Research Article

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Dietary Fat, Fatty Acids, and Risk of Prostate Cancer in the NIH-AARP Diet and Health Study

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Abstract

Background: Observational studies report inconsistent associations of fat and fatty acids with prostate cancer.

Methods: We investigated associations between dietary fats and fatty acids and risk of prostate cancer in the NIH-American Association of Retired Persons (AARP) Diet and Health Study. Diet was assessed at baseline with self-administered food-frequency questionnaires. Cases were determined by linkage with state cancer registries. HR and 95% confidence intervals (CI) were estimated with Cox proportional hazards models.

Results: Among 288,268 men with average follow-up of nine years, 23,281 prostate cancer cases (18,934 nonadvanced and 2,930 advanced including 725 fatal cases) were identified. Total fat and mono- and polyunsaturated fat intakes were not associated with incidence of prostate cancer. Saturated fat intake was related to increased risk of advanced prostate cancer ($HR_{Quintile\ 5\ vs.\ Qunitile\ 1\ (Q1\ vs.\ Q5)}$, 1.21; 95% CI, 1.00–1.46; $P_{trend} = 0.03$) and fatal prostate cancer ($HR_{Q5\ vs.\ Q1}$, 1.47; 95% CI, 1.01–2.15; $P_{trend} = 0.04$). α-Linolenic acid (ALA) intake was related to increased risk of advanced prostate cancer ($HR_{Q5\ vs.\ Q1}$, 1.17; 95% CI, 1.04–1.31; $P_{trend} = 0.01$). Eicosapentanoic acid (EPA) intake was related to decreased risk of fatal prostate cancer ($HR_{Q5\ vs.\ Q1}$, 0.82; 95% CI, 0.64–1.04; $P_{trend} = 0.02$).

Conclusion: Our study suggests that the associations of fat and fatty acids differ by prostate cancer severity. Saturated fat, ALA, and EPA intakes were related to the risk of advanced or fatal prostate cancer but not to nonadvanced prostate cancer.

Impact: Identifying factors associated with advanced prostate cancer could reduce morbidity and mortality.
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Introduction

Prostate cancer incidence varies internationally, with the highest rates in Western industrialized countries (1). For example, incidence in the United States is 83.8 per 100,000 men, compared with 22.7 in Japan and 22.4 in the Republic of Korea (2). Furthermore, migration studies show that prostate cancer incidence is higher among Japanese immigrants to the United States than in their Japan, suggesting that diet or lifestyle factors may contribute to carcinogenesis (3, 4).

One of the characteristics of Western diets is a high intake of fat, and dietary fat and several fatty acids, such *n*-3 and *n*-6 polyunsaturated fatty acids (PUFA), have been postulated to play a role in prostate cancer etiology and progression. Fatty acids and their metabolites are involved in numerous pathways with potential impact on carcinogenesis. For example, *n*-6 fatty acids serve as precursors to eicosanoids, which in turn are converted to prostaglandins and other inflammatory molecules. Metabolic pathways of *n*-3 fatty acids are less well known, but among nude mice fed diets high in the *n*-3 long-chain fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), reduced growth of prostate cancer xenografts was observed (5). EPA and DHA also inhibited *in vitro* proliferation of prostate cancer cell lines, whereas the *n*-6 fatty acids linoleic acid and arachidonic acid stimulated proliferation (6, 7). More recently, EPA and DHA were shown to inhibit conversion to androgen-independence in an *in vitro* model of prostate cancer progression (8), and this effect was correlated with inhibition of pathways involved with expression of fatty acid synthase, a protein upregulated in prostate cancer development (9).

Epidemiologic studies of total dietary fat intake and prostate cancer risk are inconsistent and do not support a strong positive association (10, 11). A summary estimate of 7 prospective cohort studies showed no association between total fat and types of fat intakes and risk of prostate cancer (12). Studies of specific fatty acids have been similarly inconsistent; no congruent pattern of

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increased or decreased risk of prostate cancer with higher intakes of *n*-6 or *n*-3 fatty acids, respectively, has emerged from the literature. Most analyses show no association of individual PUFAs with prostate cancer (13–15), whereas a few have reported an increased risk of prostate cancer with higher intakes of α-linolenic acid (ALA), an *n*-3 fatty acid, (11, 16–18).

However, some studies suggested that the association differed by prostate cancer severity: intake of saturated fat has been associated with advanced prostate cancer in some (19–22), but not all studies (11, 23). In addition, one study of serum fatty acid concentrations found that higher circulating levels of *n*-3 fatty acids were related to an increased risk of high-grade, but not low-grade, prostate cancer (24). Another found that a higher ratio of *n*-6/*n*-3 fatty acids intake was related to an increased risk for high-grade prostate cancer (25).

Previous observational studies had relatively small number of cases with a narrow range of fat intake and many lacked statistical power to detect modest associations between fat intake and risk of advanced or fatal prostate cancer. Therefore, we examined associations between total dietary fat, types of fat, and individual fatty acids with incidence of overall as well as advanced and fatal prostate cancer in a very large prospective cohort with a wide range of fat intake.

Materials and Methods

Study population

Details of the NIH-American Association of Retired Persons (AARP) Diet and Health Study have been previously described (26). Briefly, the study consists of more than 500,000 men and women of ages 50 to 71 years, who resided in 1 of 6 states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or in 1 of 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). Participants completed a mailed questionnaire at baseline between 1995 and 1996, and an additional risk factor questionnaire was subsequently mailed in 1996 to 1997 to people who did not have self-reported prevalent cancer at baseline. The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute and informed consent was obtained from all participants at baseline. Among the 339,667 men who completed the baseline questionnaire, we excluded those whose questionnaires were completed by proxy (n = 14,495); who reported a history of cancer (except nonmelanoma skin cancer) at baseline (n = 28,641); who had end-stage renal disease at baseline (n = 485); who had self-reported poor health at baseline (n = 4,958); or who reported extreme intakes of total energy (n = 2,503) or total fat (n = 317). Our final analytic cohort consisted of 288,268 men.

Cancer ascertainment

Incident prostate cancer was ascertained through December 31, 2006 by probabilistic linkage to 8 state cancer registries and 3 additional state cancer registries (Arizona, Nevada, and Texas) where participants tended to move to during follow-up. These cancer registries have been certified by the North American Association of Central Cancer Registries to capture at least 90% of cancer incidences within 2 years of cancer incidence. Cancer registry data included cancer diagnosed, diagnosis date, morphology code, grade, and stage information. Participants were also followed by annual matching of the cohort database with the National Change of Address database maintained by the U.S. Postal Service and through processing of undeliverable mail, other address update services, and direct responses from participants. Vital status was ascertained through December 31, 2008 by linkage with the Social Security Administration death master file and the National Death Index Plus.

Total prostate cancer cases included all men diagnosed with first primary prostate cancer of any grade. Nonadvanced prostate cancer cases were defined as men whose tumors that had not penetrated the prostate capsule and did not have lymph node involvement or metastases [stage T0–T2 and N0 and M0 of the American Joint Commission on Cancer 1997 tumor–node–metastasis (TNM) classification system]. Advanced prostate cancer were those with tumors that penetrated the prostate capsule (stage T3–T4), or had lymph node involvement (N1), or metastasis (M1), or who died of prostate cancer during follow-up. Fatal cases were participants with a first primary diagnosis of prostate cancer and who died of prostate cancer during follow-up.

Assessment of diet and other risk factors

At baseline diet was assessed using a self-administered food-frequency questionnaire (FFQ), which asked participants to report their usual intake of 124 food items during the previous year. We assessed frequency of food and beverage consumption for the previous 12 months using 10 predefined categories of intake ranging from "never" to "6+ times per day" for beverages and "never" to "2+ times per day" for solid foods. Portion sizes and nutrient intakes were estimated from the 1994 to 1996 U.S. Department of Agriculture's Continuing Survey of Food Intakes by Individuals. To more accurately quantify fat intake, the FFQ also included 21 questions about consumption of foods that were low fat and those that contained added fats or creamers used in food preparation. This FFQ was validated by comparing intake estimates with that of 2 nonconsecutive 24-hour food recalls among a subset of 2,053 participants. Correlation coefficients between instruments for total fat intake (adjusted for energy intake) were 0.72 for men and 0.62 for women (27). The validity of FFQs to measure polyunsaturated and fatty acid intake has been reported for the all-male participants of the Health Professionals Follow-up Study (HPFS; ref. 28). The Spearman correlation coefficients between an FFQ and a subcutaneous fat aspirate for total PUFAs and EPA were 0.50 and 0.47, respectively.

The baseline questionnaire also collected information about nondiet risk factors, including demographic characteristics, height, body weight, medical history, family history of cancer, smoking status, and vigorous physical activity. A subsequent risk factor questionnaire administered in 1996 to 1997 asked for more detailed medical history including prostate-specific antigen (PSA) screening. In this risk-factor questionnaire, men were asked whether they had had a PSA screening test within the past 3 years.

Statistical analyses

HR and 95% confidence intervals (CI) for associations with prostate cancer were estimated using Cox proportional hazards models, with person-years as the time variable. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of cancer diagnosis, death from any cause, move out of the cancer registry area, or end of follow-up, whichever was first. For analysis of fatal prostate cancer, cases were followed from study entry until death, therefore, person-years were calculated from baseline to prostate cancer death, death from other causes, or end of follow-up, whichever was first. Variables were considered as potential confounding variables and included in models, if they were known or hypothesized to be associated with either fatty acid intake or risk of prostate cancer, based on results from previous studies or exploration of these data. Age, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Pacific Islander, or American Indian/Alaskan Native), and family history of prostate cancer (having a first-degree relative with prostate cancer) were included because of well-known associations with prostate cancer incidence. Marital status (married or not), education (high school or less, some college, or college graduate), self-reported diabetes (yes or no), and PSA screening within 3 years before the baseline assessment (yes, no, or unknown) were included. Models were also adjusted for total energy, alcohol intake, intake of tomatoes, body mass index (BMI) in 3 levels (<25, 25 to <30, and 30 kg/m^2 and above), the frequency of engaging in 20 minutes or more vigorous physical activity (never or rarely, 1–3 times per month, 1–2 times per week, 3–4 times per week, or 5+ times per week), and a smoking variable, which combined information of current smoking status and average dose during periods of smoking (never smoker, former smoker of $\leq$20 cigarettes per day, former smoker of >20 cigarettes per day, current smoker of $\leq$20 cigarettes per day, and current smoker of >20 cigarettes per day). For participants with missing data on covariates, an indicator variable was included in the models. In addition to full models, parsimonious models were created for advanced and fatal prostate cancers. Covariates were included in these models if they changed the estimate of effect for saturated fat by 10% or more. Because results from these parsimonious models and results from the fully adjusted models did not differ, and to allow for comparison with previous studies that adjusted for similar covariates, only the fully adjusted results are presented. The proportional hazards assumption was evaluated by modeling interaction terms of time and each exposure of interest.

Fat and fatty acid intakes were expressed as percentages of total energy, tomatoes were expressed servings per 1,000 calories, and all models included adjustment for total calories. Percentage of calories from *trans*-fat was calculated by summing percentage of calories from *trans*-hexadecenoic acid (16:1), *trans*-octadecenoic acid (18:1), and *trans*-octadecadienoic acid (18:2). Percentage of calories from total *n*-3 PUFAs was calculated similarly to a prior study in this cohort (29) by summing percentage calories of ALA (18:3), parinaric acid (PNA; 18:4), EPA (20:5), docosapentanoic acid (DPA; 22:5), and DHA (22:6). In addition, because ALA is metabolically different from other long-chain *n*-3 fatty acids and tends to come from different food sources, we created an additional variable summing percentage of calories from EPA and DHA, which have been shown to be metabolically active (5–8) and at least for EPA, have been shown to be measured with some validity by FFQ (28). Percentage of calories from total *n*-6 PUFAs was calculated by summing linoleic acid (18:2) and arachidonic acid (20:4). The ratio of *n*-6 to *n*-3 PUFAs was calculating by dividing the total percentage of calories from *n*-6 by the total percentage of calories from total *n*-3 fatty acids.

Intakes of fat and fatty acids were categorized into quintiles and entered into models as nominal variables with the lowest category as the reference group. Tests for trend of categorical variables were conducted by assigning each participant the median value of their quintile of intake and modeling these values as a continuous variable. For analyses of saturated, mono-, and polyunsaturated fat, all models were mutually adjusted for each type of fat.

Results

During an average of 9 years of follow-up, a total of 23,281 incident prostate cancer cases were ascertained. Of these, 18,934 were nonadvanced cases, 1,417 had lack of information on stage and grade, and 2,930 were advanced cases (including 725 fatal prostate cancer cases).

Median dietary fat intake was 20% of calories from fat for the lowest quintile of intake and 40% calories from fat for the highest quintile. Compared with men in the lowest quintile of total fat intake, men in the highest quintile tended to be White, have less education, have higher BMI at baseline, and be less likely to engage in physical activity or to have had a PSA test in the last 3 years. They also were more likely to have self-reported history of any type of diabetes and to be a current smoker but were less likely to drink 15 g or more of alcohol per day (Table 1).

Main food sources for saturated fatty acids included margarine, butter, beef, milk, and other dairy products. Main food sources for monounsaturated fatty acids

Table 1. Baseline characteristics by quintile of percentage of energy from total fat among 288,268 men in the NIH-AARP Diet and Health Study

	Quintile I	Quintile II	Quintile III	Quintile IV	Quintile V
Median total fat intake, % of energy	20.3	26.5	30.6	34.6	39.9
Race/ethnicity%[b]					
Non-Hispanic White	90.8	92.3	92.9	93.3	93.7
Non-Hispanic Black	2.8	2.7	2.6	2.6	2.6
Hispanic	2.5	2.1	1.9	1.7	1.3
Other	2.7	1.9	1.5	1.3	1.1
Education, %[b]					
≤11 y	4.8	5.0	5.5	6.1	6.9
12 y or completed high school	13.2	14.0	15.4	16.9	18.1
Posthigh school or some college	28.5	30.2	31.4	32.4	34.2
College and postgraduate	50.9	48.2	45.3	42.0	37.9
Married, %	82.7	85.7	86.3	86.5	84.5
Family history of prostate cancer, %	8.0	8.2	8.5	8.5	8.4
PSA test in last 3 years, %[a]	75.1	74.2	71.9	69.1	65.2
Self-reported diabetes, %	6.5	8.2	9.2	10.5	14.0
Tomato (pyramid servings/1,000 kcal)					
0–0.25	73.3	73.2	74.5	76.7	80.1
>0.25	26.7	26.8	25.5	23.3	19.9
Alcohol					
<15 g/d	58.6	67.2	72.4	77.9	84.7
≥15 g/d	41.4	32.8	27.6	22.1	15.3
Smoking history, %[b]					
Never smoked	30.6	30.6	30.6	29.0	26.2
Former smoker	58.5	58.1	56.7	55.4	53.3
Current smoker	6.8	7.5	9.0	11.7	16.4
Median BMI at baseline	25.9	26.5	26.6	27.1	27.4
Physical activity 5 or more times/wk, %	29.1	23.0	20.3	18.2	16.8

[a]Among 178,331 men who answered the risk factor questionnaire.
[b]Proportions may not total to 100% due to missing or incomplete information.

included margarine, butter, oils, mayonnaise, salad dressings, and beef. Among the *n*-3 PUFAs, ALA came mainly from oils, mayonnaise, salad dressings, margarine, butter, desserts, and baked goods (e.g., cakes, pies, brownies, etc.), whereas the other *n*-3 PUFAs (EPA, DHA, DPA, and PNA) came from intake of fish, poultry, and eggs. The *n*-6 PUFA arachidonic acid was largely supplied by poultry, beef, and eggs in the diet, whereas linoleic acid came from oils, mayonnaise, salad dressings, margarine, butter, nuts, and seeds.

Intakes of total fat, poly-unsaturated fat, and total *trans*-fatty acids were not associated with incidence of total, nonadvanced, advanced, or fatal prostate cancer (Table 2). Saturated fat intake was related to an increased risk of advanced prostate cancer (highest vs. lowest quintile HR, 1.21; 95% CI, 1.00–1.46; $P_{trend} = 0.03$) and to fatal prostate cancer (HR, 1.47; 95% CI, 1.01–2.15; $P_{trend} = 0.04$). There was a suggestive trend for decreased risk of advanced prostate cancer with increasing intake of monounsaturated fat (HR, 0.80; 95% CI, 0.64–1.01), although it was not statistically significant ($P_{trend} = 0.08$). These associations were not attenuated when adjusting for total meat or red meat intake.

There were no associations between total *n*-3 or *n*-6 PUFAs and risk of overall or any subset of prostate cancer, nor was there any association with the ratio of *n*-6/*n*-3 fatty acids (Table 3). In analyses of EPA+DHA, there were decreased HRs for fatal prostate cancer in the top 3 quintiles of intake but neither the estimates nor the trend were statistically significant. ALA intake was related to an increased risk of advanced prostate cancer (highest vs. lowest quintile HR, 1.17; 95% CI, 1.04–1.31; $P_{trend} = 0.01$) but not fatal prostate cancer. There was a suggestive trend of decreased risk of fatal prostate cancer with increasing intake of EPA (highest vs. lowest quintile HR, 0.82; 95% CI, 0.64–1.04; $P_{trend} = 0.02$).

We also explored the association of other individual fatty acids with risk of prostate cancer. There were no associations between any of these of individual fatty acids with nonadvanced prostate cancer (Supplementary Table S1). There was a statistically significant trend of decreased risk between eruic acid (22:1) and risk of fatal prostate

Table 2. Risk of prostate cancer with increasing quintiles of total dietary fat, and saturated, monounsaturated, polyunsaturated, and *trans*-fat

	Quintiles of intake					
	I	II	III	IV	V	P_{trend}
Total dietary fat						
Quintile median (% energy)	20.3	26.5	30.6	34.6	40.0	
Nonadvanced cases (*n*)	4,013	3,912	3,792	3,754	3,463	
Multivariable HR	1.00	1.00	1.00	1.03	1.01	0.43
95% CI		(0.96–1.05)	(0.95–1.04)	(0.98–1.07)	(0.96–1.06)	
Advanced cases (*n*)	571	593	583	613	570	
Multivariable HR	1.00	1.04	1.03	1.11	1.07	0.16
95% CI		(0.93–1.17)	(0.92–1.16)	(0.98–1.24)	(0.95–1.21)	
Fatal cases (*n*)	128	128	154	164	151	
Multivariable HR	1.00	0.98	1.15	1.19	1.09	0.24
95% CI		(0.77–1.25)	(0.91–1.46)	(0.94–1.52)	(0.85–1.40)	
Saturated fat						
Quintile median (% energy)	5.8	7.8	9.4	10.9	13.3	
Nonadvanced cases (*n*)	4,031	3,968	3,757	3,730	3,448	
Multivariable HR	1.00	1.01	0.99	1.02	1.01	0.76
95% CI		(0.96–1.07)	(0.93–1.05)	(0.95–1.09)	(0.94–1.08)	
Advanced cases (*n*)	582	567	595	616	570	
Multivariable HR	1.00	1.05	1.14	1.22	1.21	0.03
95% CI		(0.91–1.20)	(0.97–1.33)	(1.03–1.45)	(1.00–1.46)	
Fatal cases (*n*)	125	118	162	160	160	
Multivariable HR	1.00	1.07	1.50	1.47	1.47	0.04
95% CI		(0.79–1.44)	(1.08–2.08)	(1.04–2.10)	(1.01–2.15)	
Monounsaturated fat						
Quintile median (% energy)	7.4	9.9	11.6	13.3	15.5	
Nonadvanced cases (*n*)	3,963	3,931	3,819	3,748	3,473	
Multivariable HR	1.00	1.02	1.01	1.04	1.04	0.46
95% CI		(0.96–1.08)	(0.95–1.09)	(0.96–1.13)	(0.94–1.13)	
Advanced cases (*n*)	601	554	614	593	568	
Multivariable HR	1.00	0.88	0.91	0.85	0.80	0.08
95% CI		(0.76–1.02)	(0.76–1.09)	(0.69–1.04)	(0.64–1.01)	
Fatal cases (*n*)	137	132	139	161	156	
Multivariable HR	1.00	0.90	0.83	0.88	0.78	0.31
95% CI		(0.66–1.22)	(0.57–1.20)	(0.58–1.33)	(0.49–1.24)	
Polyunsaturated fat						
Quintile median (% energy)	4.4	5.7	6.7	7.7	9.5	
Nonadvanced cases (*n*)	3,822	3,854	3,848	3,734	3,676	
Multivariable HR	1.00	1.01	1.01	0.99	0.99	0.54
95% CI		(0.96–1.06)	(0.96–1.06)	(0.93–1.04)	(0.93–1.05)	
Advanced cases (*n*)	595	554	565	601	615	
Multivariable HR	1.00	0.94	0.96	1.03	1.09	0.09
95% CI		(0.82–1.06)	(0.84–1.10)	(0.89–1.19)	(0.93–1.28)	
Fatal cases (*n*)	160	132	123	143	167	
Multivariable HR	1.00	0.80	0.72	0.82	0.96	0.65
95% CI		(0.62–1.03)	(0.55–0.96)	(0.61–1.10)	(0.70–1.31)	
Total *trans*-fatty acids						
Quintile median (% energy)	1.1	1.6	2.0	2.4	3.2	
Nonadvanced cases (*n*)	3,918	3,798	3,750	3,770	3,698	
Multivariable HR	1.00	0.99	1.00	1.03	1.00	0.53
95% CI		(0.95–1.04)	(0.96–1.05)	(0.98–1.08)	(0.96–1.05)	

(Continued on the following page)

Table 2. Risk of prostate cancer with increasing quintiles of total dietary fat, and saturated, monounsaturated, polyunsaturated, and *trans*-fat (Cont'd)

	Quintiles of intake					
	I	II	III	IV	V	P_{trend}
Advanced cases (*n*)	582	606	552	632	558	
Multivariable HR	1.00	1.04	0.95	1.10	0.97	0.79
95% CI		(0.92–1.16)	(0.85–1.07)	(0.98–1.23)	(0.85–1.09)	
Fatal cases (*n*)	143	139	137	147	159	
Multivariable HR	1.00	0.92	0.90	0.92	0.95	0.80
95% CI		(0.73–1.17)	(0.71–1.14)	(0.73–1.17)	(0.75–1.21)	

NOTE: All HR include adjustment for age at entry, race, family history of prostate cancer, education, marital status, PSA testing in the past 3 years, physical activity, smoking, self-reported diabetes, BMI at baseline, calories, alcohol, and intake of tomatoes.

cancer (highest vs. lowest quintile HR, 0.75; 95% CI, 0.59–0.96; $P_{trend} = 0.02$) and increased risk of fatal prostate cancer with higher intake of *trans*-hexadecenoic acid (16:1; highest vs. lowest quintile HR, 1.32; 95% CI, 1.03–1.68; $P_{trend} = 0.04$).

There were no significant interactions between PSA screening and the results for saturated fat, ALA or EPA.

Discussion

In this study, we found that higher dietary intakes of saturated fat and ALA were associated with increased risk of advanced prostate cancer. Our findings on saturated fat are consistent with results reported for another large cohort study, the HPFS (19). Several case–control studies also showed a positive relationship of dietary saturated fat with risk of advanced prostate cancer (20–22, 30), or total prostate cancer (30, 31). In contrast, in one other cohort study (15) and a few small case–control studies (32, 33), the authors found no association of saturated fat intake with advanced prostate cancer. In our previous study, red meat intake (a main source of dietary saturated fat in this population) was positively associated with risk of advanced prostate cancer (34). However, the results for saturated fat and advanced prostate cancer did not change appreciably with adjustment for red meat intake or with total meat intake, so the association is unlikely due to confounding with meat.

Our findings about an association of ALA with advanced prostate cancer are also consistent with results of the HPFS (18, 19, 35) and with one other case control study (17). In contrast, among studies that specifically examined aggressive prostate cancer (either advanced stage, high grade, or both), 2 prospective studies (13, 14) and 3 case–control studies failed to find an association (25, 36, 37).

There are various differences between the studies that could account for the different findings, such as varying sample sizes, dietary instruments and databases, ranges of fat intake, adjustment for potential confounders, and variation between study populations in factors such as PSA screening and stage distribution. On substantial difference between our study and other studies of ALA and advanced prostate cancer is sample size. Most studies that examined the association of ALA had relatively small numbers of advanced cases (ranging from 36 to 858), whereas in our study, we had 2,935 advanced prostate cancer cases available for analysis. In addition, with exception of the Netherlands Cohort Study, which had a similar range of ALA intake (13), the range in median intake between the lowest and the highest quintile (from 0.87 to 2.0 g/d) was higher in our study than most of the other studies (average of about 1.0–1.5 g/d).

Differences in PSA screening practices could also affect studies of advanced prostate cancer, especially if the exposure is associated with rate of progression. Among frequently screened populations, associations could be masked because the stage distribution would be skewed toward earlier stages, resulting in fewer advanced cases and less power to detect modest associations. This could be one explanation why a null association was found among the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, whereas these men were screened yearly (14). However, the lack of association among participants of the Netherlands Cohort Study, which was conducted in Europe where PSA screening was not widely adopted (13), remains to be explained.

A few of the earlier studies using fatty acid content of blood, serum, or plasma as biomarkers of fat intake found a positive association of ALA with prostate cancer risk (38–40), however, these studies were small, with the number of cases ranging from 67 to 120, and they were not able to specifically examine associations with advanced or high-grade disease. Later, 3 of 4 studies that examined the relation of circulating ALA concentrations to the risk of advanced or high-grade cancers found no association. Comparing the highest category with the lowest category of ALA concentration in relation to high-grade (Gleason ≥ 7) prostate cancer, the Physician's Health Study (PHS; ref. 41) trial found a risk ratio (RR) of 1.49 (95% CI, 0.67–3.27; $P_{trend} = 0.29$), the Multiethnic Cohort Study (MEC; ref. 42) found an OR of 0.60 (95% CI, 0.17–2.14; $P_{trend} = 0.39$), and the Prostate Cancer Prevention Trial (PCPT; ref. 24) found an OR of 0.64 (95% CI, 0.38–1.11; $P_{trend} = 0.17$). Recently, the European Prospective

Table 3. Risk of prostate cancer with increasing quintiles of *n*-6 and *n*-3 PUFAs, ratio of *n*-6 to *n*-3 PUFAs, essential fatty acids, and marine PUFAs

	Quintiles of intake					
	I	II	III	IV	V	P_{trend}
Total *n*-6 fatty acids						
Quintile median (% energy)	3.8	5.0	5.9	6.9	8.6	
Nonadvanced cases (*n*)	3,796	3,897	3,837	3,758	3,646	
Multivariable HR	1.00	1.04	1.03	1.02	1.01	0.92
95% CI		(0.99–1.09)	(0.98–1.08)	(0.97–1.07)	(0.97–1.06)	
Advanced cases (*n*)	596	562	568	601	603	
Multivariable HR	1.00	0.93	0.94	1.00	1.02	0.42
95% CI		(0.83–1.05)	(0.84–1.06)	(0.89–1.12)	(0.91–1.14)	
Fatal cases (*n*)	162	131	128	142	162	
Multivariable HR	1.00	0.80	0.76	0.83	0.95	0.98
95% CI		(0.63–1.01)	(0.60–0.97)	(0.60–0.97)	(0.76–1.19)	
Total *n*-3 fatty acids						
Quintile median (% energy)	0.45	0.57	0.66	0.77	0.95	
Nonadvanced cases (*n*)	3,685	3,810	3,883	3,833	3,723	
Multivariable HR	1.00	1.04	1.06	1.06	1.04	0.14
95% CI		(0.99–1.09)	(1.02–1.11)	(1.01–1.11)	(0.99–1.09)	
Advanced cases (*n*)	586	554	575	583	632	
Multivariable HR	1.00	0.93	0.96	0.98	1.06	0.13
95% CI		(0.83–1.05)	(0.86–1.08)	(0.87–1.10)	(0.95–1.20)	
Fatal cases (*n*)	151	148	129	138	159	
Multivariable HR	1.00	0.97	0.82	0.87	1.00	1.00
95% CI		(0.76–1.20)	(0.65–1.05)	(0.67–1.11)	(0.79–1.26)	
Ratio *n*-6/*n*-3						
Quintile median	6.9	8.0	8.8	9.7	11	
Nonadvanced cases (*n*)	3,796	3,897	3,837	3,758	3,646	
Multivariable HR	1.00	1.02	1.03	1.03	0.98	0.44
95% CI		(0.98–1.07)	(0.98–1.07)	(0.98–1.08)	(0.94–1.03)	
Advanced cases (*n*)	588	597	619	565	561	
Multivariable HR	1.00	1.01	1.06	0.97	0.98	0.51
95% CI		(0.90–1.14)	(0.95–1.19)	(0.87–1.09)	(0.87–1.10)	
Fatal cases (*n*)	147	143	149	147	139	
Multivariable HR	1.00	0.97	1.01	1.00	0.93	0.62
95% CI		(0.77–1.22)	(0.80–1.27)	(0.79–1.26)	(0.74–1.18)	
Linoleic acid						
Quintile median (% energy)	3.8	5.0	5.9	6.9	8.5	
Nonadvanced cases (*n*)	3,791	3,901	3,834	3,762	3,646	
Multivariable HR	1.00	1.04	1.03	1.02	1.01	0.94
95% CI		(0.99–1.09)	(0.98–1.08)	(0.98–1.07)	(0.97–1.06)	
Advanced cases (*n*)	596	565	563	603	603	
Multivariable HR	1.00	0.94	0.93	1.00	1.02	0.44
95% CI		(0.83–1.05)	(0.83–1.05)	(0.89–1.12)	(0.90–1.14)	
Fatal cases (*n*)	162	133	125	140	165	
Multivariable HR	1.00	0.81	0.74	0.82	0.96	0.95
95% CI		(0.64–1.02)	(0.59–0.94)	(0.65–1.04)	(0.77–1.21)	
ALA						
Quintile median (% energy)	0.41	0.52	0.60	0.70	0.88	
Nonadvanced cases (*n*)	3,746	3,810	3,875	3,752	3,751	
Multivariable HR	1.00	1.04	1.06	1.03	1.05	0.11
95% CI		(0.99–1.08)	(1.02–1.11)	(0.98–1.08)	(1.00–1.10)	

(Continued on the following page)

Table 3. Risk of prostate cancer with increasing quintiles of *n*-6 and *n*-3 PUFAs, ratio of *n*-6 to *n*-3 PUFAs, essential fatty acids, and marine PUFAs (Cont'd)

	Quintiles of intake					
	I	II	III	IV	V	P_{trend}
Advanced cases (*n*)	550	586	563	592	639	
Multivariable HR	1.00	1.06	1.02	1.07	1.17	0.01
95% CI		(0.94–1.19)	(0.90–1.15)	(0.95–1.20)	(1.04–1.31)	
Fatal cases (*n*)	136	152	129	144	164	
Multivariable HR	1.00	1.09	0.91	1.00	1.13	0.39
95% CI		(0.86–1.38)	(0.71–1.16)	(0.78–1.27)	(0.89–1.43)	
EPA						
Quintile median (% energy)	0.003	0.007	0.012	0.018	0.036	
Nonadvanced cases (*n*)	3,487	3,865	3,831	3,842	3,909	
Multivariable HR	1.00	1.09	1.07	1.07	1.05	0.69
95% CI		(1.04–1.14)	(1.02–1.12)	(1.02–1.12)	(1.00–1.10)	
Advanced cases (*n*)	568	583	596	627	556	
Multivariable HR	1.00	1.01	1.02	1.06	0.93	0.15
95% CI		(0.90–1.13)	(0.91–1.15)	(0.95–1.19)	(0.82–1.04)	
Fatal cases (*n*)	165	175	138	121	126	
Multivariable HR	1.00	1.08	0.87	0.76	0.82	0.02
95% CI		(0.87–1.34)	(0.69–1.09)	(0.60–0.97)	(0.64–1.04)	
DPA						
Quintile median (% energy)	0	0.0040	0.0058	0.0084	0.014	
Nonadvanced cases (*n*)	3,593	3,789	3,871	3,900	3,781	
Multivariable HR	1.00	1.06	1.05	1.06	1.02	0.55
95% CI		(1.01–1.11)	(1.00–1.10)	(1.01–1.11)	(0.98–1.07)	
Advanced cases (*n*)	569	609	610	560	582	
Multivariable HR	1.00	1.07	1.04	0.95	0.99	0.43
95% CI		(0.95–1.20)	(0.93–1.17)	(0.85–1.07)	(0.88–1.11)	
Fatal cases (*n*)	176	160	136	115	138	
Multivariable HR	1.00	0.94	0.82	0.71	0.88	0.12
95% CI		(0.75–1.18)	(0.65–1.02)	(0.56–0.90)	(0.70–1.11)	
DHA						
Quintile median (% energy)	0.0010	0.0019	0.0028	0.0040	0.0068	
Nonadvanced cases (*n*)	3,611	3,820	3,825	3,852	3,826	
Multivariable HR	1.00	1.05	1.05	1.05	1.02	0.82
95% CI		(1.00–1.10)	(1.00–1.10)	(1.00–1.10)	(0.98–1.07)	
Advanced cases (*n*)	531	617	613	604	565	
Multivariable HR	1.00	1.14	1.13	1.11	1.03	0.56
95% CI		(1.02–1.29)	(1.01–1.27)	(0.99–1.25)	(0.91–1.16)	
Fatal cases (*n*)	154	175	132	133	131	
Multivariable HR	1.00	1.16	0.89	0.91	0.92	0.19
95% CI		(0.93–1.44)	(0.70–1.12)	(0.72–1.15)	(0.73–1.17)	
EPA + DHA						
Quintile median (% energy)	0.013	0.026	0.039	0.058	0.103	
Nonadvanced cases (*n*)	3,557	3,865	3,778	3,847	3,887	
Multivariable HR	1.00	1.07	1.05	1.06	1.04	0.45
95% CI		(1.03–1.12)	(1.00–1.10)	(1.01–1.11)	(1.00–1.10)	
Advanced cases (*n*)	557	582	628	601	562	
Multivariable HR	1.00	1.03	1.10	1.05	0.97	0.31
95% CI		(0.91–1.15)	(0.98–1.23)	(0.93–1.18)	(0.86–1.09)	
Fatal cases (*n*)	161	166	140	130	128	
Multivariable HR	1.00	1.05	0.91	0.86	0.87	0.10
95% CI		(0.85–1.31)	(0.72–1.14)	(0.68–1.09)	(0.68–1.10)	

NOTE: All HR include adjustment for age at entry, race, family history of prostate cancer, education, marital status, PSA testing in the past 3 years, physical activity, smoking, self-reported diabetes, BMI at baseline, calories, alcohol, and intake of tomatoes.

Investigation into Cancer (EPIC) study (12) found a suggestive increased risk of high-grade prostate (RR comparing the highest with the lowest, 1.79; 95% CI, 0.91–3.53; $P_{trend} = 0.014$). Overall, studies of ALA concentration in blood do not support a hypothesis of increased risk of prostate cancer with higher ALA level.

In our study, we also found suggestive inverse association between EPA and fatal prostate cancer, a long-chain fatty acid derived mainly from fish. This observation is consistent with animal and *in vitro* data showing protective effect of marine *n*-3 fatty acids on prostate cancer development and progression (5–8). It is also consistent with some prospective epidemiologic studies that investigated the association of either total fish, or marine *n*-3 PUFAs with advanced prostate cancer or with prostate cancer mortality (35, 43, 44) but not with others (15, 22, 45). Furthermore, in another analysis among this cohort, the fish component subscore of the Alternate Mediterranean Diet Score and the *n*-3 fatty acid component subscore of the Alternate Healthy Eating Index were associated with an inverse association of fatal prostate cancer (46). On the other hand, in our study, we found no association of prostate cancer with intake of DHA, an important marine fatty acid that has been shown to have antiproliferative effects *in vitro* (5–9), nor with the combination of EPA and DHA. Overall, our study only weakly supports a possible inverse association of marine fatty acids or fish intake with advanced or fatal prostate cancer.

Several studies have examined associations of EPA and DHA in blood with advanced or high-grade prostate cancer (12, 24, 41, 42) and reported inconsistent results. Three studies found no association between EPA in blood and risk of advanced or high-grade prostate cancer (24, 42, 47), whereas the EPIC study (12) found that EPA concentration in plasma was related to an increased risk of high-grade prostate cancer (RR, 2.00; 95% CI, 1.07–3.76; $P_{trend} = 0.031$). DHA in blood was not related to the risk of advanced or high-grade prostate cancer in the PHS, the MEC, or in the EPIC studies (42, 47) but was associated with a significantly increased risk of high-grade prostate cancer (OR, 2.50; 95% CI, 1.34–4.65; $P_{trend} = 0.04$) in the PCPT (24). Relationships of the marine fatty acids to advanced, high-grade, and fatal prostate cancer remain to be elucidated.

A major strength of this study was the large sample size, which allowed investigation of fats and fatty acids with advanced and fatal prostate cancer. In addition, dietary data were measured prospectively, which reduced error from recall bias, and this population had a relatively wide intake of dietary fat. On the other hand, measurement error is an inherent limitation in self-reported dietary assessment. In addition, in this study, we assessed diet only once, at baseline. Therefore, we could not examine the effects of early-life exposure (e.g., childhood and young adulthood), or prolonged cumulative exposure to fat and fatty acids on the risk of prostate cancer. In addition, considering the long latency period of cancer, the duration of follow-up in our study may have been insufficient to detect an association. Furthermore, among our investigations of fats and fatty acids with prostate cancer outcomes, many different exposures were evaluated, increasing the likelihood that chance findings could arise among the multiple comparisons. Among the association that we did find, none were strikingly strong. Therefore, we feel these findings should be interpreted cautiously and in light of the other relevant literature.

In summary, our large prospective cohort study found that the associations of fat and fatty acids differed by prostate cancer severity. Fat and fatty acid intakes were not related to the risk of nonadvanced prostate cancer, whereas intakes of saturated fat, ALA, and EPA were related to the risk of advanced or fatal prostate cancer. More studies are needed to elucidate the role of fat and fatty acids in prostate cancer etiology.

Disclosure of Potential Conflicts of Interest

A.R. Hollenbeck is a consultant/advisory board of Scientific Advisory Board, Love/Avon Army of Women. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The views expressed herein are solely those of the authors and do not necessarily reflect those of the Florida Cancer Data System (FCDC) or Florida Department of Health (FDOH). The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.R. Hollenbeck, Y. Park
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