Fatty acid composition of plasma phospholipids and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition[1–3]

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ABSTRACT

Background: Plausible biological mechanisms underlie possible associations between fatty acids in blood and risk of prostate cancer; epidemiologic evidence for an association, however, is inconsistent.

Objective: The objectives were to assess the association between plasma phospholipid fatty acids and risk of total prostate cancer by stage and grade.

Design: This was a nested case-control analysis of 962 men with a diagnosis of prostate cancer after a median follow-up time of 4.2 y and 1061 matched controls who were taking part in the European Prospective Investigation into Cancer and Nutrition. The fatty acid composition of plasma phospholipids was measured by gas chromatography, and the risk of prostate cancer was estimated by using conditional logistic regression with adjustment for lifestyle variables.

Results: We found a positive association between palmitic acid and risk of total, localized, and low-grade prostate cancer. The risk of prostate cancer for men in the highest quintile compared with the lowest quintile of palmitic acid was 1.47 (95% CI: 0.97, 2.23; *P* for trend = 0.032). We found an inverse association between stearic acid and the risk of total, localized, and low-grade prostate cancer; men in the highest quintile of stearic acid had a relative risk of 0.77 (95% CI: 0.56, 1.06; *P* for trend = 0.03). There were significant positive associations between myristic, α-linolenic, and eicosapentaenoic acids and risk of high-grade prostate cancer.

Conclusion: The associations between palmitic, stearic, myristic, α-linolenic, and eicosapentaenoic acids and prostate cancer risk may reflect differences in intake or metabolism of these fatty acids between the precancer cases and controls and should be explored further. *Am J Clin Nutr* 2008;88:1353–63.

INTRODUCTION

Worldwide, prostate cancer is the second most common type of cancer in men, although incidence rates vary considerably between countries (1). Results from ecologic studies suggest that modifiable factors such as diet may contribute to the variation in prostate cancer incidence throughout the world (2); however, no dietary components are established risk factors (3).

Results from prospective cohort studies suggest that the intake of dietary fat is not associated with the risk of prostate cancer (4); however, most dietary assessment techniques cannot provide accurate and precise measures of individual fatty acid intake because of incomplete information in nutrient databases and the under- or overreporting of fat intake (5, 6). The fatty acid composition of adipose tissue or blood lipids may be a better alternative for assessing the various types and sources of fat consumed (7–9). Evidence for an association between fatty acids in blood and the risk of prostate cancer is equivocal (10–17). The proportion of the essential n−3 polyunsaturated fatty acid α-linolenic acid (18:3n−3) has been associated with a greater risk of prostate cancer in some (10, 12, 14) but not all (11, 15, 17) studies. Although the findings from in vitro and animal studies suggest a role for the 2 major n−3 long-chain polyunsaturated fatty acids, eicosapentaenoic (20:5n−3) and docosahexaenoic (22:6n−3) acids, in reducing the risk of prostate cancer (18–22), there is limited evidence from epidemiologic studies to support

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this hypothesis (13, 17). The association between the saturated fatty acids myristic (14:0), pentadecanoic (15:0), and heptadecanoic acids (17:0), which are valid biomarkers of dairy fat consumption (8, 23) and the risk of prostate cancer, has not been well described. The objective of the present study was to determine the association between the fatty acid composition of plasma phospholipids and the risk of prostate cancer in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC).

MATERIALS AND METHODS

Study population

The detailed recruitment procedures and collection of questionnaire data, anthropometric measurements, and blood samples for the EPIC study have been published elsewhere (24). Briefly, dietary and nondietary variables were assessed with standardized questionnaires that were administered between 1992 and 2000 to 519 978 persons across Europe, including 153 457 men, of whom 137 001 provided a blood sample. The present study included prostate cancer cases that occurred after blood collection and matched control subjects from 8 of the 10 participating countries: Denmark, Germany, Greece, Italy, Netherlands, Spain, Sweden, and the United Kingdom. No data are presented for France, Norway, or the regional centers in Naples (Italy) and Utrecht (Netherlands), because these cohorts included only women. The center in Malmö (Sweden) also did not contribute data for the present analysis.

Blood samples for plasma were drawn from participants into monovettes containing sodium citrate as an anticoagulant except in Umeå, Sweden, where EDTA-treated vials were used. Participants were not required to fast, although time since the last consumption of food or drink was recorded. All samples except those from the Oxford center were stored at 5–10 °C and were protected from light from the time of collection through their transfer to local laboratories, where they were further processed and separated into aliquots. For study subjects recruited through the Oxford center, blood samples were collected by a network of general practitioners in the United Kingdom and were transported to a central laboratory in Norfolk by mail; they were protected from light but were exposed to ambient temperature. For participants in all centers except Denmark and Umeå, 0.5-mL plasma aliquots were placed in plastic straws, which were heat-sealed and stored in liquid nitrogen (−196 °C). In Denmark, 1-mL aliquots of plasma were placed into Nunc tubes and stored in the vapor phase of liquid nitrogen containers (−150 °C), and in Umeå, plasma samples were stored in 1.5-mL plastic tubes at −70 °C.

Follow-up for cancer incidence and vital status

In Denmark, Italy, Netherlands, Spain, Sweden, and the United Kingdom, incident cancer cases were identified through record linkage with regional or national cancer registries. In Germany and Greece, follow-up was based on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin. Data on vital status in most EPIC study centers were collected from mortality registries at the regional or national level, in combination with data collected by active follow-up (Greece). For each EPIC study center, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status. By March 2007, complete follow-up data had been reported to the International Agency for Research on Cancer up to December 2003 or December 2004 for most centers (dates varied between centers, from June 1999 to January 2003). For Germany and Greece, the censoring date was considered to be the date of the last known contact, date of diagnosis, or death, whichever came first. The 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death was used to code cancer site, and cancer of the prostate as analyzed here was defined as code C61.

Selection of case and control subjects

In total, the 8 countries contributing to the present study included 962 men diagnosed with incident prostate cancer by the end of each center's follow-up period. Cases with no available blood sample and those who had missing information on the date of blood donation or who had a history of another cancer (except nonmelanoma skin cancer) at the time of blood donation were excluded. An incidence density sampling protocol for control selection was used, such that controls could include participants who became a case later in time, whereas each control subject could also be sampled more than once. Laboratory measurements for the fatty acid analysis were available for 962 cases: 292 cases in Denmark, 203 in Germany, 9 in Greece, 61 in Italy, 25

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TABLE 1
Fatty acid composition of plasma phospholipids among controls by country[1]

Fatty acid	Denmark (n = 292)	Germany (n = 203)	Greece (n = 9)	Italy (n = 61)	Netherlands (n = 25)	Spain (n = 95)	Sweden (n = 198)	United Kingdom (n = 178)
				mol%				
Saturated fatty acids								
Myristic acid (14:0)	0.33 (0.32, 0.34)	0.28 (0.27, 0.29)	0.17 (0.14, 0.21)	0.30 (0.27, 0.32)	0.25 (0.22, 0.28)	0.26 (0.25, 0.28)	0.37 (0.35, 0.38)	0.32 (0.30, 0.33)
Pentadecanoic acid (15:0)	0.16 (0.15, 0.16)	0.15 (0.14, 0.15)	0.10 (0.08, 0.12)	0.15 (0.14, 0.16)	0.10 (0.09, 0.12)	0.14 (0.13, 0.15)	0.17 (0.17, 0.18)	0.15 (0.15, 0.16)
Palmitic acid (16:0)	27.60 (27.30, 27.90)	26.30 (26.00, 26.60)	22.00 (20.70, 23.20)	25.10 (24.50, 25.70)	21.20 (20.40, 21.90)	27.00 (26.50, 27.50)	27.20 (26.90, 27.50)	26.30 (25.90, 26.70)
Heptadecanoic acid (17:0)	0.38 (0.37, 0.39)	0.40 (0.38, 0.41)	0.39 (0.33, 0.46)	0.36 (0.34, 0.38)	0.36 (0.32, 0.39)	0.38 (0.36, 0.40)	0.38 (0.37, 0.40)	0.41 (0.39, 0.42)
Stearic acid (18:0)	11.40 (11.30, 11.50)	11.70 (11.60, 11.90)	12.30 (11.70, 13.00)	11.40 (11.20, 11.60)	13.00 (12.60, 13.50)	11.30 (11.10, 11.50)	11.30 (11.10, 11.40)	11.60 (11.50, 11.80)
Monounsaturated fatty acids								
Palmitoleic acid (16:1n-7)	0.87 (0.84, 0.90)	0.79 (0.76, 0.83)	0.47 (0.39, 0.58)	0.77 (0.71, 0.83)	0.63 (0.56, 0.71)	0.59 (0.55, 0.62)	0.84 (0.81, 0.88)	0.79 (0.75, 0.83)
Oleic acid (18:1n-9)	10.20 (10.00, 10.30)	9.80 (9.60, 10.00)	12.40 (11.20, 13.80)	12.60 (12.10, 13.10)	9.70 (9.10, 10.30)	10.50 (10.20, 10.80)	10.80 (10.60, 11.00)	9.70 (9.40, 9.90)
n−6 Polyunsaturated fatty acids								
Linoleic acid (18:2n-6)	24.80 (24.40, 25.20)	26.20 (25.70, 26.70)	27.00 (24.70, 29.60)	23.30 (22.50, 24.10)	27.20 (25.80, 28.70)	25.40 (24.70, 26.10)	24.80 (24.30, 25.30)	27.30 (26.70, 27.90)
Dihomo-γ-linolenic acid (20:3n-6)	3.61 (3.53, 3.70)	4.05 (3.94, 4.17)	4.76 (4.15, 5.47)	5.20 (4.94, 5.49)	4.53 (4.17, 4.93)	3.96 (3.79, 4.13)	4.06 (3.94, 4.18)	4.09 (3.95, 4.24)
Arachidonic acid (20:4n-6)	8.81 (8.63, 8.99)	10.11 (9.86, 10.36)	10.11 (9.00, 11.37)	10.94 (10.46, 11.44)	11.14 (10.38, 11.95)	10.04 (9.68, 10.41)	8.57 (8.35, 8.79)	8.98 (8.72, 9.25)
n−3 Polyunsaturated fatty acids								
α-Linolenic acid (18:3n-3)	0.29 (0.28, 0.30)	0.23 (0.21, 0.24)	0.17 (0.13, 0.21)	0.18 (0.16, 0.20)	0.24 (0.20, 0.27)	0.12 (0.11, 0.13)	0.34 (0.33, 0.36)	0.24 (0.22, 0.25)
Eicosapentaenoic acid (20:5n-3)	1.64 (1.54, 1.73)	1.05 (0.98, 1.12)	0.78 (0.56, 1.08)	0.81 (0.71, 0.92)	1.20 (0.98, 1.46)	0.94 (0.85, 1.05)	1.53 (1.42, 1.64)	1.03 (0.95, 1.12)
n−3 Docosapentaenoic acid (22:5n-3)	1.26 (1.23, 1.28)	1.16 (1.13, 1.19)	0.92 (0.81, 1.04)	0.99 (0.95, 1.04)	1.48 (1.38, 1.60)	0.76 (0.74, 0.79)	1.34 (1.30, 1.37)	1.25 (1.21, 1.29)
Docosahexaenoic acid (22:6n-3)	4.59 (4.45, 4.74)	3.79 (3.65, 3.93)	4.20 (3.53, 5.00)	3.77 (3.53, 4.03)	4.53 (4.08, 5.03)	4.81 (4.55, 5.07)	4.37 (4.20, 4.54)	4.03 (3.85, 4.21)

[1] All values are geometric mean; 95% CI in parentheses.

TABLE 2
Baseline characteristics of prostate cancer cases and matched controls

	Cases (n = 962)	Controls (n = 1061)	P^1
Age (y)	60.4 ± 5.8[2]	60.1 ± 5.7	—
Height (m)[3]	173.6 ± 6.9	173.8 ± 6.9	0.928
Weight (kg)[3]	80.1 ± 11.2	81.1 ± 11.9	0.033
BMI (kg/m^2)[3]	26.6 ± 3.4	26.8 ± 3.6	0.019
Smoking [% (n)][3]			
Never	32.4 (305)	31.3 (316)	
Former	43.3 (407)	40.0 (404)	
Current	24.3 (229)	28.7 (290)	0.021
Alcohol intake (g/d) [% (n)]			
<8	34.5 (323)[4]	37.5 (380)	
8-15	20.0 (187)	20.6 (209)	
16-39	26.6 (249)	23.1 (234)	
>40	19.0 (178)	18.8 (190)	0.697
Physical activity[3] [% (n)]			
Inactive	21.7 (196)	18.7 (179)	
Moderately inactive	35.1 (318)	31.9 (306)	
Active	43.2 (391)	49.4 (473)	0.016
Marital status[3] [% (n)]			
Married or cohabiting	88.7 (496)	88.2 (569)	
Not married or cohabiting	11.3 (63)	11.8 (76)	0.826
Educational attainment[3] [% (n)]			
Primary or none	38.0 (352)	40.6 (410)	
Secondary	35.6 (330)	37.0 (373)	
Degree	26.3 (244)	22.4 (226)	0.241
Cases only			
Year of diagnosis	2000 (1994-2005)[5]	—	
Age at diagnosis (y)	64.9 ± 5.6	—	
Months from blood collection to diagnosis	50 (0-181)[5]	—	
Stage [n (%)][6]			
Localized	483 (50.2)	—	
Advanced	204 (21.2)	—	
Unknown	275 (28.6)	—	
Grade [n (%)][7]			
Low	441 (45.8)	—	
High	286 (29.7)	—	
Unknown	235 (24.4)	—	

[1] Weighted tests of mean difference between cases and controls in each matched set, or tests of association between category and case-control status by using conditional logistic regression, as appropriate.
[2] Mean ± SD (all such values).
[3] Unknown for some participants.
[4] Percentages may not add to 100 as the result of rounding.
[5] Median; range in parentheses.
[6] TNM staging score of T0 or T1 or T2 and N0 or NX and M0 (localized); TNM staging score of T3 or T4 and/or N1+ and/or M1 (advanced).
[7] Gleason sum < 7 or equivalent or well or moderately differentiated (low grade); Gleason sum 7 or poorly differentiated or undifferentiated (high grade).

in Netherlands, 95 in Spain, 99 in Sweden, and 178 in the United Kingdom. For each case, one male control (or in Umeå, 2) was chosen at random from appropriate risk sets consisting of all cohort members alive and free of cancer (except nonmelanoma skin cancer) at the time of diagnosis of the index case. Matching criteria were study center, age at enrolment (±6 mo), time of day of blood collection (±1 h), and time between blood draw and last consumption of food or drink (<3, 3–6, or >6 h and for Umeå <4, 4–8, or >8 h). All participants gave written informed consent to participate in the study, and the research was approved by the local ethics committees in the participating countries and the Internal Review Board of the International Agency for Research on Cancer.

Data on TNM stage and Gleason grade were collected from each center, whenever possible. Of the 962 cases, 687 (71.4%) had information on stage and 727 (75.6%) had information on grade. Tumors were classified as localized (TNM staging score of T0 or T1 or T2 and N0 or NX and M0, or stage coded in the recruitment center as localized; n = 483) or advanced (T3 or T4 and/or N1+ and/or M1, or stage coded in the recruitment center as metastatic; n = 204), or unknown. Disease was classified as low-grade [Gleason sum < 7 or equivalent (cases coded as well differentiated or moderately differentiated); n = 441) or high-grade [Gleason sum ≥ 7 or equivalent (cases coded as poorly differentiated or undifferentiated); n = 286), or unknown. For the grade of disease, results from the pathological report were used

TABLE 3
Fatty acid composition of plasma phospholipids for cases and controls

Fatty acid	Cases	Controls	P^1
	mol%		
Saturated fatty acids			
Myristic acid	0.31 (0.30, 0.32)[2]	0.31 (0.30, 0.32)	0.386
Pentadecanoic acid	0.15 (0.15, 0.16)	0.15 (0.15, 0.16)	0.546
Palmitic acid	26.68 (26.51, 26.85)	26.63 (26.47, 26.79)	0.089
Heptadecanoic acid	0.38 (0.38, 0.39)	0.38 (0.38, 0.39)	0.964
Stearic acid	11.46 (11.40, 11.52)	11.52 (11.46, 11.58)	0.032
Monounsaturated fatty acids			
Palmitoleic acid	0.79 (0.77, 0.80)	0.79 (0.77, 0.81)	0.897
Oleic acid	10.18 (10.07, 10.29)	10.29 (10.18, 10.39)	0.429
n−6 Polyunsaturated fatty acids			
Linoleic acid	25.59 (25.36, 25.82)	25.52 (25.30, 25.74)	0.951
Dihomo-γ-linolenic acid	3.98 (3.92, 4.04)	4.00 (3.95, 4.05)	0.807
Arachidonic acid	9.34 (9.22, 9.45)	9.31 (9.20, 9.42)	0.507
n−3 Polyunsaturated fatty acids			
α-Linolenic acid	0.24 (0.23, 0.25)	0.24 (0.24, 0.25)	0.301
Eicosapentaenoic acid	1.27 (1.22, 1.31)	1.24 (1.20, 1.28)	0.071
n−3 Docosapentaenoic acid	1.17 (1.15, 1.19)	1.18 (1.16, 1.20)	0.582
Docosahexaenoic acid	4.34 (4.27, 4.42)	4.25 (4.18, 4.32)	0.049

[1] Weighted tests of mean difference of the log-transformed proportion between cases and controls in each matched set.
[2] Geometric mean; 95% CI in parentheses.

where available and the World Health Organization grading system was used if the Gleason sum was not available.

Laboratory analysis

Lipids were extracted from 200 μL plasma with chloroform: methanol (2:1) according to the method of Folch et al (25) after the addition of 100 μg butylated hydroxytoluene and 20 μg internal standard (1,2-dipalmitoyl-D62-*sn*-glycero-3-phosphocholine). Phospholipids were isolated by solid-phase extraction by using aminopropyl Supelclean solid-phase extraction tubes (Le-Si; Supelco, Bellefonte, PA) by a method that has been described previously (26). Fatty acid methyl esters were formed by transmethylation of the phospholipids with METH-Prep (Alltech, Deerfield, IL). Fatty acid methyl esters were analyzed on an SP-2340 column (30 m × 0.32 mm × 0.2 μm film thickness) together with a nonpolar fused silica precolumn (1 m × 0.32 mm internal diameter) installed on an HP 5980 gas chromatograph (Agilent, Palo Alto, CA) with a flame ionization detector. Throughout all parts of the fatty acid analysis, samples from each case-control set were analyzed within the same batch. The fatty acid results are reported as percent of the total 26 fatty acids that were quantified, on a molar basis (ie, mole percent). Precision of the fatty acids was measured by analyzing pooled plasma samples; 1 approximately every 15 samples ($n = 138$). The CVs for the saturated fatty acids (14:0, 15:0, 16:0, 17:0, and 18:0) were 17.8%, 12.7%, 7.1%, 5.8%, and 4.0%, respectively. For monounsaturated fatty acids (16:1n−7 and 18:1n−9), the CVs were 8.2% and 2.2%, respectively. For the n−6 polyunsaturated fatty acids (18:2n−6, 20:3n−6, and 20:4n−6), these values were 1.7%, 5.1%, and 5.8%, respectively, and for the n−3 polyunsaturated fatty acids (18:3n−3, 20:5n−3, 22:5n−3, and 22:6n−3), the CVs were 6.5%, 5.3%, 8.3%, and 6.8%, respectively. All fatty acid analysis was conducted in the Nutrition and Hormones Laboratory at the International Agency for Research on Cancer in Lyon, France.

Statistical analysis

Differences in height, weight, body mass index (BMI), and the fatty acid composition of phospholipids were investigated by using a weighted version of the paired-samples *t* test (27). For each matched set, the difference between the case and the control values was calculated, the control value being set equal to the mean of the control values where there were 2 controls in the matched set. A test of whether the weighted mean of these differences was significantly different from zero was then performed by using weights of one-half or two-thirds according to whether the difference was based on 2 (1 case and 1 control) or 3 (1 case and 2 controls) observations. Conditional logistic regression was used to test for differences in the categorical variables between cases and controls. We chose to present results for the 14 fatty acids in plasma phospholipids that make up almost 95% of total fatty acids and were most commonly reported in similar analyses. The relative risks for the fatty acids in relation to the risk of prostate cancer were estimated by using conditional logistic regression models conditioned on the matching variables. To normalize the distribution, fatty acids were log-transformed and analyzed as categorical variables based on quintiles of the distribution of plasma fatty acids among the controls. All models were adjusted for fourths of BMI, smoking (never, former, or current), alcohol intake (<8, 8–15, 16–39, or ≥40 g/d), educational level (none/primary, secondary, or degree), marital status (married/cohabiting, not married/cohabiting, or unknown), and physical activity (inactive, moderately inactive, or active) (28). Tests for trend for the association between fatty acids and risk of total prostate cancer and by stage and grade were assessed by using the logarithm values of fatty acids as a continuous variable. Likelihood ratio chi-square tests were used to examine the heterogeneity of the trends in prostate cancer risk with the logarithm of plasma fatty acid composition between tumor stage (localized or advanced), histologic grade (low or high grade), the interval between blood collection and diagnosis

TABLE 4
Relative risk (RR) and 95% CI of prostate cancer by quintiles of fatty acid composition of plasma phospholipids

	Quintile of fatty acid					
	1 (reference)	2	3	4	5	*P* for trend[1]
Saturated fatty acids						
Myristic acid						
Range (mol%)	0.06–0.24	0.24–0.29	0.29–0.34	0.34–0.41	0.41–1.02	
Cases/controls (*n*)	205/213	187/212	195/212	187/212	188/212	
RR (95% CI)	1.0	0.96 (0.72, 1.29)	1.04 (0.77, 1.40)	1.07 (0.78, 1.47)	1.10 (0.79, 1.54)	0.386
Adjusted RR (95% CI)[2]	1.0	0.97 (0.72, 1.30)	1.05 (0.77, 1.42)	1.08 (0.77, 1.50)	1.12 (0.79, 1.59)	0.322
Pentadecanoic acid						
Range (mol%)	0.00–0.12	0.12–0.15	0.15–0.17	0.17–0.20	0.20–1.71	
Cases/controls (*n*)	196/213	197/212	186/212	203/212	180/212	
RR (95% CI)	1.0	1.06 (0.80, 1.41)	1.03 (0.77, 1.39)	1.16 (0.85, 1.58)	1.05 (0.75, 1.45)	0.543
Adjusted RR (95% CI)	1.0	1.06 (0.79, 1.43)	1.02 (0.75, 1.38)	1.07 (0.78, 1.49)	0.96 (0.68, 1.37)	0.910
Palmitic acid						
Range (mol%)	14.08–24.84	24.84–26.37	26.38–27.74	27.74–28.86	28.87–33.98	
Cases/controls (*n*)	181/213	193/212	220/212	176/212	192/212	
RR (95% CI)	1.0	1.21 (0.88, 1.66)	1.44 (1.02, 2.02)	1.19 (0.83, 1.72)	1.31 (0.89, 1.92)	0.086
Adjusted RR (95% CI)	1.0	1.23 (0.88, 1.70)	1.49 (1.05, 2.12)	1.22 (0.83, 1.80)	1.47 (0.97, 2.23)	0.032
Heptadecanoic acid						
Range (mol%)	0.00–0.32	0.32–0.37	0.37–0.41	0.41–0.45	0.45–2.32	
Cases/controls (*n*)	182/213	188/212	201/212	210/212	181/212	
RR (95% CI)	1.0	1.09 (0.82, 1.45)	1.19 (0.90, 1.59)	1.22 (0.92, 1.62)	1.01 (0.75, 1.35)	0.964
Adjusted RR (95% CI)	1.0	1.04 (0.78, 1.40)	1.11 (0.82, 1.51)	1.08 (0.79, 1.47)	0.93 (0.67, 1.29)	0.444
Stearic acid						
Range (mol%)	8.54–10.76	10.76–11.29	11.29–11.74	11.74–12.31	12.31–15.88	
Cases/controls (*n*)	202/213	193/212	202/212	189/212	176/212	
RR (95% CI)	1.0	0.98 (0.75, 1.29)	0.98 (0.75, 1.29)	0.89 (0.67, 1.18)	0.78 (0.58, 1.05)	0.032
Adjusted RR (95% CI)	1.0	0.92 (0.69, 1.22)	0.96 (0.72, 1.27)	0.86 (0.64, 1.16)	0.77 (0.56, 1.06)	0.030
Monounsaturated fatty acids						
Palmitoleic acid						
Range (mol%)	0.09–0.61	0.61–0.73	0.73–0.84	0.84–1.02	1.02–3.40	
Cases/controls (*n*)	217/213	183/212	177/212	206/212	179/212	
RR (95% CI)	1.0	0.90 (0.67, 1.20)	0.90 (0.67, 1.22)	1.04 (0.77, 1.39)	0.87 (0.64, 1.18)	0.896
Adjusted RR (95% CI)	1.0	0.91 (0.67, 1.23)	0.92 (0.68, 1.25)	1.05 (0.77, 1.43)	0.94 (0.67, 1.32)	0.469
Oleic acid						
Range (mol%)	6.06–9.02	9.02–9.88	9.88–10.59	10.59–11.65	11.65–22.79	
Cases/controls (*n*)	229/213	201/212	170/212	167/212	195/212	
RR (95% CI)	1.0	0.91 (0.69, 1.20)	0.80 (0.60, 1.05)	0.79 (0.59, 1.05)	0.93 (0.70, 1.25)	0.424
Adjusted RR (95% CI)	1.0	0.95 (0.72, 1.26)	0.85 (0.64, 1.13)	0.84 (0.63, 1.14)	1.02 (0.75, 1.38)	0.770
n−6 Polyunsaturated fatty acids						
Linoleic acid						
Range (mol%)	12.50–22.74	22.75–24.80	24.80–26.57	26.58–28.77	28.77–41.75	
Cases/controls (*n*)	192/213	176/212	191/212	217/212	186/212	
RR (95% CI)	1.0	0.96 (0.72, 1.26)	1.01 (0.76, 1.34)	1.12 (0.84, 1.5)	0.93 (0.69, 1.24)	0.951
Adjusted RR (95% CI)	1.0	0.92 (0.69, 1.22)	1.02 (0.76, 1.36)	1.09 (0.81, 1.47)	0.88 (0.64, 1.19)	0.770
Dihomo-γ-linolenic acid						
Range (mol%)	1.89–3.31	3.31–3.84	3.84–4.28	4.28–4.85	4.86–8.27	
Cases/controls (*n*)	198/213	192/212	213/212	193/212	166/212	
RR (95% CI)	1.0	1.00 (0.75, 1.33)	1.12 (0.84, 1.48)	1.01 (0.76, 1.35)	0.84 (0.62, 1.15)	0.808
Adjusted RR (95% CI)	1.0	1.02 (0.77, 1.37)	1.15 (0.86, 1.54)	1.05 (0.77, 1.42)	0.91 (0.65, 1.26)	0.779
Arachidonic acid						
Range (mol%)	4.40–7.93	7.93–8.89	8.90–9.86	9.86–10.98	10.99–19.14	
Cases/controls (*n*)	174/213	219/212	218/212	163/212	188/212	
RR (95% CI)	1.0	1.30 (0.98, 1.71)	1.20 (0.91, 1.58)	0.83 (0.62, 1.12)	0.92 (0.67, 1.26)	0.508
Adjusted RR (95% CI)	1.0	1.28 (0.96, 1.70)	1.17 (0.88, 1.56)	0.81 (0.60, 1.10)	0.91 (0.65, 1.25)	0.419
n−3 Polyunsaturated fatty acids						
α-Linolenic acid						
Range (mol%)	0.00–0.18	0.18–0.23	0.23–0.29	0.29–0.36	0.36–2.63	
Cases/controls (*n*)	223/213	174/212	181/212	199/212	185/212	
RR (95% CI)	1.0	0.8 (0.59, 1.07)	0.91 (0.66, 1.23)	1.05 (0.76, 1.44)	1.06 (0.75, 1.49)	0.298
Adjusted RR (95% CI)	1.0	0.8 (0.59, 1.08)	0.88 (0.65, 1.21)	1.07 (0.77, 1.47)	1.06 (0.75, 1.50)	0.301

(*Continued*)

TABLE 4 (*Continued*)

	Quintile of fatty acid					
	1 (reference)	2	3	4	5	*P* for trend[1]
Eicosapentaenoic acid						
Range (mol%)	0.16–0.80	0.80–1.04	1.05–1.34	1.34–1.95	1.95–9.49	
Cases/controls (*n*)	183/213	158/212	201/212	218/212	202/212	
RR (95% CI)	1.00	0.94 (0.71, 1.25)	1.28 (0.97, 1.70)	1.47 (1.09, 1.97)	1.30 (0.96, 1.75)	0.072
Adjusted RR (95% CI)	1.00	0.92 (0.69, 1.23)	1.32 (0.98, 1.76)	1.47 (1.08, 2.00)	1.31 (0.96, 1.81)	0.090
n−3 Docosapentaenoic acid						
Range (mol%)	0.44–0.98	0.98–1.14	1.14–1.27	1.27–1.45	1.45–2.59	
Cases/controls (*n*)	187/213	212/212	187/212	219/212	157/212	
RR (95% CI)	1.0	1.29 (0.94, 1.77)	1.18 (0.84, 1.64)	1.48 (1.05, 2.08)	1.05 (0.73, 1.51)	0.583
Adjusted RR (95% CI)	1.0	1.29 (0.93, 1.78)	1.15 (0.82, 1.61)	1.42 (1.00, 2.03)	0.95 (0.65, 1.39)	0.998
Docosahexaenoic acid						
Range (mol%)	1.62–3.34	3.35–3.99	3.99–4.59	4.59–5.34	5.34–10.37	
Cases/controls (*n*)	158/213	204/212	180/212	201/212	219/212	
RR (95% CI)	1.0	1.32 (0.98, 1.76)	1.2 (0.89, 1.62)	1.35 (1.00, 1.83)	1.48 (1.09, 2.01)	0.052
Adjusted RR (95% CI)	1.0	1.28 (0.95, 1.72)	1.17 (0.86, 1.58)	1.30 (0.95, 1.78)	1.39 (1.02, 1.90)	0.158

[1] Tests for trend were obtained by replacing the categorical variable with the logarithm of the fatty acid in the conditional logistic regression model.
[2] Matched by study center and age and adjusted for BMI, smoking, alcohol intake, education, marital status, and physical activity by using conditional logistic regression

(<4 or ≥4 y), and country. All statistical analyses were carried out by using Stata Statistical Software: Release 9 (StataCorp LP, College Station, TX). All *P* values reported are two-tailed, and a *P* value < 0.05 was considered statistically significant.

RESULTS

The results in **Table 1** show the fatty acid composition of plasma phospholipids for the controls by country. For all 14 fatty acids, the tests for heterogeneity between countries were statistically significant. Men from Sweden had the highest proportion of both myristic and pentadecanoic acids, and these fatty acids were lowest among the Greek men. The Danish men had the highest proportion of palmitic acid (16:0), and this was 6.4 mol% lower in the Dutch men, who also had the highest proportion of stearic acid (18:0). Men from Italy had the highest proportion of oleic acid (18:1n−9) and the lowest proportion of linoleic acid (18:2n−6), whereas men from the United Kingdom had the lowest percent of oleic acid and the highest percent of linoleic acid. Swedish men had the highest proportion of α-linolenic acid, and this was lowest in the Spanish men. Danish men had the highest percent of eicosapentaenoic and Dutch men the highest n−3 docosapentaenoic acid (22:5n−3); these 2 fatty acids were lowest in men from Greece and Spain, respectively. The range in docosahexaenoic acid was >1 mol% across the countries and was highest in men from Spain and lowest among the Italian men.

The baseline characteristics of the prostate cancer cases and their matched controls are shown in **Table 2**. In comparison with the controls, men diagnosed with prostate cancer had a lower body weight and a slightly lower BMI. A lower proportion of the cases were categorized as current smokers and as physically active compared with the controls.

The mean proportions of fatty acids in plasma phospholipids for cases and controls are shown in **Table 3**. The mean proportion of stearic acid was 0.08 mol% lower ($P = 0.032$) and that of docosahexaenoic acid was 0.09 mol% higher ($P = 0.049$) in cases than controls. The mean percentages of all other fatty acids were not significantly different between cases and controls.

The relative risks (RRs) of prostate cancer for 14 fatty acids are shown in **Table 4**. There was a positive association between the percent of palmitic acid in plasma phospholipids and prostate cancer risk. Men in the highest quintile had an RR of 1.31 (95% CI: 0.89, 1.92; *P* for trend = 0.086) for prostate cancer in comparison with men in the lowest quintile of palmitic acid. After adjustment for BMI, smoking, alcohol intake, education, marital status, and physical activity, the risk increased to 1.47 (95% CI: 0.97, 2.23; *P* for trend = 0.032). There was an inverse association between the percent of stearic acid and risk of prostate cancer; the multivariate RR for men in the highest quintile was 0.77 (95% CI: 0.56, 1.06; *P* for trend = 0.03) compared with men in the lowest quintile of stearic acid. There was a suggestion of a positive association between eicosapentaenoic acid and the risk of prostate cancer, but neither the unadjusted nor the adjusted analysis was statistically significant. The multivariate RR for men in the highest quintile of docosahexaenoic acid was 1.39 (95% CI: 1.02, 1.90) in comparison with men in the lowest quintile, but the overall test for association was not statistically significant. There was no association between the other 12 fatty acids identified in plasma phospholipids and risk of prostate cancer (results not shown). There was a strong inverse association between the mol% of palmitic and stearic acid in plasma phospholipids ($r = -0.66$, $P < 0.001$) and a positive association between eicosapentaenoic and docosahexaenoic acid ($r = 0.67$, $P < 0.001$).

The results in **Table 5** show the relation between quintiles of fatty acids and the risk of prostate cancer by stage and grade. There was a positive association between the percent of myristic acid and the risk of advanced and high-grade prostate cancer; the test of heterogeneity between trends was statistically significant for low- and high-grade prostate cancer ($P = 0.011$) but not for localized or advanced prostate cancer ($P = 0.062$). There was a suggestion of an inverse association for both pentadecanoic and heptadecanoic acids and risk of low-grade prostate cancer, but neither of the overall tests for association were statistically significant. There was a positive association for palmitic acid and an inverse association for stearic acid with the risk of localized and low-grade prostate cancer; men categorized into the highest

TABLE 5
Multivariate adjusted relative risk (RR) and 95% CI of prostate cancer by stage and grade in association with the fatty acid composition of plasma phospholipids[1]

	Quintile of fatty acid					*P* for trend[2]	*P* for heterogeneity[3]
	1	2	3	4	5		
Saturated fatty acids							
Myristic acid							
Localized (*n* = 485)	1.0	1.03 (0.68, 1.58)	0.98 (0.63, 1.53)	0.84 (0.52, 1.37)	1.04 (0.63, 1.75)	0.860	0.062
Advanced (*n* = 204)	1.0	0.79 (0.40, 1.54)	1.13 (0.55, 2.32)	2.00 (0.88, 4.54)	1.79 (0.80, 3.98)	0.040	
Low-grade (*n* = 443)	1.0	1.03 (0.67, 1.58)	0.92 (0.59, 1.45)	0.82 (0.51, 1.34)	0.80 (0.48, 1.36)	0.407	0.011
High-grade (*n* = 286)	1.0	0.72 (0.38, 1.36)	1.04 (0.55, 1.97)	1.96 (0.98, 3.90)	1.64 (0.81, 3.31)	0.015	
Pentadecanoic acid							
Localized	1.0	0.81 (0.53, 1.24)	0.76 (0.49, 1.18)	0.80 (0.51, 1.26)	0.71 (0.43, 1.17)	0.455	0.392
Advanced	1.0	1.58 (0.80, 3.10)	1.75 (0.89, 3.41)	1.87 (0.88, 4.01)	1.63 (0.75, 3.54)	0.378	
Low-grade	1.0	0.99 (0.64, 1.53)	0.92 (0.59, 1.44)	0.79 (0.48, 1.30)	0.58 (0.34, 0.98)	0.065	0.269
High-grade	1.0	1.00 (0.55, 1.79)	1.09 (0.60, 1.99)	0.80 (0.42, 1.54)	1.43 (0.71, 2.86)	0.563	
Palmitic acid							
Localized	1.0	1.80 (1.10, 2.93)	1.92 (1.13, 3.26)	1.58 (0.89, 2.81)	1.90 (1.03, 3.49)	0.013	0.584
Advanced	1.0	1.22 (0.54, 2.76)	1.23 (0.53, 2.88)	2.03 (0.81, 5.11)	1.37 (0.51, 3.65)	0.451	
Low-grade	1.0	1.27 (0.78, 2.06)	1.62 (0.98, 2.67)	1.46 (0.81, 2.65)	1.93 (1.02, 3.64)	0.045	0.664
High-grade	1.0	1.27 (0.67, 2.42)	1.78 (0.85, 3.74)	1.90 (0.90, 3.99)	1.44 (0.64, 3.27)	0.204	
Heptadecanoic acid							
Localized	1.0	0.88 (0.58, 1.33)	0.97 (0.63, 1.49)	0.98 (0.63, 1.51)	0.71 (0.45, 1.12)	0.173	0.492
Advanced	1.0	1.68 (0.81, 3.47)	1.88 (0.95, 3.75)	1.49 (0.71, 3.14)	1.47 (0.65, 3.28)	0.594	
Low-grade	1.0	1.38 (0.87, 2.18)	1.15 (0.73, 1.81)	1.08 (0.67, 1.74)	0.66 (0.41, 1.08)	0.058	0.884
High-grade	1.0	0.86 (0.46, 1.60)	1.17 (0.63, 2.17)	0.85 (0.46, 1.57)	1.20 (0.62, 2.32)	0.959	
Stearic acid							
Localized	1.0	1.09 (0.74, 1.62)	1.05 (0.71, 1.55)	0.95 (0.64, 1.42)	0.60 (0.38, 0.94)	0.014	0.236
Advanced	1.0	0.79 (0.41, 1.52)	0.68 (0.36, 1.29)	0.77 (0.40, 1.50)	1.01 (0.50, 2.07)	0.678	
Low-grade	1.0	0.84 (0.55, 1.30)	0.75 (0.49, 1.15)	0.73 (0.47, 1.12)	0.77 (0.48, 1.24)	0.048	0.312
High-grade	1.0	1.12 (0.66, 1.89)	1.12 (0.66, 1.90)	1.13 (0.66, 1.95)	0.92 (0.51, 1.65)	0.777	
Monounsaturated fatty acids							
Palmitoleic acid							
Localized	1.0	0.74 (0.48, 1.14)	0.73 (0.46, 1.16)	0.86 (0.55, 1.35)	0.82 (0.50, 1.33)	0.986	0.376
Advanced	1.0	0.78 (0.39, 1.55)	1.21 (0.60, 2.46)	1.15 (0.56, 2.36)	1.19 (0.57, 2.47)	0.393	
Low-grade	1.0	0.94 (0.60, 1.47)	0.95 (0.60, 1.49)	1.21 (0.77, 1.92)	1.05 (0.63, 1.74)	0.472	0.217
High-grade	1.0	1.13 (0.63, 2.02)	1.08 (0.58, 2.01)	1.42 (0.79, 2.55)	1.39 (0.71, 2.72)	0.269	
Oleic acid							
Localized	1.0	1.07 (0.71, 1.60)	1.03 (0.70, 1.53)	0.98 (0.64, 1.50)	1.18 (0.77, 1.82)	0.658	0.760
Advanced	1.0	0.80 (0.43, 1.50)	0.56 (0.28, 1.12)	0.89 (0.46, 1.70)	0.83 (0.42, 1.65)	0.903	
Low-grade	1.0	0.96 (0.63, 1.47)	0.95 (0.63, 1.43)	0.79 (0.50, 1.23)	1.15 (0.71, 1.86)	0.829	0.477
High-grade	1.0	1.12 (0.64, 1.93)	0.79 (0.44, 1.42)	1.12 (0.62, 2.05)	1.28 (0.72, 2.26)	0.364	
n−6 polyunsaturated fatty acids							
Linoleic acid							
Localized	1.0	0.84 (0.57, 1.25)	1.03 (0.69, 1.54)	0.99 (0.65, 1.53)	0.84 (0.54, 1.31)	0.652	0.561
Advanced	1.0	0.56 (0.30, 1.07)	0.93 (0.47, 1.84)	1.07 (0.57, 2.02)	0.60 (0.28, 1.29)	0.648	
Low-grade	1.0	0.80 (0.52, 1.23)	0.80 (0.52, 1.25)	0.84 (0.53, 1.33)	0.70 (0.43, 1.14)	0.176	0.808
High-grade	1.0	0.82 (0.47, 1.43)	0.80 (0.46, 1.42)	1.09 (0.62, 1.93)	0.83 (0.46, 1.50)	0.509	
Dihomo-γ-linolenic acid							
Localized	1.0	0.99 (0.67, 1.46)	1.05 (0.70, 1.56)	1.00 (0.66, 1.53)	0.92 (0.58, 1.46)	0.809	0.368
Advanced	1.0	1.13 (0.57, 2.24)	0.89 (0.44, 1.82)	1.11 (0.53, 2.33)	0.86 (0.41, 1.83)	0.613	
Low-grade	1.0	1.14 (0.72, 1.79)	1.23 (0.78, 1.92)	0.98 (0.62, 1.55)	1.00 (0.61, 1.63)	0.697	0.519
High-grade	1.0	0.87 (0.48, 1.58)	1.02 (0.57, 1.81)	1.65 (0.87, 3.10)	0.92 (0.48, 1.75)	0.392	
Arachidonic acid							
Localized	1.0	1.05 (0.71, 1.55)	1.04 (0.71, 1.54)	0.79 (0.52, 1.20)	0.84 (0.53, 1.33)	0.766	0.632
Advanced	1.0	1.46 (0.70, 3.06)	1.31 (0.62, 2.76)	1.00 (0.46, 2.16)	1.21 (0.56, 2.65)	0.985	
Low-grade	1.0	1.32 (0.86, 2.03)	1.35 (0.88, 2.07)	0.89 (0.57, 1.39)	1.15 (0.72, 1.86)	0.807	0.232
High-grade	1.0	1.02 (0.61, 1.72)	0.57 (0.32, 1.02)	0.63 (0.34, 1.15)	0.65 (0.35, 1.19)	0.107	

(*Continued*)

TABLE 5 (*Continued*)

	Quintile of fatty acid					*P* for trend[2]	*P* for heterogeneity[3]
	1	2	3	4	5		
n−3 polyunsaturated fatty acids							
α-Linolenic acid							
Localized	1.0	0.73 (0.47, 1.12)	0.83 (0.51, 1.35)	1.31 (0.80, 2.14)	1.08 (0.64, 1.83)	0.426	0.872
Advanced	1.0	0.62 (0.31, 1.25)	1.20 (0.59, 2.41)	0.70 (0.33, 1.46)	1.08 (0.50, 2.34)	0.466	
Low-grade	1.0	0.80 (0.52, 1.22)	0.67 (0.42, 1.06)	0.77 (0.48, 1.25)	0.70 (0.42, 1.18)	0.327	0.029
High-grade	1.0	0.92 (0.50, 1.67)	1.79 (0.96, 3.37)	1.53 (0.80, 2.93)	1.79 (0.91, 3.53)	0.014	
Eicosapentaenoic acid							
Localized	1.0	0.99 (0.65, 1.52)	1.51 (0.98, 2.33)	1.65 (1.06, 2.59)	1.33 (0.84, 2.13)	0.284	0.928
Advanced	1.0	0.69 (0.35, 1.37)	1.38 (0.72, 2.65)	0.89 (0.44, 1.78)	0.99 (0.49, 2.01)	0.858	
Low-grade	1.0	0.89 (0.59, 1.35)	1.10 (0.71, 1.69)	1.30 (0.84, 2.03)	1.18 (0.74, 1.89)	0.660	0.116
High-grade	1.0	1.30 (0.69, 2.44)	2.10 (1.18, 3.74)	2.04 (1.08, 3.85)	2.00 (1.07, 3.76)	0.031	
Docosapentaenoic acid							
Localized	1.0	1.14 (0.72, 1.82)	1.10 (0.67, 1.79)	1.40 (0.83, 2.38)	0.76 (0.43, 1.34)	0.616	0.994
Advanced	1.0	0.94 (0.48, 1.87)	0.94 (0.48, 1.85)	1.06 (0.51, 2.18)	0.91 (0.42, 2.00)	0.734	
Low-grade	1.0	1.02 (0.64, 1.63)	0.97 (0.59, 1.61)	1.71 (1.01, 2.90)	0.97 (0.54, 1.72)	0.538	0.304
High-grade	1.0	1.30 (0.69, 2.46)	0.80 (0.40, 1.57)	0.89 (0.45, 1.76)	0.71 (0.35, 1.46)	0.462	
Docosahexaenoic acid							
Localized	1.0	1.45 (0.96, 2.21)	1.38 (0.90, 2.10)	1.20 (0.77, 1.88)	1.32 (0.84, 2.08)	0.769	0.895
Advanced	1.0	1.64 (0.84, 3.17)	0.84 (0.44, 1.59)	1.44 (0.72, 2.89)	1.22 (0.62, 2.40)	0.738	
Low-grade	1.0	1.34 (0.87, 2.07)	1.24 (0.79, 1.95)	1.70 (1.07, 2.69)	1.53 (0.96, 2.44)	0.141	0.480
High-grade	1.0	1.36 (0.78, 2.37)	1.11 (0.62, 2.00)	0.80 (0.43, 1.50)	1.41 (0.76, 2.62)	0.739	

[1] Matched by study center and age and adjusted for BMI, smoking, alcohol intake, education, marital status, and physical activity by using conditional logistic regression

[2] Tests for trend were obtained by replacing the categorical variable with the logarithm of the fatty acid in the conditional logistic regression model.

[3] *P* for heterogeneity values relate to likelihood ratio chi-square tests of heterogeneity between trends for localized and advanced-stage and low- and high-grade prostate cancer

quintile of palmitic acid had risks of localized and low-grade prostate cancer of 1.90 (95% CI: 1.03, 3.49) and 1.93 (95% CI: 1.02, 3.64), respectively, compared with men in the lowest quintile. None of the tests for heterogeneity between the stage and grade of prostate cancer for palmitic or stearic acids was statistically significant. There was a positive relation between the percent of α-linolenic and eicosapentaenoic acid and risk of high-grade prostate cancer; the RRs for the highest versus the lowest quintile was 1.79 (95% CI: 0.91, 3.53) and 2.00 (95% CI: 1.07, 3.76), respectively. The test for heterogeneity between the risk of low- and high-grade prostate cancer was statistically significant for α-linolenic acid ($P = 0.029$) but not for eicosapentaenoic acid ($P = 0.116$).

There was no evidence for heterogeneity for the association between plasma fatty acids and risk of prostate cancer between men with an early (<4 y) versus a later (≥4 y) diagnosis. There was, however, significant heterogeneity for the association between stearic acid and risk of prostate cancer by country ($P = 0.042$, results not shown).

DISCUSSION

In this large multicenter study, our results suggested a positive association between palmitic acid and overall risk of prostate cancer and an inverse association with stearic acid. To date, this is the largest study to examine prospectively the association between the fatty acid composition of blood lipids and prostate cancer risk. We included men from several European countries with a variety of dietary patterns. For several fatty acids, measuring the fatty acid composition of plasma phospholipids may give a better reflection of actual consumption of dietary fat than dietary assessment techniques (6, 29). Fatty acids in plasma reflect dietary fat intake in the postabsorptive phase, so processes that affect the bioavailability of fatty acids, such as their transport, excretion, and metabolism, are taken into account (30). Moreover, fatty acids in phospholipids are located near the sites thought to be involved in processes associated with the development of prostate cancer (18, 19, 21, 22).

We found that a higher proportion of palmitic acid was associated with a greater risk of overall risk of prostate cancer as well as for localized and low-grade prostate cancer. This agrees with the results of 1 (12) of 3 (10, 15) prospective studies that have examined this association. Although the diet is abundant in palmitic acid, sources are ubiquitous, and results from most studies have shown that palmitic acid in blood is poorly correlated with dietary intake (7, 31–33). Palmitic acid can be synthesized from other fatty acids and is the major fatty acid produced by de novo lipogenesis from acetyl CoA and malonyl CoA by the enzyme fatty acid synthase (34). Some evidence suggests that the expression of fatty acid synthase *m*RNA and protein is upregulated in prostate cancer tumor tissues, an event that occurs early on in the development of prostate cancer (35). Therefore, it is possible that the association between palmitic acid and prostate cancer is a marker of higher fatty acid synthase activity.

Our results showed an inverse association between stearic acid and risk of overall, localized, and low-grade prostate cancer. Three other studies have reported the association between stearic acid and prostate cancer risk; none showed a statistically significant association (10, 12, 15). In the absence of a potential dietary explanation, these findings may in part be due to the inverse

association between palmitic and stearic acids in plasma phospholipids. We chose to express fatty acids as a mol%; the elevation of a fatty acid that makes up a large percent of the total will cause the relative contribution of other fatty acids to be lower. In phosphatidylcholine—the major phospholipid—most palmitic and stearic acid molecules are esterified at the *sn*-1 position of the molecule (36). In all participants, the mol% of palmitic acid was inversely related to stearic acid ($r = -0.66$, $P < 0.001$). A greater contribution of palmitic acid may have led to a lower percent of stearic acid, and our finding of an inverse association between stearic acid and prostate cancer risk might be interpreted as being indirect.

There was the suggestion of a positive association between the percent of myristic acid and the risk of advanced and high-grade prostate cancer. Only 2 other studies addressed the association between myristic acid and prostate cancer; results from one study showed a statistically significant (15) association, and the other showed a nonsignificant positive association (12), but neither study reported the association by stage or grade. There may have been publication bias, with some authors failing to report a nonsignificant association between myristic acid and prostate cancer. A major source of myristic acid in the diet is dairy products, and our results suggested there was a positive association between other biomarkers of dairy fat, pentadecanoic and heptadecanoic acids, and risk of advanced prostate cancer, but neither association was statistically significant. Myristic acid can also come from other sources that contain little or no odd-chain fatty acids, such as tropical oils that may be used in commercially manufactured foods (37), and is also produced—albeit in relatively small amounts—by de novo lipogenesis by fatty acid synthase (38).

Our results showed a positive association between α-linolenic acid and the risk of high-grade prostate cancer but not for the risk of total or advanced prostate cancer. Brouwer et al (39) concluded from the results of a meta-analysis of 9 observational studies that a higher intake of α-linolenic acid was associated with a greater risk of overall prostate cancer, despite evidence of considerable heterogeneity between the studies, possibly because both the composition of α-linolenic acid in blood and information on dietary intake were combined. Since this analysis was published, 2 prospective studies have reported no association between the proportion of α-linolenic acid in blood and risk of prostate cancer (15, 17). Others have suggested that the association between α-linolenic acid and prostate cancer may reflect a higher intake of cooked red meat (10); however, we found no evidence for a strong association between the proportion of α-linolenic acid in phospholipids and fat from red meat ($r = 0.11$, $P < 0.001$). Although α-linolenic acid is an essential fatty acid and results from other studies indicate that the percent of α-linolenic acid in blood lipids is related to intake of foods that are predominantly of plant origin (7, 31–33), a substantial portion of α-linolenic acid is partitioned toward the β-oxidative pathway (40) and is not esterified into plasma lipid fractions. Thus, the positive association between α-linolenic acid and high-grade prostate cancer could be the result of a higher intake or, alternatively, a lower turnover of α-linolenic acid.

We found no evidence for a lower risk of prostate cancer in men with higher proportions of the n−3 long-chain polyunsaturated fatty acids. On the contrary, our results suggest that there was a greater risk of high-grade prostate cancer for men with a higher percent of eicosapentaenoic acid. Both Norrish et al (13) and Chavarro et al (17) reported inverse associations between the proportion of eicosapentaenoic and docosahexaenoic acids in blood and risk of prostate cancer, whereas the results from 5 other studies showed no association (10–12, 14, 15). There have been many potential mechanisms described for the putative cancer-preventing effects of the n−3 long-chain polyunsaturated fatty acids (18–22), but on the other hand, almost no evidence supports a potential carcinogenic effect of eicosapentaenoic acid. Given that there was no significant association for eicosapentaenoic acid and risk of advanced or total prostate cancer, this positive association could have been due to chance.

Our study had several limitations. Fatty acids in adipose tissue are a better reflection of habitual dietary fat intake of some fatty acids than is the proportion in blood (29, 41); however, adipose tissue aspirates are more difficult to collect than blood samples in large-scale prospective studies. Moreover, adipose tissue is predominantly made up of triacylglycerol and may not be the lipid of choice for measuring the n−3 long-chain polyunsaturated fatty acids because of a smaller proportion of these fatty acids being incorporated into this lipid fraction (42). We also chose to analyze the association between 14 fatty acids and prostate cancer by stage and grade. Given this large number of comparisons, we cannot rule out the possibility that several of our findings were due to chance.

In conclusion, the results from this large case-control study nested within EPIC provide evidence for a positive association between the palmitic acid composition of plasma phospholipids and an inverse association between stearic acid and risk of prostate cancer. There was also evidence for a greater risk of high-grade prostate cancer in men with higher proportions of myristic, α-linolenic, and eicosapentaenoic acids. These findings warrant further attention.

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