Dietary intake of n−3 and n−6 fatty acids and the risk of prostate cancer[1–3]

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ABSTRACT

Background: Laboratory studies have shown that n−3 fatty acids inhibit and n−6 fatty acids stimulate prostate tumor growth, but whether the dietary intake of these fatty acids affects prostate cancer risk in humans remains unclear.

Objective: We prospectively evaluated the association between intakes of α-linolenic (ALA; 18:3n−3), eicosapentaenoic (EPA; 20:5n−3), docosahexaenoic (DHA; 22:6n−3), linoleic (LA; 18:2n−6), and arachidonic (AA; 20:4n−6) acids and prostate cancer risk.

Design: A cohort of 47 866 US men aged 40–75 y with no cancer history in 1986 was followed for 14 y.

Results: During follow-up, 2965 new cases of total prostate cancer were ascertained, 448 of which were advanced prostate cancer. ALA intake was unrelated to the risk of total prostate cancer. In contrast, the multivariate relative risks (RRs) of advanced prostate cancer from comparisons of extreme quintiles of ALA from nonanimal sources and ALA from meat and dairy sources were 2.02 (95% CI: 1.35, 3.03) and 1.53 (0.88, 2.66), respectively. EPA and DHA intakes were related to lower prostate cancer risk. The multivariate RRs of total and advanced prostate cancer from comparisons of extreme quintiles of the combination of EPA and DHA were 0.89 (0.77, 1.04) and 0.74 (0.49, 1.08), respectively. LA and AA intakes were unrelated to the risk of prostate cancer. The multivariate RR of advanced prostate cancer from a comparison of extreme quintiles of the ratio of LA to ALA was 0.62 (0.45, 0.86).

Conclusions: Increased dietary intakes of ALA may increase the risk of advanced prostate cancer. In contrast, EPA and DHA intakes may reduce the risk of total and advanced prostate cancer. *Am J Clin Nutr* 2004;80:204–16.

KEY WORDS Diet, n−3 fatty acids, n−6 fatty acids, prostate cancer, cohort study

INTRODUCTION

Dietary fat has been one of the most frequently investigated modifiable risk factors for prostate cancer, yet findings from epidemiologic investigations of total fat intake are inconclusive (1). In recent years, interest has turned to the intake of specific fatty acids rather than to total fat intake, notably n−3 and n−6 fatty acids, and their ratios (2). α-Linolenic acid (ALA; 18:3n−3) is the principal dietary n−3 fatty acid in most Western diets; it is present in some vegetable oils and nuts, leafy vegetables, and animal fats (3). ALA can serve in a limited capacity as a precursor for eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3) (4). The concentrations of EPA and DHA are high in fish oils and they consistently inhibit tumor cell growth in animal models and in cell lines from human prostate tumors (5). Linoleic acid (LA; 18:2n−6) is the most abundant n−6 fatty acid in the human diet, and it is found primarily in vegetable oils. Long-chain n−6 fatty acids enhance prostate tumor cell growth in human prostate tumor-derived cell lines (6).

Several biological mechanisms have been proposed to explain these observations. Among the most salient of these mechanisms is the inhibition of eicosanoid biosynthesis by arachidonic acid (AA; 20:4n−6), an n−6 fatty acid derived from LA by the action of cyclooxygenase-2 (5). AA-derived eicosanoids, such as prostaglandin E_2, strongly stimulate prostate tumor growth in animal models or prostate tumor-derived cell lines (7–9). In contrast, EPA and DHA inhibit cyclooxygenase-2 and the formation of prostaglandin E_2 from AA (5). However, whether dietary n−3 and n−6 fatty acids and the ratio of these 2 classes of fatty acids affect the risk of prostate cancer in humans remains unclear (10).

In 1993, we reported on the association between dietary fat and risk of prostate cancer from a prospective study of male health professionals (11). The first study report was based on a single dietary assessment with follow-up from 1986 to 1990 and included 300 incident cases of prostate cancer. In that study, ALA was positively related to risk of advanced prostate cancer, whereas no association with prostate cancer was seen with n−3 fatty acids from fish and LA. More recently, with follow-up time through 1998 (2482 cases), we reported an inverse relation of fish and marine fatty acid intake with prostate cancer risk (12). The

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present analyses extend those findings to evaluate in detail the association between n−3 and n−6 fatty acids and prostate cancer based on repeated dietary assessments with follow-up from 1986 to 2000 and including 2965 incident cases of prostate cancer.

SUBJECTS AND METHODS

Study population

The Health Professionals Follow-Up Study was initiated in 1986 when 51 529 US male health professionals aged 40–65 y responded to a mailed questionnaire concerning their medical history and known or suspected risk factors for cancer and other chronic diseases. Subsequently, follow-up questionnaires have been mailed every 2 y to the entire cohort to update information on potential risk factors and to identify newly diagnosed illnesses. The overall follow-up rate was 94%. We excluded at baseline men who had previously been diagnosed with cancer other than nonmelanoma skin cancer (1996 men excluded) and men who provided inadequate information on diet (1667 men excluded). After these exclusions, the analytic cohort consisted of 47 866 men, and they were followed to 2000. This study was approved by the Institutional Review Board on the Use of Human Subjects in Research of the Harvard School of Public Health.

Assessment of diet

Dietary intake was assessed in 1986, 1990, and 1994 by using a 131-item semiquantitative food-frequency questionnaire. To calculate intakes of nutrients and individual food items, a commonly used unit or portion size for each food (eg, one pat of margarine) was specified and the participants were asked to report how often, on average over the past year, they had consumed that amount. There were 9 possible response categories for each food item that ranged from never or less than once per month to ≥6 times/d. The dietary questionnaire inquired specifically about the kind of fat usually used for frying, sautéing, and baking (vegetable oil, solid vegetable oil shortening, butter, margarine, lard, or none). In addition, we requested information on individual type and brand of cooking oil and margarine using one open-ended question each. We specifically queried about the frequency of intake of canned tuna, dark-meat fish (mackerel, salmon, sardines, bluefish, and swordfish), other fish (not specified), and shrimp, lobster, and scallops. We also inquired about the use of fish-oil supplements starting in 1988 (yes or no). Our assessment of fish-oil supplement use was expanded starting in 1990 (none, <2.5 g/d, 2.5–4.9 g/d, 5.0–9.9 g/d, and ≥10 g/d). This information was used to update exposure to EPA during follow-up.

Nutrient intakes were calculated for each participant by multiplying the frequency of consumption for each item by the nutrient content of the specified portion size. Food-composition data were primarily based on values obtained from the US Department of Agriculture but were supplemented with information from the manufacturers. We considered total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources separately.

The validity and reproducibility of the food-frequency questionnaire were assessed by comparing nutrient intakes from two 1-wk diet records with those of the food-frequency questionnaire among a random sample of 127 Boston area participants. The correlation between energy-adjusted intake of polyunsaturated fat measured by diet records and by food-frequency questionnaire was 0.37 (13). The correlations between intakes of total polyunsaturated fat, LA, and EPA as a proportion of dietary fat and the proportion of fatty acids in adipose tissue samples were 0.50, 0.48, and 0.47, respectively (14).

Case ascertainment

On each follow-up questionnaire, we asked participants to report any diagnosis of prostate cancer during the previous 2 y. For men who reported prostate cancer (or next of kin for decedents), we requested permission to obtain their medical records and pathology reports to confirm the diagnosis and obtain further details. The response rate was >96%, and medical records and pathology reports were successfully obtained for 90% of the cases. The remaining cases included in the analysis were based on self-report. We included self-reports because the reporting of the diagnosis of prostate cancer was found to be highly accurate in these health professionals. A study physician who was unaware of the questionnaire data used the information received from any procedures or tests conducted during the initial diagnosis, including pathologic stage (or clinical stage, if a prostatectomy was not done), and Gleason histologic grade for the prostatectomy specimen (or biopsy specimen if a prostatectomy was not done) to stage the prostate cancer cases. Because cases with incidental microscopic focal tumors (T1a) are generally indolent and are more susceptible to detection bias due to differential rates of undergoing surgery for benign prostatic hyperplasia, we excluded these from our primary analysis. Because dietary fats have been reported to be more strongly related to metastatic prostate cancer than to incident prostate cancer (15), we considered total nonstage T1a prostate cancer, organ-confined prostate cancer, and advanced prostate cancer as separate prostate cancer endpoints. The latter were defined as cancers that were fatal by the end of follow-up or cancers extending regionally to the seminal vesicle, other adjacent organs, pelvic lymph nodes, or distal organs (usually bone) at the time of diagnosis.

Data analysis

Person-time of follow-up for each participant was calculated from the date of return of the 1986 questionnaire to the date of prostate cancer diagnosis, the date of death, or the end of the study period on 1 January 2000. For each fatty acid, the relative risk (RR) was calculated as the Mantel-Haenszel summary rate ratio of prostate cancer (16), with adjustment for age. Multivariate RRs were computed by using Cox proportional hazards regression (17). We used multivariate nutrient-density models because of their intuitive interpretation as a measure of dietary composition (18). The basic model included total energy intake; the percentages of energy derived from polyunsaturated fat, saturated fat, monounsaturated fat, *trans* fat, protein, and alcohol; and other potentially confounding variables. The coefficients from these models can be interpreted as the estimated effect of substituting a specific percentage of energy from a specific type of fat for the same percentage of energy from carbohydrates. To distinguish between individual polyunsaturates, we entered all major polyunsaturated fatty acids into the model simultaneously. Because intakes of EPA and DHA were highly correlated ($r = 0.95$) because of shared food sources, we entered the sum of EPA and DHA (EPA + DHA) into the model. We also examined EPA and DHA as separate variables unadjusted for each other.

TABLE 1
Mean intakes and correlations of n−3 and n−6 fatty acids in the Health Professionals Follow-Up Study at baseline in 1986[1]

Variable	ALA from meat and dairy sources	ALA from nonanimal sources	EPA	DHA	LA	AA
Mean intake (% of energy)	0.16	0.33	0.05	0.08	5.22	0.04
Pearson correlation coefficient[2]						
ALA (18:3n−3)						
From meat and dairy sources[3]	1.0					
From nonanimal sources[4]	−0.35	1.0				
EPA (20:5n−3)[5]	−0.22	0.07	1.0			
DHA (22:6n−3)[5]	−0.25	0.09	0.95	1.0		
LA (*cis*-18:2n−6)[6]	−0.10	0.66	−0.12	−0.11	1.0	
AA (20:4n−6)[7]	0.30	0.09	0.25	0.27	0.12	1.0

[1] ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid.
[2] All correlations are significant ($P < 0.0001$).
[3] The major 3 food items contributing to ALA intakes from meat and dairy sources were beef, pork, or lamb as a main dish; cheese (eg, American or cheddar); and skim milk.
[4] The major 3 food items contributing to ALA intakes from nonanimal sources were mayonnaise or other creamy salad dressings, oil and vinegar dressings, and margarine.
[5] The major 2 food items contributing to EPA and DHA intakes were fish and chicken.
[6] The major 3 food items contributing to LA intakes were mayonnaise, oil and vinegar dressings, and peanut butter.
[7] The major 3 food items contributing to AA intakes were chicken, eggs, and hamburgers.

In addition to these variables, the basic model included known or suspected risk factors for prostate cancer, such as family history of prostate cancer (yes or no), major ancestry (Scandinavian, Southern European, other Caucasian, and other ancestry), BMI at age 21 y (kg/m^2, ordinal), height (inches, ordinal), history of type 2 diabetes mellitus (yes or no), history of vasectomy (yes or no), vigorous physical activity (yes or no), cigarette smoking in the past 10 y (yes or no), intakes of energy-adjusted lycopene (μg/d, ordinal), calcium (energy-adjusted from diet plus supplements, mg/d, ordinal), and supplemental vitamin E (yes or no). Tests of linear trend across increasing categories of fatty acid consumption were conducted by modeling the median values of quintiles of fatty acids as a continuous variable in the multivariate model.

We determined categories of exposure on the basis of cumulative average updating to compute the best assessment of average long-term fatty acid intake based on all available questionnaires and to allow for changes in fatty acid consumption over time. In this approach, we used the 1986 intakes to predict outcomes between 1986 and 1990, the average of the 1986 and the 1990 intakes to predict outcomes between 1990 and 1994, and the average of the 1986, 1990, and 1994 intakes to predict outcomes between 1994 and 2000. All hypothesis tests were two sided and were conducted by using SAS release 8.2 (SAS Institute, Cary, NC).

RESULTS

During 598 321 person-years of follow-up between 1986 and 2000, we documented 2965 new cases of prostate cancer. In our study population, ALA from meat and dairy sources tended to be inversely correlated with other polyunsaturates, with the exception of arachidonic acid, with which it was positively correlated (**Table 1**). ALA from nonanimal sources was positively correlated with LA ($r = 0.66$) but was not correlated with EPA ($r = 0.07$), DHA ($r = 0.09$), and AA ($r = 0.09$). LA showed weak inverse correlations with EPA (−0.12) and DHA ($r = -0.11$) and a weak positive correlation with AA ($r = 0.12$). The range of exposure varied ≈3-fold between means of extreme quintiles of ALA from meat and dairy sources. The variation between means of extreme quintiles was 4-fold for ALA from nonanimal sources, >10-fold for EPA and DHA, 2-fold for LA, and 3-fold for AA.

We evaluated intakes of ALA from meat and dairy sources, ALA from nonanimal sources, and EPA, DHA, LA, and AA in relation to various risk factors for prostate cancer to assess the potential for confounding (**Table 2**). In general, men with higher intakes of ALA from meat and dairy sources smoked more but were less likely to undergo prostate-specific antigen (PSA) tests and be physically active, and they consumed less lycopene and fish than did men with low intakes of ALA from meat and dairy sources. In contrast, men with greater intakes of ALA from nonanimal sources and greater intakes of EPA and DHA smoked less, and they were more likely to undergo PSA tests and be physically active, and they consumed more lycopene, fish, and supplemental vitamin E than did men with low intakes of ALA from nonanimal sources and low intakes of EPA and DHA. No clear risk factor patterns were observed for LA and AA.

We next examined intakes of total ALA, ALA from meat and dairy sources, ALA from nonanimal sources, and EPA, DHA, EPA + DHA, LA, and AA in relation to risk of total prostate cancer (**Table 3**). No association was observed for intakes of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources. Intakes of EPA, DHA, and EPA + DHA showed a significant or borderline significant inverse relation with total prostate cancer. In contrast, LA and AA were unrelated to risk of total prostate cancer. The ratio of LA to ALA and the ratio of LA to EPA + DHA showed no association with total prostate cancer.

To address the influence of fatty acids on early stage prostate cancer, we repeated our analysis after restricting the outcome to organ-confined prostate cancers. The relations were similar to those for total prostate cancer, albeit somewhat weaker; only EPA was statistically significant (**Table 4**). There were only minor differences between the age-adjusted and multivariate RRs, suggesting no major confounding. In contrast to the results

TABLE 2
Selected characteristics of 47 864 participants in the Health Professionals Follow-Up Study by extreme quintile (Q) of intakes of major n−3 and n−6 fatty acids at baseline in 1986[1]

	ALA (18:3n−3) from meat and dairy sources		ALA (18:3n−3) from nonanimal sources		EPA (20:5n−3)		DHA (22:6n−3)		LA (*cis*-18:2n−6)		AA (20:4n−6)	
Characteristic	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Age in 1986 (y)	55.2 ± 9.9[2]	54.8 ± 9.6	55.9 ± 9.8	53.7 ± 9.6	53.9 ± 9.9	55.8 ± 9.7	53.6 ± 9.8	55.8 ± 9.7	56.1 ± 9.9	53.9 ± 9.5	54.3 ± 10.0	55.2 ± 9.5
Current BMI (kg/m^2)	24.7 ± 3.1	26.0 ± 3.5	25.6 ± 3.4	25.6 ± 3.4[3]	25.4 ± 3.3	25.5 ± 3.4[4]	25.5 ± 3.4	25.5 ± 3.4[3]	25.4 ± 3.4	25.6 ± 3.3[4]	24.9 ± 2.9	26.0 ± 3.6
BMI at age 21 y (kg/m^2)	22.9 ± 2.8	23.2 ± 3.1	22.9 ± 2.9	23.1 ± 2.9	22.8 ± 2.8	23.3 ± 3.0	22.8 ± 2.9	23.3 ± 3.1	23.0 ± 3.0	23.1 ± 2.9[3]	22.8 ± 2.7	23.3 ± 3.1
Height (in)[5]	69.9 ± 2.9	70.2 ± 2.8	70.1 ± 2.8	70.1 ± 2.9[3]	70.2 ± 2.7	69.8 ± 2.9	70.2 ± 2.8	69.9 ± 2.9	70.0 ± 2.9	70.2 ± 2.8	70.1 ± 2.7	70.0 ± 2.9[3]
Family history of prostate cancer (%)	11.6	12.3[4]	11.6	11.7[3]	12.1	11.2[4]	12.4	11.3[4]	11.1	12.4[4]	11.9	11.9[3]
History of type 2 diabetes (%)	2.2	4.1	3.6	3.3[4]	3.2	3.7[6]	3.1	3.7[4]	2.9	3.9	2.7	4.6
Screening for PSA by 2000 (%)	79.6	74.3	75.8	78.1	76.3	78.4	75.6	79.1	75.9	78.7	78.1	75.6[4]
Smoked in the past 10 y (%)	16.6	26.8	24.5	20.1	21.8	19.8	23.0	19.5	22.9	21.8[3]	18.2	24.7
Vigorous exercise (METs/wk)	18.7 ± 32.3	8.6 ± 19.5	11.0 ± 23.8	12.7 ± 26.5[4]	10.3 ± 23.2	16.2 ± 27.2	9.9 ± 24.8	16.1 ± 26.8	14.8 ± 27.1	10.9 ± 22.0	14.8 ± 28.3	11.2 ± 26.1
Intakes												
ALA from meat and dairy (% of energy)	0.09 ± 0.02	0.25 ± 0.06	0.21 ± 0.07	0.14 ± 0.05	0.18 ± 0.07	0.14 ± 0.06	0.18 ± 0.07	0.14 ± 0.06	0.17 ± 0.08	0.15 ± 0.06	0.13 ± 0.06	0.19 ± 0.07
ALA from nonanimal sources (% of energy)	0.39 ± 0.19	0.24 ± 0.15	0.13 ± 0.05	0.54 ± 0.16	0.32 ± 0.19	0.35 ± 0.2	0.31 ± 0.19	0.36 ± 0.17	0.20 ± 0.09	0.49 ± 0.22	0.29 ± 0.15	0.36 ± 0.21
EPA (% of energy)	0.06 ± 0.06	0.03 ± 0.03	0.03 ± 0.04	0.04 ± 0.04	0.01 ± 0.005	0.11 ± 0.05	0.01 ± 0.01	0.10 ± 0.05	0.05 ± 0.05	0.04 ± 0.03	0.03 ± 0.03	0.06 ± 0.06
DHA (% of energy)	0.11 ± 0.10	0.06 ± 0.05	0.06 ± 0.06	0.09 ± 0.08	0.02 ± 0.01	0.19 ± 0.09	0.01 ± 0.01	0.19 ± 0.08	0.09 ± 0.09	0.07 ± 0.06	0.05 ± 0.04	0.11 ± 0.10
LA (% of energy)	5.3 ± 1.9	4.9 ± 1.4	4.2 ± 1.2	6.8 ± 1.6	5.4 ± 1.7	4.9 ± 1.5	5.4 ± 1.8	4.9 ± 1.6	3.3 ± 0.5	7.6 ± 1.3	4.9 ± 1.7	5.5 ± 1.7
AA (% of energy)	0.03 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.02 ± 0.005	0.06 ± 0.02
Lycopene (μg/d)[7]	12 148 ± 9263	8933 ± 6611	8502 ± 6528	11 932 ± 9285	8915 ± 7100	12 320 ± 8652	8904 ± 7162	12 332 ± 8657	10 394 ± 7998	10 246 ± 7883[4]	10 300 ± 8464	10 550 ± 7498[4]
Calcium (mg/d)[7]	874 ± 442	947 ± 445	959 ± 475	854 ± 394	921 ± 449	897 ± 452[4]	905 ± 441	905 ± 459[3]	985 ± 497	839 ± 384	972 ± 470	860 ± 435
Red meat (servings/wk)	9.8 ± 2.2	16.8 ± 4.6	14.9 ± 4.3	12.8 ± 3.7	14.6 ± 4.5	11.9 ± 3.4	14.8 ± 4.5	11.8 ± 3.4	13.0 ± 4.3	13.4 ± 3.9	12.3 ± 3.9	14.3 ± 4.3
Fish (servings/wk)	3.3 ± 2.6	1.6 ± 1.4	1.9 ± 1.7	2.5 ± 2.1	0.8 ± 0.9	4.9 ± 2.5	0.5 ± 0.4	5.3 ± 2.2	2.7 ± 2.4	2.1 ± 1.8	1.6 ± 1.4	3.1 ± 2.6
Supplemental vitamin E (%)	41.1	29.5	32.6	34.2[3]	31.2	38.9	30.7	39.6	35.7	34.3[4]	35.6	35.5[3]
Dairy products (servings/wk)	15.7 ± 5.6	24.6 ± 10.2	22.9 ± 9.6	18.1 ± 7.0	20.9 ± 8.9	18.7 ± 7.2	20.9 ± 9.1	18.7 ± 7.3	21.6 ± 9.5	18.5 ± 7.3	20.6 ± 8.9	19.3 ± 7.8

[1] All values (except age) were standardized to the age distribution of the study population. The variability of potential risk factors for prostate cancer across increasing intakes of fatty acids was evaluated by using quintiles of fatty acids, but only values for Q1 and Q5 are shown. All *P* values for the tests of trend are significant ($P < 0.0001$), except when noted otherwise. ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid; MET, metabolic equivalents; PSA, prostate-specific antigen.

[2] $\bar{x} \pm$ SD (all such values).

[3] *P* for trend > 0.10.

[4] *P* for trend: $0.0001 \leq P < 0.05$.

[5] To convert inches to centimeters, multiply by 2.54.

[6] *P* for trend: $0.05 \leq P \leq 0.10$.

[7] Nutrients were adjusted for total energy intake.

TABLE 3
Relative risk (RR) of total prostate cancer in relation to quintile (Q) of intakes of major n−3 and n−6 fatty acids in the Health Professionals Follow-Up Study, 1986–2000[1]

Variable	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total ALA (18:3n−3)						
Intake (% of energy)	<0.37	0.37–0.43	0.44–0.49	0.50–0.58	>0.58	—
Cases (*n*)	578	622	610	621	534	—
Age-adjusted RR	1.0	1.09	1.11	1.18	1.10	0.07
Multivariate RR	1.0	1.09	1.10	1.18	1.09	0.26
95% CI	—	(0.97, 1.23)	(0.97, 1.25)	(1.03, 1.34)	(0.93, 1.26)	—
ALA (18:3n−3) from meat and dairy sources						
Intake (% of energy)	<0.11	0.11–0.14	0.15–0.17	0.18–0.21	>0.21	—
Cases (*n*)	619	582	551	573	640	—
Age-adjusted RR	1.0	1.01	0.97	1.04	1.07	0.18
Multivariate RR	1.0	0.96	0.90	0.97	1.02	0.72
95% CI	—	(0.84, 1.09)	(0.77, 1.05)	(0.81, 1.16)	(0.82, 1.27)	—
ALA (18:3n−3) from nonanimal sources						
Intake (% of energy)	<0.18	0.18–0.26	0.27–0.34	0.35–0.44	>0.44	—
Cases (*n*)	676	582	589	567	551	—
Age-adjusted RR	1.0	0.92	1.01	1.01	0.97	0.91
Multivariate RR	1.0	0.92	1.00	0.99	0.98	0.92
95% CI	—	(0.82, 1.04)	(0.88, 1.14)	(0.86, 1.13)	(0.84, 1.15)	—
LA (*cis*-18:2n−6)						
Intake (% of energy)	<4.03	4.03–4.71	4.72–5.34	5.35–6.18	>6.18	—
Cases (*n*)	597	634	595	573	566	—
Age-adjusted RR	1.0	1.11	1.09	1.09	1.13	0.08
Multivariate RR	1.0	1.05	1.00	1.00	1.06	0.66
95% CI	—	(0.93, 1.19)	(0.88, 1.15)	(0.86, 1.16)	(0.89, 1.26)	—
AA (20:4n−6)						
Intake (% of energy)	<0.028	0.028–0.035	0.036–0.041	0.042–0.049	>0.049	—
Cases (*n*)	568	603	608	579	607	—
Age-adjusted RR	1.0	1.07	1.05	1.02	1.06	0.57
Multivariate RR	1.0	1.06	1.04	1.02	1.08	0.44
95% CI	—	(0.94, 1.19)	(0.92, 1.18)	(0.89, 1.16)	(0.94, 1.25)	—
LA:ALA (*cis*-18:2n−6:18:3n−3)						
Ratio	<9.1	9.1–10.3	10.4–11.1	11.2–12.7	>12.7	—
Cases (*n*)	577	576	596	588	628	—
Age-adjusted RR	1.0	1.07	1.09	1.06	1.05	0.65
Multivariate RR	1.0	1.03	1.05	1.01	1.00	0.84
95% CI	—	(0.91, 1.16)	(0.93, 1.18)	(0.89, 1.14)	(0.89, 1.14)	—
EPA (20:5n−3)						
Intake (% of energy)	<0.014	0.014–0.027	0.028–0.042	0.043–0.066	>0.066	—
Cases (*n*)	497	625	608	615	620	—
Age-adjusted RR	1.0	1.15	1.08	1.06	0.92	0.005
Multivariate RR	1.0	1.13	1.06	1.01	0.88	0.002
95% CI	—	(0.99, 1.27)	(0.94, 1.20)	(0.89, 1.16)	(0.76, 1.01)	—
DHA (22:6n−3)						
Intake (% of energy)	<0.032	0.032–0.053	0.054–0.079	0.080–0.122	>0.122	—
Cases (*n*)	505	595	584	647	634	—
Age-adjusted RR	1.0	1.08	0.99	1.05	0.93	0.08
Multivariate RR	1.0	1.06	0.96	1.02	0.89	0.07
95% CI	—	(0.94, 1.19)	(0.84, 1.09)	(0.89, 1.16)	(0.78, 1.04)	—
EPA + DHA (20:5n−3 + 22:6n−3)						
Intake (% of energy)	<0.057	0.057–0.098	0.099–0.143	0.144–0.214	>0.214	—
Cases (*n*)	498	620	587	619	641	—
Age-adjusted RR	1.0	1.09	0.99	1.02	0.94	0.05
Multivariate RR	1.0	1.07	0.96	0.97	0.89	0.04
95% CI	—	(0.94, 1.20)	(0.84, 1.09)	(0.85, 1.12)	(0.77, 1.04)	—
LA:EPA + DHA [*cis*-18:2n−6:(20:5n−3 + 22:6n−3)]						
Ratio	<23.57	23.57–37.51	37.52–58.32	58.33–102.34	>102.34	—
Cases (*n*)	603	622	603	591	546	—
Age-adjusted RR	1.0	1.12	1.12	1.15	1.11	0.27
Multivariate RR	1.0	1.12	1.13	1.15	1.14	0.42
95% CI	—	(0.99, 1.26)	(0.99, 1.28)	(1.00, 1.32)	(0.98, 1.33)	—

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, and intakes of calcium, supplemental vitamin E, and lycopene. Individual polyunsaturated fatty acids were mutually adjusted for each other. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were not adjusted for each other. Stage T1a lesions (≤3% of the total) were excluded because these lesions are typically indolent and are especially prone to detection bias. ALA, α-linolenic acid; LA, linoleic acid; AA, arachidonic acid.

TABLE 4
Relative risk (RR) of organ-confined prostate cancer in relation to quintile (Q) of intakes of major n−3 and n−6 fatty acids in the Health Professionals Follow-Up Study, 1986–2000[1]

Variable	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total ALA (18:3n−3)						
Intake (% of energy)	<0.37	0.37–0.43	0.44–0.49	0.50–0.58	>0.58	—
Cases (*n*)	300	349	354	379	297	—
Age-adjusted RR	1.0	1.08	1.12	1.24	1.11	0.10
Multivariate RR	1.0	1.04	1.05	1.16	1.04	0.54
95% CI	—	(0.89, 1.22)	(0.89, 1.25)	(0.97, 1.39)	(0.85, 1.27)	—
ALA (18:3n−3) from meat and dairy sources						
Intake (% of energy)	<0.11	0.11–0.14	0.15–0.17	0.18–0.21	>0.21	—
Cases (*n*)	338	335	328	333	345	—
Age-adjusted RR	1.0	1.04	1.03	1.17	1.03	0.71
Multivariate RR	1.0	0.98	0.94	0.98	0.96	0.79
95% CI	—	(0.82, 1.17)	(0.76, 1.15)	(0.77, 1.24)	(0.72, 1.27)	—
ALA (18:3n−3) from nonanimal sources						
Intake (% of energy)	<0.18	0.18–0.26	0.27–0.34	0.35–0.44	>0.44	—
Cases (*n*)	373	333	329	339	305	—
Age-adjusted RR	1.0	0.95	0.99	1.07	0.95	0.96
Multivariate RR	1.0	0.91	0.94	0.99	0.89	0.51
95% CI	—	(0.77, 1.07)	(0.79, 1.12)	(0.82, 1.19)	(0.72, 1.10)	—
LA (*cis*-18:2n−6)						
Intake (% of energy)	<4.03	4.03–4.71	4.72–5.34	5.35–6.18	>6.18	—
Cases (*n*)	294	373	356	342	314	—
Age-adjusted RR	1.0	1.25	1.25	1.22	1.24	0.03
Multivariate RR	1.0	1.19	1.17	1.16	1.24	0.15
95% CI	—	(1.01, 1.42)	(0.97, 1.40)	(0.95, 1.41)	(0.99, 1.56)	—
AA (20:4n−6)						
Intake (% of energy)	<0.028	0.028–0.035	0.036–0.041	0.042–0.049	>0.049	—
Cases (*n*)	319	372	343	319	326	—
Age-adjusted RR	1.0	1.13	1.03	0.99	1.06	0.99
Multivariate RR	1.0	1.10	0.99	0.97	1.05	0.98
95% CI	—	(0.94, 1.29)	(0.84, 1.17)	(0.81, 1.16)	(0.86, 1.27)	—
LA:ALA (*cis*-18:2n−6:18:3n−3)						
Ratio	<9.1	9.1–10.3	10.4–11.1	11.2–12.7	>12.7	—
Cases (*n*)	291	333	351	352	352	—
Age-adjusted RR	1.0	1.17	1.18	1.19	1.15	0.20
Multivariate RR	1.0	1.12	1.14	1.13	1.10	0.45
95% CI	—	(0.95, 1.31)	(0.97, 1.34)	(0.96, 1.34)	(0.93, 1.31)	—
EPA (20:5n−3)						
Intake (% of energy)	<0.014	0.014–0.027	0.028–0.042	0.043–0.066	>0.066	—
Cases (*n*)	282	353	347	343	354	—
Age-adjusted RR	1.0	1.14	1.06	1.03	0.92	0.04
Multivariate RR	1.0	1.09	1.02	0.97	0.87	0.03
95% CI	—	(0.93, 1.28)	(0.87, 1.21)	(0.81, 1.15)	(0.72, 1.06)	—
DHA (22:6n−3)						
Intake (% of energy)	<0.032	0.032–0.053	0.054–0.079	0.080–0.122	>0.122	—
Cases (*n*)	273	349	333	350	374	—
Age-adjusted RR	1.0	1.16	1.03	1.03	1.03	0.63
Multivariate RR	1.0	1.13	0.99	0.99	1.02	0.77
95% CI	—	(0.96, 1.33)	(0.83, 1.17)	(0.83, 1.19)	(0.84, 1.25)	—
EPA + DHA (20:5n−3 + 22:6n−3)						
Intake (% of energy)	<0.057	0.057–0.098	0.099–0.143	0.144–0.214	>0.214	—
Cases (*n*)	281	349	344	342	363	—
Age-adjusted RR	1.0	1.08	1.02	0.99	0.96	0.23
Multivariate RR	1.0	1.03	0.96	0.94	0.91	0.21
95% CI	—	(0.88, 1.22)	(0.81, 1.14)	(0.78, 1.13)	(0.74, 1.11)	—
LA:EPA + DHA [*cis*-18:2n−6:(20:5n−3 + 22:6n−3)]						
Ratio	<23.57	23.57–37.51	37.52–58.32	58.33–102.34	>102.34	—
Cases (*n*)	330	352	337	331	329	—
Age-adjusted RR	1.0	1.11	1.08	1.09	1.13	0.26
Multivariate RR	1.0	1.09	1.07	1.10	1.17	0.22
95% CI	—	(0.93, 1.29)	(0.90, 1.28)	(0.91, 1.32)	(0.95, 1.44)	—

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, and intakes of calcium, supplemental vitamin E, and lycopene. Individual polyunsaturated fatty acids were mutually adjusted for each other. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were not adjusted for each other. ALA, α-linolenic acid; LA, linoleic acid; AA, arachidonic acid.

for total prostate cancer, intake of LA was positively associated with risk of organ-confined prostate cancer in age-adjusted analysis. However, the relation became statistically non-significant in multivariate analysis.

We also considered more aggressive forms of prostate cancer as an outcome. In our previous report (11), ALA intake in 1986 was positively associated with the risk of advanced prostate cancer from 1986 to 1990 for high versus low quintile of intake (multivariate RR: 3.43; 95% CI: 1.67, 7.04; *P* for trend = 0.002). In new analyses from 1990 to 2000, the association for ALA intake persisted, although it was somewhat weaker (multivariate RR: 1.70; 95% CI: 1.08, 2.68; *P* for trend = 0.04). We then examined the entire follow-up period (1986–2000) (**Table 5**). For total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources, the age-adjusted RRs for the comparison of extreme quintiles were 1.69 (95% CI: 1.26, 2.27), 1.29 (95% CI: 0.98, 1.70), and 1.39 (95% CI: 1.05, 1.85), respectively. After adjustment for potentially confounding variables, the RRs for comparisons of extreme quintiles of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources were 1.98 (95% CI: 1.34, 2.93), 1.53 (95% CI: 0.88, 2.66), and 2.02 (95% CI: 1.35, 3.03), respectively. Adjustment for LA accounted for most of the difference between the age-adjusted and multivariate findings. After further adjustment for red meat, the multivariate RR of advanced prostate cancer for comparisons of extreme quintiles of total ALA was 1.92 (95% CI: 1.29, 2.84; *P* for trend = 0.0002).

EPA + DHA was suggestively related to a lower risk of advanced prostate cancer, which was mainly due to DHA and to a lesser extent to EPA. When we analyzed EPA + DHA as a continuous variable instead of ordinal, an increase in 0.5 g/d (approximately equivalent to 3 servings of fish per week) was associated with a multivariate RR of advanced prostate cancer of 0.53 (95% CI: 0.26, 1.08). LA and AA showed no association with risk of advanced prostate cancer. LA:ALA was inversely related to risk of advanced prostate cancer. In contrast, LA:EPA + DHA was positively associated with risk of advanced prostate cancer in an age-adjusted analysis, but the relation became statistically nonsignificant in multivariate analysis.

Fish-oil supplement use showed no relation with risk of prostate cancer. Compared with nonusers of fish-oil supplements, the multivariate RRs of total, organ-confined, and advanced prostate cancer for men at a dose of ≥2.5 g supplemental fish oil/d were 0.89 (95% CI: 0.62, 1.30; *P* for trend = 0.91), 0.81 (95% CI: 0.49, 1.33; *P* for trend = 0.44), and 0.91 (95% CI: 0.33, 2.55; *P* for trend = 0.80), respectively.

When ALA from individual food sources was examined, the risk of advanced prostate cancer with intake of ALA from meat and dairy sources appeared to increase more strongly among men with low intakes of ALA from nonanimal sources than among men with high intakes of ALA from nonanimal sources (**Table 6**). Similarly, the risk of advanced prostate cancer with intake of ALA from nonanimal sources was suggestively more pronounced among men with low intakes of ALA from meat and dairy sources than among those with high intakes of ALA from meat and dairy sources (*P* for interaction = 0.07). We also examined the combination of ALA and LA and the combination of ALA and EPA + DHA in relation to the risk of advanced prostate cancer. The relation of ALA to risk of advanced prostate cancer did not differ by level of LA intake (*P* for interaction = 0.49; **Table 7**), and it did not differ by level of EPA + DHA intake (*P* for interaction = 0.96; **Table 8**).

To evaluate further the association with ALA, we examined the major food sources of this fatty acid in our study population (**Table 9**); these foods provided 41% of ALA intake at baseline. Most food items were unrelated or weakly positively related to risk of advanced prostate cancer. After adjustment for potentially confounding variables, increasing intakes of mayonnaise or other creamy salad dressings was the only food group that showed a statistically significant positive trend, although men ($n = 15$ cases) in the highest category had no increased risk. In age-adjusted analysis, intake of one or more servings per day of beef, pork, or lamb as a main dish was related to increased risk of advanced prostate cancer compared with intake at <1/mo. However, that relation became statistically nonsignificant in multivariate analysis.

Stronger associations for ALA were seen when we used cases of fatal prostate cancer as an endpoint. The multivariate RRs for comparisons of extreme quintiles of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources were 2.12 (95% CI: 1.24, 3.64; *P* for trend = 0.007), 2.74 (95% CI: 1.27, 5.88; *P* for trend = 0.004), and 2.33 (95% CI: 1.33, 4.08; *P* for trend = 0.004), respectively. For fatal prostate cancer, the multivariate RRs for comparisons of extreme quintiles of EPA, DHA, and EPA + DHA were 0.89 (95% CI: 0.55, 1.46; *P* for trend = 0.51), 0.65 (95% CI: 0.39, 1.09; *P* for trend = 0.18), and 0.68 (95% CI: 0.40, 1.17; *P* for trend = 0.12), respectively.

To examine whether increased PSA screening among men with high intake of ALA from nonanimal sources and men with high intake of EPA + DHA may have accounted for the observed associations, we excluded all noncases who did not have a PSA test by 2000. The relations were essentially unaltered. The multivariate RRs of advanced prostate cancer for comparisons of extreme quintiles of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources were 1.99 (95% CI: 1.36, 2.94; *P* for trend = 0.0009), 1.61 (95% CI: 0.93, 2.81; *P* for trend = 0.049), and 2.06 (95% CI: 1.38, 3.08; *P* for trend = 0.0004), respectively. The multivariate RRs of total prostate cancer for comparisons of extreme quintiles of EPA, DHA, and EPA + DHA were 0.85 (95% CI: 0.74, 0.98; *P* for trend = 0.0005), 0.87 (95% CI: 0.75, 1.00; *P* for trend = 0.02), and 0.85 (95% CI: 0.73, 0.99; *P* for trend = 0.01), respectively. Similar results were observed when we limited the analysis to men who did not have a PSA test by 1994.

We also examined whether latent symptoms of prostate cancer may have caused a change in fatty acid consumption by repeating our analysis after excluding the first 4 y of follow-up and relating the 1986 fatty acid intake to incidence of prostate cancer from 1990 to 2000. The relations with EPA and DHA remained essentially unchanged. The multivariate RRs of total prostate cancer for comparisons of extreme quintiles of EPA, DHA, and EPA + DHA were 0.78 (95% CI: 0.67, 0.89; *P* for trend = 0.0002), 0.78 (95% CI: 0.67, 0.91; *P* for trend = 0.0003), and 0.86 (95% CI: 0.73, 1.00; *P* for trend = 0.01), respectively. The multivariate RR of advanced prostate cancer for comparisons of extreme quintiles of EPA + DHA was 0.65 (95% CI: 0.41, 1.01; *P* for trend = 0.08). In contrast, the associations with ALA were attenuated. The multivariate RRs of advanced prostate cancer for comparisons of extreme quintiles of total ALA, ALA from meat and dairy sources, and ALA from nonanimal sources were 1.41 (95% CI: 0.90, 2.19; *P* for trend = 0.08), 1.12 (95% CI: 0.58,

TABLE 5
Relative risk (RR) of advanced prostate cancer in relation to quintile (Q) of intakes of major n−3 and n−6 fatty acids in the Health Professionals Follow-Up Study, 1986–2000[1]

Variable	Q1	Q2	Q3	Q4	Q5	*P* for trend
Total ALA (18:3n−3)						
Intake (% of energy)	<0.37	0.37–0.43	0.44–0.49	0.50–0.58	>0.58	—
Cases (*n*)	82	89	87	90	100	—
Age-adjusted RR	1.0	1.33	1.41	1.53	1.69	0.0005
Multivariate RR	1.0	1.47	1.57	1.77	1.98	0.001
95% CI	—	(1.07, 2.01)	(1.12, 2.21)	(1.24, 2.53)	(1.34, 2.93)	—
ALA (18:3n−3) from meat and dairy sources						
Intake (% of energy)	<0.11	0.11–0.14	0.15–0.17	0.18–0.21	>0.21	—
Cases (*n*)	95	74	82	82	115	—
Age-adjusted RR	1.0	0.87	0.97	1.01	1.29	0.02
Multivariate RR	1.0	0.83	0.99	1.13	1.53	0.06
95% CI	—	(0.58, 1.19)	(0.66, 1.49)	(0.71, 1.82)	(0.88, 2.66)	—
ALA (18:3n−3) from nonanimal sources						
Intake (% of energy)	<0.18	0.18–0.26	0.27–0.34	0.35–0.44	>0.44	—
Cases (*n*)	96	79	89	79	105	—
Age-adjusted RR	1.0	0.92	1.12	1.11	1.39	0.007
Multivariate RR	1.0	1.11	1.44	1.43	2.02	0.0004
95% CI	—	(0.80, 1.54)	(1.03, 2.03)	(0.98, 2.08)	(1.35, 3.03)	—
LA (*cis*-18:2n−6)						
Intake (% of energy)	<4.03	4.03–4.71	4.72–5.34	5.35–6.18	>6.18	—
Cases (*n*)	97	86	77	91	97	—
Age-adjusted RR	1.0	1.06	0.99	1.23	1.26	0.06
Multivariate RR	1.0	0.90	0.73	0.84	0.80	0.39
95% CI	—	(0.65, 1.24)	(0.51, 1.05)	(0.57, 1.24)	(0.52, 1.24)	—
AA (20:4n−6)						
Intake (% of energy)	<0.028	0.028–0.035	0.036–0.041	0.042–0.049	>0.049	—
Cases (*n*)	83	81	93	92	99	—
Age-adjusted RR	1.0	1.04	1.16	1.12	1.07	0.62
Multivariate RR	1.0	1.01	1.11	1.09	1.11	0.54
95% CI	—	(0.73, 1.40)	(0.79, 1.52)	(0.77, 1.53)	(0.78, 1.59)	—
LA:ALA (*cis*-18:2n−6:18:3n−3)						
Ratio	<9.1	9.1–10.3	10.4–11.1	11.2–12.7	>12.7	—
Cases (*n*)	105	85	86	88	84	—
Age-adjusted RR	1.0	0.94	0.98	0.94	0.76	0.06
Multivariate RR	1.0	0.84	0.86	0.81	0.62	0.005
95% CI	—	(0.63, 1.13)	(0.63, 1.15)	(0.59, 1.09)	(0.45, 0.86)	—
EPA (20:5n−3)						
Intake (% of energy)	<0.014	0.014–0.027	0.028–0.042	0.043–0.066	>0.066	—
Cases (*n*)	87	92	94	86	89	—
Age-adjusted RR	1.0	1.01	1.03	0.89	0.82	0.08
Multivariate RR	1.0	1.05	0.99	0.87	0.82	0.18
95% CI	—	(0.75, 1.37)	(0.73, 1.35)	(0.63, 1.21)	(0.58, 1.17)	—
DHA (22:6n−3)						
Intake (% of energy)	<0.032	0.032–0.053	0.054–0.079	0.080–0.122	>0.122	—
Cases (*n*)	94	82	94	89	89	—
Age-adjusted RR	1.0	0.84	0.91	0.86	0.73	0.06
Multivariate RR	1.0	0.79	0.84	0.82	0.71	0.13
95% CI	—	(0.58, 1.07)	(0.62, 1.15)	(0.59, 1.13)	(0.49, 1.08)	—
EPA + DHA (20:5n−3 + 22:6n−3)						
Intake (% of energy)	<0.057	0.057–0.098	0.099–0.143	0.144–0.214	>0.214	—
Cases (*n*)	83	98	86	95	86	—
Age-adjusted RR	1.0	1.11	0.93	0.98	0.78	0.04
Multivariate RR	1.0	1.04	0.85	0.92	0.74	0.08
95% CI	—	(0.76, 1.40)	(0.61, 1.18)	(0.65, 1.29)	(0.49, 1.08)	—
LA:EPA + DHA [*cis*-18:2n−6:(20:5n−3 + 22:6n−3)]						
Ratio	<23.57	23.57–37.51	37.52–58.32	58.33–102.34	>102.34	—
Cases (*n*)	85	88	94	92	89	—
Age-adjusted RR	1.0	1.20	1.35	1.39	1.46	0.03
Multivariate RR	1.0	1.14	1.27	1.29	1.38	0.20
95% CI	—	(0.83, 1.57)	(0.91, 1.78)	(0.91, 1.86)	(0.94, 2.04)	—

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, and intakes of calcium, supplemental vitamin E, and lycopene. Individual polyunsaturated fatty acids were mutually adjusted for each other. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were not adjusted for each other. ALA, α-linolenic acid; LA, linoleic acid; AA, arachidonic acid.

TABLE 6
Multivariate relative risks (RRs) (and 95% CIs) of advanced prostate cancer in relation to the combined intake of α-linolenic acid (ALA) from meat and dairy sources and ALA from nonanimal sources in the Health Professionals Follow-Up Study, 1986–2000[1]

	Tertile of ALA from meat and dairy sources (% of energy)		
Variable	1 (<0.13)	2 (0.13–0.18)	3 (>0.18)
Tertile of ALA from nonanimal sources (% of energy)			
1 (<0.24)	1.0 (—)	1.33 (0.72, 2.44)	1.68 (0.88, 3.15)
2 (0.24–0.37)	1.16 (0.89, 2.74)	1.78 (0.98, 3.25)	2.34 (1.21, 4.53)
3 (>0.37)	2.29 (1.31, 4.01)	2.30 (1.24, 4.25)	2.05 (1.00, 4.17)
P for interaction	—	—	0.07

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, percentage of energy from linoleic acid (LA) intake, percentage of energy from eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) intake, percentage of energy from arachidonic acid intake, and intakes of calcium, supplemental vitamin E, and lycopene.

2.18; *P* for trend = 0.48), and 1.65 (95% CI: 1.02, 2.67; *P* for trend = 0.04), respectively.

The associations between intake of total ALA, ALA from meat and dairy sources, ALA from nonanimal sources, and EPA, DHA, EPA + DHA, LA, and AA and total, organ-confined, and advanced prostate cancer risk were not modified by each other or by other potential prostate cancer risk factors, such as time period, age, family history of prostate cancer, major ancestry, BMI, height, history of type 2 diabetes, history of vasectomy, vigorous physical activity, cigarette smoking in the previous decade, and intakes of total energy, lycopene, calcium, vitamin E, red meat, fish, and alcohol (all *P* for interaction > 0.05).

DISCUSSION

In this large prospective study, we found that ALA from nonanimal sources and ALA from meat and dairy sources were associated or suggestively associated with an increased risk of advanced prostate cancer. This finding agrees with the finding of a single previous study (19) that evaluated ALA intake by food source. That case-control study (19) reported odds ratios of 2.03 (95% CI: 1.01, 4.07) and 2.98 (95% CI: 1.02, 8.68) for advanced prostate cancer for comparisons of extreme quartiles of nonanimal and animal ALA intakes, respectively. Although we cannot rule out the possibility that ALA from both nonanimal and animal sources represents a marker of a correlated component of fat or fat-containing food, such as red meat, one prospective study and 6 case-control studies reported a statistically significant (19–23) or nonsignificant (24, 25) 2- to 4-fold increased risk of prostate cancer in men with high ALA exposure determined by dietary or blood assessment.

In contrast, 3 case-control studies (26–28), all of which examined advanced prostate cancer outcomes separately, observed no association between ALA intake and prostate cancer. Only 2 studies (29, 30) suggest a potential benefit of ALA on prostate cancer risk. One was a prospective study from the Netherlands (29) that found a decreased risk of total prostate cancer ($P = 0.09$) and no association between total linolenic acid intake and advanced prostate cancer. The range of linolenic acid intake in that study largely overlapped with that in our study. However, LA intake in the Dutch study was considerably higher than in our study. Because ALA and LA compete for key enzymes, such as Δ^6-desaturase, which is involved in parallel pathways for eicosanoid synthesis (31), low intakes of LA may further exaggerate the risk of prostate cancer related to ALA intake. Thus, one possible explanation for the disparate results between the Dutch study (29) and ours is that a high intake of LA alleviates the increased risk of prostate cancer associated with a high intake of ALA.

TABLE 7
Multivariate relative risks (RRs) (and 95% CIs) of advanced prostate cancer in relation to the combined intake of total α-linolenic acid (ALA) and linoleic acid (LA) in the Health Professionals Follow-Up Study, 1986–2000[1]

	Tertile of total ALA intake (% of energy)		
Variable	1 (<0.41)	2 (0.41–0.52)	3 (>0.52)
Tertile of LA (% of energy)			
1 (<4.49)	1.43 (0.74, 2.78)	2.13 (1.07, 4.23)	2.96 (1.20, 7.28)
2 (4.49–5.60)	1.64 (0.82, 3.26)	1.54 (0.79, 3.01)	2.26 (1.14, 4.45)
3 (>5.60)	1.0 (—)	2.35 (1.20, 4.58)	2.07 (1.09 3.91)
P for interaction			0.49

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, percentage of energy from eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) intake, percentage of energy from arachidonic acid intake, and intakes of calcium, supplemental vitamin E, and lycopene. The reference group consisted of the men who were in the bottom tertile of total ALA intake and the top tertile of LA intake.

TABLE 8
Multivariate relative risks (RRs) (and 95% CIs) of advanced prostate cancer in relation to the combined intake of total α-linolenic acid (ALA) and eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) (EPA + DHA) in the Health Professionals Follow-up Study, 1986–2000[1]

	Tertile of total ALA intake (% of energy)		
Variable	1 (<0.41)	2 (0.41–0.52)	3 (>0.52)
Tertile of EPA + DHA (% of energy)			
1 (<0.08)	1.35 (0.86, 2.13)	1.68 (1.04, 2.73)	2.08 (1.28, 3.37)
2 (0.08–0.16)	0.97 (0.62, 1.52)	1.51 (0.97, 2.33)	1.72 (1.07, 2.75)
3 (>0.16)	1.0 (—)	1.46 (0.96, 2.22)	1.57 (0.99, 2.48)
P for interaction	—	—	0.96

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, intake of total energy, percentage of energy from protein intake, percentage of energy from monounsaturated fat intake, percentage of energy from saturated fat intake, percentage of energy from *trans* unsaturated fat intake, percentage of energy from α-linoleic acid (LA) intake, percentage of energy from arachidonic acid intake, and intakes of calcium, supplemental vitamin E and lycopene. The reference group consisted of the men who were in the bottom tertile of total ALA intake and the top tertile of EPA + DHA intake.

The other inverse study (30) found lower prostatic tissue concentrations of ALA in cases than in controls ($P = 0.008$). However, little is known about whether ALA concentrations in prostate cancer cases are altered by the malignancy (32). Circumstantial evidence suggests that ALA may differentially influence aggressive prostate cancer types and indolent types. An intervention study (33) using a flaxseed-supplemented diet in prostate cancer patients reported a suggestive decrease in PSA in men with Gleason sums of ≤6 ($P = 0.10$), whereas a suggestive increase in PSA ($P = 0.13$) was observed in men with Gleason

TABLE 9
Relative risk (RR) of advanced prostate cancer in relation to intakes of major food contributors of α-linolenic acid (ALA) in the Health Professionals Follow-Up Study, 1986–2000[1]

	Frequency of intake						
Variable	<1 time/mo	1–3 times/mo	1 time/wk	2–4 times/wk	5–6 times/wk	≥1 time/d	*P* for trend
Beef, pork, or lamb as a main dish							
Cases (*n*)	32	54	112	162	73	15	—
Age-adjusted RR	1.0	0.91	1.16	1.05	1.41	1.84	0.03
Multivariate RR	1.0	0.89	1.04	0.89	1.17	1.58	0.28
95% CI	—	(0.57, 1.39)	(0.69, 1.56)	(0.60, 1.33)	(0.75, 1.82)	(0.83, 2.99)	—
Cheese (eg, American or cheddar)							
Cases (*n*)	25	77	90	166	66	24	—
Age-adjusted RR	1.0	1.67	2.25	1.57	1.93	1.39	0.87
Multivariate RR	1.0	1.67	2.15	1.41	1.68	1.19	0.25
95% CI	—	(1.05, 2.67)	(1.35, 3.41)	(0.91, 2.19)	(1.03, 2.74)	(0.66, 2.13)	—
Skim milk							
Cases (*n*)	88	25	16	73	70	176	—
Age-adjusted RR	1.0	0.86	1.02	1.01	1.06	1.10	0.28
Multivariate RR	1.0	0.89	1.08	1.04	1.07	1.07	0.50
95% CI	—	(0.57, 1.41)	(0.63, 1.85)	(0.75, 1.43)	(0.77, 1.48)	(0.82, 1.39)	—
Mayonnaise or other creamy salad dressings							
Cases (*n*)	70	79	83	134	67	15	—
Age-adjusted RR	1.0	1.02	1.23	1.35	2.14	0.98	0.002
Multivariate RR	1.0	0.96	1.11	1.17	1.84	0.86	0.04
95% CI	—	(0.69, 1.33)	(0.80, 1.54)	(0.87, 1.59)	(1.28, 2.62)	(0.49, 1.53)	—
Oil and vinegar dressing							
Cases (*n*)	94	89	72	122	46	25	—
Age-adjusted RR	1.0	1.12	1.29	1.04	1.05	1.05	0.76
Multivariate RR	1.0	1.15	1.24	1.03	1.05	1.17	0.91
95% CI	—	(0.86, 1.56)	(0.91, 1.71)	(0.77, 1.37)	(0.72, 1.52)	(0.74, 1.84)	—
Margarine							
Cases (*n*)	82	30	15	90	81	150	—
Age-adjusted RR	1.0	0.81	0.69	1.02	1.16	1.13	0.06
Multivariate RR	1.0	0.85	0.69	0.99	1.09	1.02	0.40
95% CI	—	(0.55, 1.29)	(0.39, 1.24)	(0.73, 1.35)	(0.79, 1.49)	(0.77, 1.35)	—

[1] Values were adjusted for current age, time period, major ancestry, family history of prostate cancer, BMI at age 21 y, height, history of type 2 diabetes, history of vasectomy, cigarette smoking in the previous decade, vigorous physical activity, and intakes of total energy and supplemental vitamin E.

sums of ≥7. In our study, ALA was not associated with total or organ-confined prostate cancer, but it was positively related to risk of advanced prostate cancer.

The increased risk of advanced prostate cancer with ALA observed in the current study was within the range of adequate intake of 2.2 g/d, or 1% of energy, for adults recommended by the International Society for the Study of Fatty Acids and Lipids (34). The significance of a potentially adverse effect of ALA intake on prostate cancer risk is accentuated by a 40% increased availability of ALA as a proportion of total energy intake in recent decades in the United States (35). We were unable to identify individual foods responsible for an increased risk of advanced prostate cancer, although suggestive positive relations were observed for intakes of beef, pork, or lamb as a main dish and for mayonnaise or other creamy salad dressings. The most likely explanations for these findings are that most foods contribute only a fraction to overall ALA intake and that overall ALA intake rather than intake of any particular food item may be the main determinant of risk.

A high intake of EPA + DHA was associated or suggestively associated with a decreased risk of total and advanced prostate cancer. This finding is largely consistent with the findings of a recent analysis of fish consumption from our cohort (12), another prospective study (36), and 6 case-control studies (25, 37–41) that found decreased prostate cancer risk associated with high intakes of fish or marine n−3 fatty acids, all but one (41) of which were statistically significant. However, the results of 9 prospective studies (21, 24, 29, 42–47) and 4 case-control studies (23, 48–50) argue against a relation between marine fatty acids or fish and prostate cancer; one cohort study (51) reported a borderline statistically significant increased risk with greater fish intake. Our results for fish-oil supplement use were weaker than those for EPA + DHA from diet and supplements combined, which suggests that fish may contain additional protective agents not contained in fish-oil supplements, such as vitamin D and retinol.

A high LA intake was unrelated to the risk of prostate cancer. Previous investigations on LA and prostate cancer are mixed; 3 case-control studies observed a statistically significant (25) or nonsignificant (23, 27) positive association, 2 prospective studies (21, 29) and 3 case-control studies (22, 26, 42) reported no association, and one additional prospective study (24) and 3 case-control studies (19, 28, 52) observed a statistically significant (52) or nonsignificant (19, 24, 28) inverse relation. We, as did others (21–24, 29), observed no association with AA. Our null findings for LA and AA are in contrast with hypothetical biological mechanisms, which suggests that n−6 fatty acids enhance prostate tumor growth (6).

Our results of a decreased risk of advanced prostate cancer with increasing ratios of LA to ALA, the main n−6 and n−3 fatty acids in Western diets, agree with the results of 2 prospective studies (21, 24) that reported an inverse relation with prostate cancer. In contrast, the positive association we observed between the ratio of LA to EPA + DHA and advanced prostate cancer was not consistent with the finding in one study (21), which found a statistically nonsignificant inverse relation. Taken together, the sparse data available suggest that decreasing the overall ratio of n−6 to n−3 fatty acids does not favorably affect prostate cancer risk. However, because the risk estimates for the ratio of LA to ALA and of LA to EPA + DHA in relation to advanced prostate cancer were in opposite directions, evaluation of these fatty acids independently, rather than as ratios, is likely to be more informative.

Fatty acids may modulate prostate carcinogenesis through numerous processes, such as modification of membrane phospholipid composition (53), alteration of cell signaling and receptor activity (54–56), lipid peroxidation (57), cyclooxygenase inhibition (58), cytokine production (59), and interference with androgen activity (60). Experimental studies show that prostate tumor growth is inhibited by EPA and DHA (6, 61). In contrast, ALA shows no protective effect on prostate tumor growth in animal models (6, 61), and ALA can promote prostate cancer cell growth in vitro (62). Thus, laboratory studies of prostate carcinogenesis comparing the effects of ALA with those of EPA and DHA provide no evidence in support of a protective influence of ALA in its own right.

The specific mechanisms underlying why n−3 fatty acids mainly from terrestrial and those mainly from marine sources may have divergent effects on prostate cancer risk are unclear. One possibility is that ALA is less effective than are EPA and DHA in displacing AA from cell membrane phospholipids (63, 64) and in inhibiting prostaglandin synthesis (65). ALA conversion is limited for EPA (66) and severely constrained for DHA (67), particularly under conditions of adequate supply of preformed EPA and DHA (68). Increased dietary availability of ALA does not obligatorily enhance DHA synthesis and may even decrease tissue DHA concentrations (69) because DHA synthesis appears to be tightly regulated by feedback inhibition (70). Another possibility is that EPA and DHA have numerous antiinflammatory properties that have been linked with decreased cancer risk (71), whereas ALA shows little influence on immune function and inflammatory cytokine production at feasible dietary intakes (72).

In summary, our results suggest that a high ALA intake is associated with an increased risk of advanced prostate cancer. In contrast, high EPA and DHA intakes may be associated with a decreased risk of total and advanced prostate cancer. Because the apparent adverse effect of ALA on risk of advanced prostate cancer may counter the reduction in cardiovascular disease that may be achieved through ALA use (73), further research in men is imperative to resolve the relation of ALA to prostate cancer and to determine the risk-benefit tradeoffs associated with dietary intake of ALA (74).

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