. First, we examined whether age at diagnosis (<69 vs ≥69 years), BMI (<25 vs ≥25), vigorous activity (<3 vs ≥3 metabolic equivalent task [MET]-h/wk), smoking (never vs former or current), time since diagnosis (continuous), Gleason sum (<7 vs ≥7), or primary treatment (radical prostatectomy vs other) modified the relations by including a cross-product between the continuous exposure and potential effect modifier in our multivariate model and using a Wald test to test for evidence of effect modification. Second, we examined the intake of linoleic acid, α-linolenic acid, and long-chain ω-3 fatty acids (eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid) and the ratio of ω-6 to ω-3 fatty acids after diagnosis and risk of lethal prostate cancer and all-cause mortality.[17,18] Third, we analyzed the results with a 2- to 6-year lag and compared the change in fat intake from the first to the last postdiagnostic FFQ for the whole study population and among men who developed lethal prostate cancer during follow-up. Fourth, we examined prediagnostic fat intake (baseline and cumulative average) and the risk of lethal prostate cancer in our case-only study population. Finally, we examined the risk of prostate cancer–specific death to confirm that the results were similar to those for lethal prostate cancer (an outcome that combines distant metastases and prostate cancer–specific death).

Statistical tests were performed using SAS software (version 9.2; SAS Institute, Inc), and differences were considered statistically significant at $P < .05$.

Results

Among 4577 men with nonmetastatic prostate cancer, we observed 315 events of lethal prostate cancer and 1064 deaths during a median follow-up of 8.4 years (interquartile range, 4.6-12.5 years). The primary causes of death were cardiovascular disease (31.2%), prostate cancer (21.3%), and other cancers (20.6%).

At diagnosis, men who consumed more animal fat had a higher BMI (mean, 26.8 vs 24.9 for those who consumed less animal fat), engaged in less vigorous activity (mean, 9.2 vs 16.9 metabolic equivalent task hours per week), and were more likely to be current smokers (7% vs 1%). Men who consumed more vegetable fat were more likely to have moderately differentiated prostate cancer (Gleason sum, 7; 37% vs 32% for men who consumed less vegetable fat) and be treated by radical prostatectomy (50% vs 45%) (**Table 1**).

Lethal Prostate Cancer

Crude rates of lethal prostate cancer (per 1000 person-years), comparing the highest and lowest quintiles for intake of each of the fats, were 7.6 vs 7.3 for saturated, 6.4 vs 7.2 for monounsaturated, 5.8 vs 8.2 for polyunsaturated, 8.7 vs 6.1 for *trans*, 8.3 vs 5.7 for animal, and 4.7 vs 8.7 for vegetable fat.

Men who consumed more vegetable fat after diagnosis had a lower risk of lethal prostate cancer. Replacing 10% of calories from carbohydrates with vegetable fat was associated with a 29% lower risk of lethal prostate cancer (hazard ratio [HR], 0.71; 95% CI, 0.51-0.98; $P = .04$) (**Table 2**). The magnitude of the association was similar, but not statistically significant, when animal fat was replaced with vegetable fat (HR, 0.76; 95% CI, 0.52-1.10; $P = .14$). When examined categorically, men in the highest quintile of postdiagnostic vegetable fat intake had a 36% lower risk of lethal prostate cancer, a nonsignificant dif-

Table 1. Age-Standardized Characteristics in 4577 Men With Nonmetastatic Prostate Cancer by Postdiagnostic Animal and Vegetable Fat Intake

Characteristic at Diagnosis	Extreme Quintiles of Animal Fat Intake		*P* Value	Extreme Quintiles of Vegetable Fat Intake		*P* Value
	1	5		1	5	
Age, mean (SD), y	69.6 (7.1)	69.0 (7.2)	.02	69.8 (7.1)	69.3 (7.0)	.09
BMI, mean (SD)	24.9 (2.9)	26.8 (3.8)	<.001	25.7 (3.5)	25.6 (3.4)	.46
Vigorous physical activity, mean (SD), MET h/wk	16.9 (26.4)	9.2 (19.0)	<.001	12.8 (21.8)	11.8 (19.1)	.16
White race, %	91	93	.09	93	93	.72
Current smoker, %	1	7	<.001	5	3	.04
Family history of prostate cancer, %	22	22	.33	20	23	.17
Questionnaires on which a PSA screening test was reported before diagnosis, mean (SD), No.	3.6 (1.9)	3.3 (2.0)	<.001	3.3 (1.9)	3.6 (2.0)	<.001
Clinical stage, %						
T1	61	59	.22	58	62	.13
T2	35	37		39	36	
T3	4	3		3	2	
Gleason sum, %						
2-6	48	49	.48	49	48	.02
7	35	33		32	37	
8-10	11	13		14	10	
Missing	6	6		6	5	
PSA, ng/mL, %						
<4	14	12	.04	10	14	.03
4-9.9	56	55		58	59	
10-19.9	17	20		17	16	
≥20	7	7		8	7	
Missing	6	7		6	5	
Treatment, %						
Radical prostatectomy	46	45	.17	45	50	.03
Radiotherapy	40	40		41	36	
Hormone therapy	5	6		5	4	
Other	9	10		9	10	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent task; PSA, prostate-specific antigen.

ference (HR, 0.64; 95% CI, 0.40-1.01; *P* for trend = .06). Postdiagnostic intake was not associated with lethal prostate cancer for the other fats, including specific polyunsaturated fatty acids and the ratio of ω-6 to ω-3 fatty acids after diagnosis (see the Supplement [eTable]).

Results were similar, but not statistically significant, in secondary and sensitivity analyses. For a 10% increase in calories from vegetable fat, the HRs (95% CIs) were 0.71 (0.51-1.00) for a 2- to 6-year lag, 0.67 (0.44-1.01) for prostate cancer-specific death (226 events), 0.71 (0.47-1.05) for cumulative average prediagnostic diet, and 0.84 (0.63-1.12) for baseline prediagnostic diet. None of the prediagnostic fat intake levels were significantly associated with risk of lethal prostate cancer. Finally, on average, men who had lethal prostate cancer did not change their fat intake during follow-up more or less than the study population as a whole, and there was no evidence of effect modification by age at diagnosis, BMI, activity, smoking, time since diagnosis, Gleason sum, or primary treatment.

All-Cause Mortality

For all-cause mortality, the crude rates (per 1000 person-years), comparing the highest and lowest quintiles for each of the fats, were 28.4 vs 21.4 for saturated, 20.0 vs 23.7 for monounsaturated, 17.1 vs 29.4 for polyunsaturated, 32.4 vs 17.1 for *trans*, 32.0 vs 17.2 for animal, and 15.4 vs 32.7 for vegetable fat.

Men who consumed more vegetable fat after diagnosis had a lower risk of all-cause mortality. Replacing 10% of calories from carbohydrates with vegetable fat was associated with a 26% lower risk of death (HR, 0.74; 95% CI, 0.61-0.88; *P* = .001) (**Table 3**). The association was stronger when animal fat was replaced with vegetable fat (HR, 0.66; 95% CI, 0.54-0.81; *P* < .001). When examined categorically, men in the highest quintile of postdiagnostic vegetable fat intake had a 35% lower risk of death (HR for highest vs lowest quintile, 0.65; 95% CI, 0.52-0.83; *P* < .001).

In addition, a 5% increase in saturated fat was associated with a 30% higher risk of death (HR, 1.30; 95% CI, 1.05-1.60; *P* = .02), and a 1% increase in *trans* fat was associated with a 25% higher risk of death (HR, 1.25; 95% CI, 1.05-1.49: *P* = .01). When examined categorically, greater polyunsaturated fat intake after diagnosis was associated with lower all-cause mortality (HR for highest vs lowest quintile, 0.73; 95% CI, 0.57-0.94; *P* for trend = .004), and replacement of 5% of calories from

Table 2. Relative Risk of Lethal Prostate Cancer by Postdiagnostic Fat Intake in 4577 Men Initially Diagnosed With Nonmetastatic Prostate Cancer

Fat	Quintile of Intake					*P* Value for Trend[a]	Continuous Model[b]	
	1	2	3	4	5		HR (95% CI)	*P* Value
Saturated								
Percentage of energy intake, median	6.3	8.2	9.5	10.7	12.7	...	...	...
Events, No.	64	57	64	66	64	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.82 (0.57-1.17)	0.93 (0.66-1.32)	0.97 (0.69-1.38)	1.02 (0.72-1.45)	.62	1.06 (0.85-1.32)	.62
Model 2 HR (95% CI)[d]	1 [Reference]	0.79 (0.52-1.20)	0.86 (0.54-1.37)	0.88 (0.53-1.47)	0.84 (0.47-1.49)	.74	1.00 (0.68-1.49)	.99
Monounsaturated								
Percentage of energy intake, median	8.3	10.4	11.7	13.1	15.2	...	...	...
Events, No.	61	60	64	76	54	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.89 (0.62-1.28)	0.91 (0.64-1.29)	1.13 (0.80-1.59)	0.94 (0.65-1.36)	.84	0.99 (0.80-1.22)	.93
Model 2 HR (95% CI)[d]	1 [Reference]	0.98 (0.64-1.49)	0.98 (0.61-1.57)	1.09 (0.65-1.83)	0.96 (0.53-1.73)	.97	0.88 (0.60-1.29)	.51
Polyunsaturated								
Percentage of energy intake, median	4.3	5.1	5.8	6.5	7.8	...	...	...
Events, No.	70	67	63	65	50	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.92 (0.66-1.30)	0.84 (0.59-1.18)	0.87 (0.62-1.22)	0.78 (0.54-1.13)	.18	0.78 (0.51-1.18)	.23
Model 2 HR (95% CI)[d]	1 [Reference]	0.91 (0.64-1.30)	0.80 (0.55-1.17)	0.82 (0.55-1.22)	0.73 (0.47-1.15)	.17	0.82 (0.47-1.42)	.48
Trans								
Percentage of energy intake, median	0.7	1.0	1.3	1.5	2.0	...	...	...
Events, No.	52	54	64	70	75	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.93 (0.64-1.37)	1.09 (0.75-1.57)	1.15 (0.80-1.66)	1.21 (0.84-1.74)	.15	1.15 (0.92-1.43)	.22
Model 2 HR (95% CI)[d]	1 [Reference]	1.03 (0.68-1.57)	1.14 (0.73-1.79)	1.12 (0.70-1.79)	1.27 (0.76-2.12)	.31	1.16 (0.85-1.60)	.35
Animal								
Percentage of energy intake, median	8.1	11.6	14.0	16.6	21.0	...	...	...
Events, No.	50	62	63	71	69	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	1.17 (0.80-1.70)	1.15 (0.79-1.68)	1.29 (0.89-1.86)	1.40 (0.97-2.02)	.06	1.23 (0.99-1.54)	.06
Model 2 HR (95% CI)[d]	1 [Reference]	1.22 (0.81-1.83)	1.10 (0.72-1.69)	1.20 (0.76-1.89)	1.16 (0.70-1.94)	.66	0.99 (0.71-1.38)	.96
Vegetable								
Percentage of energy intake, median	10.2	13.0	15.0	17.4	21.6	...	...	...
Events, No.	71	67	66	70	41	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.87 (0.62-1.22)	0.85 (0.60-1.19)	0.88 (0.63-1.23)	0.61 (0.41-0.90)	.02	0.73 (0.56-0.96)	.03
Model 2 HR (95% CI)[d]	1 [Reference]	0.91 (0.64-1.29)	0.92 (0.63-1.33)	0.86 (0.58-1.26)	0.64 (0.40-1.01)	.06	0.71 (0.51-0.98)	.04

Abbreviations: ellipses, not applicable; HR, hazard ratio.

[a] *P* value for trend calculated by modeling the median of each category as a continuous term.

[b] For the continuous model, we modeled replacing conventional proportions of energy intake from carbohydrates with energy from the fats of interest: 5% for saturated, monounsaturated, and polyunsaturated fat; 1% for *trans* fat; and 10% for animal and vegetable fat.

[c] Cox proportional hazards regression model adjusted for age at diagnosis (continuous), energy intake (continuous), and time since diagnosis (continuous).

[d] Cox proportional hazards regression model adjusted for variables in model 1 plus treatment (prostatectomy, radiotherapy, hormone therapy, or other), Gleason sum (<7, 7, or ≥8), clinical stage (T1, T2, or T3), prostate-specific antigen (PSA) level at diagnosis (ordinal trend), number of PSA screening tests before diagnosis (continuous), body mass index (calculated as weight in kilograms divided by height in meters squared) (<25, 25-29.9, or ≥30), smoking (current smoker with ≥40 pack-years, current smoker with <40 pack-years, quit <10 years ago, quit ≥10 years ago, or never smoked), vigorous activity (ordinal trend), and intake of calcium (ordinal trend), alcohol (percentage of energy intake), and protein (percentage of energy intake). The fats were also adjusted for one another; animal and vegetable fat were adjusted for each other and *trans* fat, and all were adjusted for prediagnostic intake of the exposure of interest based on the 1986 food frequency questionnaire.

Table 3. Relative Risk of All-Cause Mortality by Postdiagnostic Fat Intake in 4577 Men With Nonmetastatic Prostate Cancer

Fat	Quintile of Intake					*P* Value for Trend[a]	Continuous Model[b]	
	1	2	3	4	5		HR (95% CI)	*P* Value
Saturated								
Percentage of energy intake, median	6.3	8.2	9.5	10.7	12.7	...	...	...
Events, No.	191	196	219	216	242	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.94 (0.77-1.15)	1.10 (0.90-1.34)	1.10 (0.91-1.35)	1.41 (1.16-1.70)	<.001	1.34 (1.18-1.52)	<.001
Model 2 HR (95% CI)[d]	1 [Reference]	0.95 (0.75-1.20)	1.05 (0.81-1.37)	1.02 (0.77-1.37)	1.19 (0.86-1.63)	.22	1.30 (1.05-1.60)	.02
Monounsaturated								
Percentage of energy intake, median	8.3	10.4	11.7	13.1	15.2	...	...	...
Events, No.	205	237	207	243	172	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	1.07 (0.89-1.29)	0.89 (0.73-1.08)	1.15 (0.95-1.38)	1.08 (0.88-1.33)	.45	1.08 (0.96-1.22)	.20
Model 2 HR (95% CI)[d]	1 [Reference]	0.99 (0.79-1.24)	0.80 (0.62-1.04)	0.96 (0.72-1.27)	0.87 (0.63-1.20)	.27	0.86 (0.69-1.07)	.18
Polyunsaturated								
Percentage of energy intake, median	4.3	5.1	5.8	6.5	7.8	...	...	...
Events, No.	254	242	225	195	148	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.92 (0.77-1.09)	0.85 (0.71-1.02)	0.73 (0.61-0.89)	0.74 (0.60-0.91)	<.001	0.72 (0.57-0.92)	.008
Model 2 HR (95% CI)[d]	1 [Reference]	0.92 (0.77-1.11)	0.85 (0.70-1.04)	0.74 (0.60-0.93)	0.73 (0.57-0.94)	.004	0.77 (0.57-1.05)	.10
Trans								
Percentage of energy intake, median	0.7	1.0	1.3	1.5	2.0	...	...	...
Events, No.	149	175	195	261	284	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	1.08 (0.87-1.35)	1.12 (0.90-1.39)	1.45 (1.18-1.77)	1.44 (1.17-1.76)	<.001	1.30 (1.15-1.47)	<.001
Model 2 HR (95% CI)[d]	1 [Reference]	1.10 (0.87-1.40)	1.18 (0.92-1.52)	1.54 (1.19-1.99)	1.51 (1.14-2.01)	.002	1.25 (1.05-1.49)	.01
Animal								
Percentage of energy intake, median	8.1	11.6	14.0	16.6	21.0	...	...	...
Events, No.	154	188	217	235	270	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	1.11 (0.89-1.37)	1.24 (1.01-1.53)	1.31 (1.07-1.61)	1.77 (1.45-2.17)	<.001	1.53 (1.35-1.73)	<.001
Model 2 HR (95% CI)[d]	1 [Reference]	1.03 (0.82-1.29)	1.12 (0.89-1.43)	1.06 (0.82-1.36)	1.19 (0.90-1.57)	.24	1.19 (0.99-1.42)	.06
Vegetable								
Percentage of energy intake, median	10.2	13.0	15.0	17.4	21.6	...	...	...
Events, No.	273	250	223	184	134	...	...	...
Model 1 HR (95% CI)[c]	1 [Reference]	0.85 (0.72-1.01)	0.77 (0.64-0.92)	0.64 (0.53-0.77)	0.64 (0.52-0.80)	<.001	0.69 (0.59-0.81)	<.001
Model 2 HR (95% CI)[d]	1 [Reference]	0.83 (0.69-1.00)	0.77 (0.64-0.94)	0.64 (0.52-0.78)	0.65 (0.52-0.83)	<.001	0.74 (0.61-0.88)	.001

Abbreviations: ellipses, not applicable; HR, hazard ratio.

[a] *P* value for trend calculated by modeling the median of each category as a continuous term.

[b] For the continuous model, we modeled replacing conventional proportions of energy intake from carbohydrates with energy from the fats of interest: 5% for saturated, monounsaturated, and polyunsaturated fat; 1% for *trans* fat; and 10% for animal and vegetable fat.

[c] Cox proportional hazards regression model adjusted for age at diagnosis (continuous), energy intake (continuous), and time since diagnosis (continuous).

[d] Cox proportional hazards regression model adjusted for variables in model 1 plus treatment (prostatectomy, radiotherapy, hormone therapy, or other), Gleason sum (<7, 7, or ≥8), clinical stage (T1, T2, or T3), prostate-specific antigen (PSA) level at diagnosis (ordinal trend), number of PSA tests before diagnosis (continuous), body mass index (calculated as weight in kilograms divided by height in meters squared) (<25, 25-29.9, or ≥30), smoking (current smoker with ≥40 pack-years, current smoker with <40 pack-years, quit smoking <10 years ago, quit smoking ≥10 years ago, never smoked), vigorous activity (ordinal trend), high blood pressure at prostate cancer diagnosis (yes or no), elevated cholesterol at prostate cancer diagnosis (yes or no), diabetes mellitus at prostate cancer diagnosis (yes or no), parental history of myocardial infarction before age 60 years, comorbid condition (yes or no; conditions included myocardial infarction, coronary artery bypass or angioplasty, stroke, emphysema or chronic obstructive pulmonary disorder, and Parkinson disease), and intake of calcium (ordinal trend), alcohol (percentage of energy intake), and protein (percentage of energy intake). The fats were also adjusted for one another; animal and vegetable fat were adjusted for each other and *trans* fat, and all were adjusted for prediagnostic intake of the exposure of interest based on the 1986 food frequency questionnaire.

saturated fat with polyunsaturated fat after diagnosis was associated with a 34% lower risk of death (HR, 0.66; 95% CI, 0.48-0.90; $P = .01$).

Postdiagnostic intake of monounsaturated fat, linoleic acid, α-linolenic acid, and long-chain ω-3 fatty acids and the ratio of ω-6 to ω-3 fatty acids were not significantly associated with risk of death (see the Supplement [eTable]). There was no evidence of effect modification by age at diagnosis, BMI, activity, smoking, time since diagnosis, Gleason sum, or primary treatment.

Food Sources of Vegetable Fat

To assess whether the observed associations with vegetable fat were driven by specific foods, we examined postdiagnostic intake of the top food sources of vegetable fat in our study population (eg, oil-based dressing, margarine, mayonnaise, and nuts) and risk of lethal prostate cancer and all-cause mortality, adjusting for all the variables in our multivariate models described above, except postdiagnostic intake of fats, protein, and alcohol and prediagnostic diet. An increase in oil-based dressing intake of 1 serving (1 tbsp) per day after diagnosis was suggestively associated with a 29% lower risk of lethal prostate cancer (HR, 0.71; 95% CI, 0.50-1.00) and a 13% lower risk of death (HR, 0.87; 95% CI, 0.72-1.05). An increase in nut intake of 1 serving (1 oz) per day after diagnosis was suggestively associated with an 18% lower risk of lethal prostate cancer (HR, 0.82; 95% CI, 0.67-1.01) and an 11% lower risk of death (HR, 0.89; 95% CI, 0.79-0.99). Postdiagnostic intake levels of mayonnaise and margarine were not associated with risk of lethal prostate cancer or all-cause mortality.

Discussion

In this prospective analysis, vegetable fat intake after diagnosis was associated with a lower risk of lethal prostate cancer and all-cause mortality. To our knowledge, no prior study has examined fat intake after diagnosis in relation to risk of lethal prostate cancer and all-cause mortality. However, 3 prior prospective case-only studies conducted in unscreened populations examined prediagnostic fat intake in relation to prostate cancer death. Among 525 Swedish men, marine fatty acid intake was associated with lower risk of prostate cancer death (222 events; HR for highest vs lowest quartile, 0.59; 95% CI, 0.40-0.87) and, among the men with localized disease (46 events), intake of myristic acid and short-chain saturated fatty acids was associated with higher risk of prostate cancer death (HR for Q4 v Q1, 2.39 [95% CI, 1.06-5.38] and 2.88 [1.24-6.67], respectively).[10] Among 384 Canadian men with prostate cancer, prediagnostic saturated fat intake was associated with higher risk of prostate cancer death (32 events; HR for tertile 3 vs tertile 1, 3.13; 95% CI, 1.28-7.67).[9] In addition, greater intake of vegetable fat before diagnosis was suggestively associated with lower risk of advanced disease at diagnosis among these men (odds ratio, 0.84; 95% CI, 0.70-1.01).[19] In a distinct cohort of 263 Canadian men, prediagnostic intake of monounsaturated fat was associated with a lower risk of prostate cancer death (58 events; HR, 0.3; 95% CI, 0.1-0.7).[11]

Fat from vegetable sources includes a heterogeneous mix of monounsaturated and polyunsaturated fats. In our study, neither monounsaturated nor polyunsaturated fat intake was associated with lethal prostate cancer, although the associations were in the protective direction. Red meat and poultry with skin were major sources of monounsaturated and polyunsaturated fat in our study population, however, and these foods are also sources of heme iron and heterocyclic amines, which may increase the risk of aggressive prostate cancer.[20] We did not have data on meat-cooking practices; thus, the relations between the intake of fats and risk of lethal prostate cancer may have been confounded by unmeasured factors associated with the consumption of animal products. It is also possible that the beneficial associations observed for vegetable fat intake result from other components of food sources of vegetable fats. Although we considered adjustment for all known dietary risk factors for prostate cancer (eg, calcium, vitamin E, lycopene, vitamin D, choline, phosphorous, and zinc) and observed little evidence of confounding, we cannot rule out confounding by unmeasured factors associated with the consumption of the fats examined.

In particular, oils and nuts were among the top food sources of vegetable fats in our population. Consumption of these foods increases plasma antioxidants and reduces circulating insulin, low-density lipoprotein cholesterol, inflammatory markers, and markers of oxidative stress,[21-33] all of which may affect prostate cancer progression.[34-37] For example, flaxseed supplementation before radical prostatectomy has been associated with lower proliferation rates in prostate tumors.[38] Additional studies are needed to examine whether the associations we observed were attributable to the fat or other components (eg, phytochemicals) in these foods or some combination thereof.

Cardiovascular disease was the leading cause of death in this cohort of men with prostate cancer, accounting for nearly one-third of deaths. The beneficial effects of unsaturated fat intake and harmful effects of saturated and *trans* fat intake on cardiovascular health are well known, and our findings among men with prostate cancer are consistent with the established relations.[39-41] Overall, our findings support counseling men with prostate cancer to follow a heart-healthy diet in which carbohydrate calories are replaced with unsaturated oils and nuts to reduce the risk of all-cause mortality.

In conclusion, among men with nonmetastatic prostate cancer, replacing carbohydrates and animal fat with vegetable fat may reduce the risk of all-cause mortality. The potential benefit of vegetable fat consumption for prostate cancer–specific outcomes merits further research.

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Invited Commentary

Dietary Fat and Reduced Prostate Cancer Mortality
Does the Type of Fat Matter?

Stephen J. Freedland, MD

There are 3 well-established risk factors for prostate cancer: race (specifically, African American race), family history, and age. Unfortunately, we cannot change our race or our parents nor can we stop time. Given this reality, there is much interest in identifying modifiable risk factors for prostate cancer. In a landmark study, Calle and colleagues followed up more than 900 000 persons for more than 16 years and found that obesity was linked with death from 17 different cancer types.[1] Although prostate cancer was one of the cancers identified, its association with obesity was modest, with mildly obese (body mass index [calculated as weight in kilograms divided by height in meters squared], 30-34.9) and moderately obese (body mass index, 35-39.9) men being 20% and 34% more likely, respectively, to die of prostate cancer. Even so, given the large number of men who die annually of prostate cancer (258 100 worldwide and 32 600 in North America in 2008)[2] and the high prevalence of obesity (35% in the United States in 2012),[3] the association means that tens of thousands of men die annually of obesity-related prostate cancer. While the exact links between obesity and prostate cancer are complex, diet and lifestyle invariably play a role.

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Further support for the role of lifestyle in prostate cancer comes from geographic differences in prostate cancer incidence, with Western countries having dramatically higher rates of prostate cancer than developing countries.[2] While these data suggest that a "Western" lifestyle may promote prostate cancer, it is difficult to discern which specific aspect is responsible, as a "Western" lifestyle involves low levels of physical activity and a diet high in calories, saturated fats, refined carbohydrates, and animal protein and low in fresh fruits, vegetables, and whole grains, resulting in lower intake of essential minerals and phytochemicals and excess intake of other factors. All of these factors have, in one study or another, been linked with prostate cancer, although a large amount of conflicting data exist.[4]

Given this uncertainty and a growing interest in the role of nutrition and prostate cancer, the article by Richman et al[5] is both timely and informative. The authors examined 4577 men with nonmetastatic prostate cancer, followed up from before diagnosis until death. Using data from food frequency questionnaires completed every 4 years during follow-up, they found that men who consumed more vegetable fat had a lower risk of prostate cancer death (P = .04). No other fat sources were linked with prostate cancer mortality.

In examining epidemiological data, one's first question should be whether unaccounted-for differences between groups could explain the results. Indeed, men who consumed more vegetable fat did have small baseline differences that would favor better prostate cancer survival (lower prostate-specific antigen levels at diagnosis, fewer high-grade cancers, and more prostate-specific antigen screening). While these variables were adjusted for in multivariable analysis, other unaccounted-for differences may have contributed to the better outcomes. For example, these same factors may correlate with increased rates of secondary treatments, such as earlier use of hormone therapy or more aggressive secondary radiotherapy for surgical failures, both of which may lower risks of metastatic and fatal prostate cancer. Thus, in the absence of randomized trial data, it is impossible to use these data as "proof" that vegetable intake lowers prostate cancer risk, and the authors have carefully avoided such statements.

Given that residual confounding is always possible, what if we accept these data at face value? What does it mean that vegetable fat intake was associated with lower prostate cancer mortality? A key point in all statistics is that they are relative. In other words, these data suggest that men who consumed more vegetable fat had lower prostate cancer mortality than men who ate less vegetable fat. Given that the results were adjusted for calories, one must ask what the men eating fewer vegetables ate instead. In this case, they ate carbohydrates. The authors state that "replacing 10% of calories from carbohydrates with vegetable fat was associated with a 29% lower risk of lethal prostate cancer." In other words, eating vegetable fat is better than eating carbohydrates. The key question is whether this is due to vegetables being beneficial, or "good"; carbohydrates being harmful, or "bad"; or a combination of both.

Increasing data suggest that carbohydrate intake and the resultant increases in serum insulin levels may promote aggressive prostate cancer. In animal models, lowering carbohydrate intake slows prostate cancer growth.[6] In men with prostate cancer, higher levels of C-peptide (a marker of insulin secretion) before diagnosis is strongly predictive of death from prostate cancer.[7] Moreover, a recent cohort study found that, whereas total carbohydrate intake may not be related to prostate cancer risk, excess intake of sugar-