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Circulating fatty acids and prostate cancer risk in a nested case–control study: the Multiethnic Cohort

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Abstract

Objective—Dietary fat, including specific fatty acids, has been proposed to contribute to prostate cancer pathogenesis, but findings from the studies based on biomarkers have been conflicting.

Methods—We examined the association between erythrocyte membrane fatty acid composition and prostate cancer risk in a nested case–control study within a multiethnic cohort of African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites. Analyses included 376 cases and 729 matched controls. Conditional logistic regression was used to estimate the odds ratios and 95% confidence intervals with adjustment for multiple covariates.

Results—No significant association was found for saturated, mono- and polyunsaturated fatty acid, or for specific n-3 and n-6 fatty acids, even when the analysis was limited to advanced or high grade prostate cancer. In ethnic specific analyses, there was a positive association with palmitic acid in Japanese Americans that was significantly different from the null results in other groups. There was also an increased risk with n-3 fatty acids and the ratio of n-3/n-6 fatty acids in Whites.

Conclusion—Although there was a suggestion of ethnic specific associations with some fatty acids, our overall findings do not support a role for fatty acids in prostate carcinogenesis.

Keywords

Prostatic neoplasms; Fatty acids; Erythrocytes; Nested case–control study

Introduction

Dietary fat, including specific fatty acids, has been proposed to contribute to prostate cancer pathogenesis [1-3]. While early studies suggested that total, saturated, or animal fat might increase prostate cancer risk, animal experiments and in vitro studies indicate that different types of fatty acids have opposing effects on the development and progression of prostate cancer: long chain n-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3), suppress the development of cancer [4], whereas n-6 fatty acids including linoleic acid (C18:2 n-6) and arachidonic acid (C20:4 n-6) promote carcinogenesis [5]. Therefore, the ratio of n-3 to n-6 fatty acids may be more important than the absolute intake of n-3 fatty acids [5]. One of the possible mechanisms for the anticarcinogenic effects of n-3 fatty acids is the suppression of arachidonic acid-derived eicosanoid biosynthesis, which is involved in tumor growth [4]. A few observational studies have found that high intake of n-3 PUFA α -linolenic acid (ALA, C18:3 n-3) increased prostate cancer risk, and have suggested interference with 5 α -reductase and formation of free radicals from fatty acid oxidation as possible mechanisms for the carcinogenic effect [6-8].

A number of epidemiologic studies have examined the intakes of specific fatty acids from foods in relation to prostate cancer risk, but not all have supported the suggested mechanisms or hypotheses [6-16]. Although not perfect biomarkers of dietary exposures, fatty acids in blood or tissue as quantitative indicators of dietary intake may provide additional insight for testing hypotheses about diet–disease relationships over self-reported dietary intake [17,18].

Previously, we reported no association between the intake of dietary fatty acids and prostate cancer risk in the Multiethnic Cohort Study [19]. In order to further investigate this association based on biomarkers, we analyzed data from a nested case–control study within our cohort that measured fatty acid composition in erythrocyte membranes.

Materials and methods

Study population

The Multiethnic Cohort Study was established to test hypotheses related to diet and cancer in Hawaii and Los Angeles, California [20]. It was designed to include adults from five targeted racial/ethnic groups: African Americans, Native Hawaiians, Japanese Americans, Latinos, and Whites. In 1993–1996, more than 215,000 participants aged 45–75 years completed a 26-page questionnaire on diet, medical history, and lifestyle. All the baseline information from the cohort questionnaire was available for the current study. Information of particular potential value for the present study included weight, height, physical activity, education, and family history of prostate cancer.

Collection and preparation of specimens

Cohort members were recruited to supply prospective biospecimens; this recruitment largely took place between 2001 and 2006. Once the subjects gave informed consent to participate, a short screening questionnaire (use of anticoagulants, blood clotting disorders, etc.) and updated information on a few items (current smoking habits, weight, vitamin supplement use, etc.) was

administered by phone. Blood collections were scheduled early in the morning so as to obtain fasting blood (minimum 10 h). After centrifugation and separation into the four components (serum, plasma, buffy coat, and red cells), aliquots of each component were sealed in 0.5 cc cryotubes using an automatic blood component dispensing machine. The specimens were stored in liquid nitrogen freezers. A total of 67,594 members contributed to the biorepository, of which 31,136 were men. When comparing the characteristics of individuals who provided specimens with those who did not, there was no substantial difference between the two groups in the family history of cancer, body mass index, fat and vegetable intake, and physical activity. Therefore, the biospecimen repository participants are broadly representative of all cohort members.

Selection of cases and controls

Identification of incident prostate cancer cases was accomplished through the tumor registries of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute covering Hawaii and California. Deaths were identified by linkage to death-certificate files in Hawaii and California and the National Death Index. For the nested case-control study of biomarkers and prostate cancer, we defined cases as men who contributed blood to the biorepository subcohort and who were diagnosed with invasive prostate cancer after blood collection up to the date of the latest tumor registry linkage in 2006; the average length between blood collection and cancer diagnosis for the cases included in the analyses was 1.9 years. Advanced prostate cancers were defined as all cancers that were regional or metastatic (not in situ or localized). High grade prostate cancers were based on Gleason score (≥ 7 categorized as poorly differentiated).

Controls were selected from among the male participants who contributed blood to the biorepository. For each case, a pool was created including potential controls who were alive and free of prostate cancer at the age of case's diagnosis and who matched the case on geographic location (Hawaii or California), race/ethnicity, birth year (± 1 year), date of blood draw (± 6 months), time of blood draw (± 2 h), and fasting hours (0 to <6 , 6 to <8 , 8 to <10 , and 10+ h). Two controls were randomly selected from each pool.

Of the 467 eligible prostate cancer cases, 77 cases were excluded from fatty acid level assessment because they did not have fasting blood samples. Additionally, 14 cases were not analyzed because of technical problems. Therefore, complete data for the present study was available for 376 cases (including 102 advanced or high grade cancer cases) and 729 matched controls.

Laboratory analyses

Erythrocyte membrane fatty acids were determined by the method of Bagga et al. [21]. Heparinized blood was centrifuged, and the plasma was removed. Approximately 4 ml of the packed heparinized red cells were suspended in phosphate buffer saline (PBS) buffer, mixed, and centrifuged for five minutes. The supernatant was removed, and the wash was repeated a second time. After the second wash, the clear supernatant was again removed. A dilution of the red cells was made: 3 ml of washed red blood cell to 1 ml of PBS. This thick mixture was aspirated into the straws.

Samples were analyzed in duplicate. For the red blood cell membrane fatty acid analysis, samples were thawed, centrifuged at 2,900g for 30 min, and the pellet was used for fatty acid analysis. Total fatty acid was extracted and converted to fatty acid methyl esters (FAMES) using methanol/benzene mixture (8:2, v:v). Heptadecanoic acid (C17:0) was used as the internal standard. The mixture was frozen at -70°C for 20 min prior to the addition of acetylchloride. The mixture was heated at 100°C for 60 min, then, cooled and neutralized with

6% potassium carbonate. Samples were centrifuged at 2,900g and the supernatant was injected into the gas chromatograph. FAME was separated and quantified by the use of Agilent Technologies (Wilmington, DE) 5890A series II gas chromatography fitted with a model 7673 automatic split-injection system and flame ionization detector and SP2380 stabilized phase fused silica capillary column (30 m × 0.32 mm i.d., 0.25 µm film thickness, Supelco, Inc, Bellefonte, PA). Quantification was based on the recovery of a known quantity of the internal standard (C17:0, NuChek Preparation Inc., Elysian, MN), and on the response ratio of fatty acid standards purchased from NuChek Preparation Inc. (Elysian, MN). For quality control, we used a pooled serum sample which was analyzed with each batch of samples. Using this pooled serum sample, the following coefficients of variation have been established: C16:0 1.6%, C16:1 2.7%, C18:0 2.6%, C18:1 3.4%, C18:2 0.7%, C18:3 0.7%, C20:2 8.7%, C20:4 0.7%, C20:5 3.2%, C22:5 4.2%, and C22:6 2.2%.

FAMES were identified by comparing with authentic FAME standards (Nu-Check Prep, Elysian, MN), and the peak areas were integrated as wt.% with a dedicated microprocessor. Individual peaks were distinguished and measured, including those constituting as little as 0.05% of the FAME.

Statistical analyses

Each fatty acid was represented as the percentage of total fatty acids in the erythrocyte membranes. The distributions of fatty acids between cases and controls were compared. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated with conditional logistic regression, modeling cancer status. Fatty acid composition was divided into quartiles or tertiles, which was determined by the overall distribution of each fatty acid in both cases and controls. Trend tests were performed by entering a variable assigned the median of the appropriate quantile group as a continuous variable. *p* values for dose-response were based on the Wald statistics for trend variables.

Matched sets were used as strata in the conditional logistic models, which accounted for the matching criteria: location, race/ethnicity, birth year, date of blood draw, time of blood draw, and fasting hours. The ORs were further adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables to account for any possible systematic differences within matched sets, as well as family history of prostate cancer, BMI, and education, which were found to be related with prostate cancer risk in the full multiethnic cohort analysis. Other potential confounders such as physical activity and alcohol consumption were evaluated, but not included in the models because they did not alter the associations. The models were repeated separately for the four larger ethnic groups. Native Hawaiians were not included in these ethnic-specific analyses due to the small number of cases. Tests for the interaction between fatty acid composition and ethnicity in relation to prostate cancer risk were based on the likelihood ratios between models with and without interaction terms. Also, the models were run including only advanced or high grade tumors as cases and their matched controls. We repeated the analyses excluding controls with high prostate specific antigen (PSA) values (>4.0 ng/ml) in order to reduce the disease misclassification in the control group. In order to find out whether obesity and smoking status affect the association between fatty acid composition and prostate cancer risk, we performed the analyses stratified by BMI (<25, 25–30, and ≥30) and smoking status (never, former, and current smokers). These analyses used unconditional logistic regression to maximize the number of subjects available and adjusting for matching criteria variables. Statistical significance was considered at *p* < 0.05 and all tests were two sided.

Results

Compared to prostate cancer controls, cases were more likely to have a family history of prostate cancer (Table 1). There were no differences in educational level, BMI, physical

activity, and alcohol consumption between cases and controls. Mean fatty acid composition in erythrocyte membranes did not differ between cases and controls either for individual fatty acids or for the ratios of n-3/n-6 or polyunsaturated/saturated fatty acids.

Table 2 presents the ORs for associations of fatty acid composition in erythrocyte membranes with prostate cancer risk. Neither saturated, monounsaturated nor polyunsaturated (n-3 or n-6) fatty acids as a group shows an association with prostate cancer. In addition, none of the 11 component fatty acids within these four groups show any association. Furthermore, the ratios of n-3 to n-6 fatty acids and polyunsaturated to saturated fatty acids show no association with prostate cancer risk. When the analysis was limited to advanced or high grade prostate cancer, the results were similar (Table 3). There were, however, two suggestive results that could be nonsignificant due to statistical power: that for EPA with ORs of 1.00, 1.44, and 1.61 (p for trend = 0.23) and that for total PUFA with ORs of 1.00, 1.08, and 1.78 (p for trend = 0.22).

For the ethnic-specific analyses, the sample sizes were limited and for Native Hawaiians in particular, they were too few to include. As shown in Table 4, a positive association with palmitic acid (C16:0) is seen among Japanese Americans (OR of the highest vs. the lowest tertile = 3.21, 95% CI = 1.21–8.53, p for trend = 0.009), but not in any of the other ethnic groups (p for interaction = 0.05). Although the test for heterogeneity was not significant, in Whites, total n-3 PUFA is also positively related to prostate cancer (OR = 2.77, 95% CI = 1.04–7.39, p for trend = 0.04, p for interaction = 0.12), as was the ratio of n-3/n-6 fatty acids (OR = 2.92, 95% CI = 1.01–8.47, p for trend = 0.04, p for interaction = 0.09).

When the analyses were repeated excluding controls with high PSA values, the results did not change (data not shown). In an analysis stratified by BMI, the obese group (BMI ≥ 30) showed an inverse association for prostate cancer risk with total saturated fatty acid and a positive association with total monounsaturated fatty acid (data not shown). However, the number of cases in each cell of the obese group was relatively small and the risk estimates uncertain. In an analysis stratified by smoking status, there were only a few statistically significant results with inconsistent patterns that may have been chance findings (data not shown).

Discussion

In this case-control study nested within the Multiethnic Cohort Study, we found no significant association between the fatty acid composition in erythrocyte membranes and the risk of total or advanced/high grade prostate cancer. In ethnic specific analyses, there was a positive association with palmitic acid in Japanese Americans that was significantly different from the null results in other groups. There was also an increased risk with n-3 fatty acids and the ratio of n-3/n-6 fatty acids in Whites, but there was no statistically significant heterogeneity across the ethnic groups for these variables.

Many epidemiological studies have investigated the relationship between dietary intake of fat components, including specific fatty acids, and prostate cancer risk [22–27]. The results have been inconsistent generally. Although some investigators have reported inverse associations with EPA and DHA or their main food source, fish [8,10,28], others did not [29,30]. Similarly, two meta-analyses found an association between ALA intake and increased risk of prostate cancer [31,32], yet the heterogeneity between the studies hampered the interpretation of the results [33].

We also investigated associations between fatty acid intake and prostate cancer risk in our cohort previously and found no relation in the overall analyses [19]. Since we and others have reviewed studies on dietary intake of fatty acids and prostate cancer [22,24,25,27], we focus here on investigations based on biomarkers of fatty acids. In the current study, we measured fatty acids in the membrane of red blood cells. An advantage of this tissue source over serum

is that red cells have an average life span of 120 days, so these measurements reflect a reasonably long period of exposure. These biomarkers complement analysis of self-reported dietary data as they are not subject to recall bias.

We identified five prospective (nested case-control) [29,34-37] and three retrospective (case-control) [38-40] studies published since 1996 that examined fatty acids in whole blood, serum, erythrocyte membranes, or adipose tissue in relation to prostate cancer risk. Findings from these studies have been as conflicting as those based on self-reported fatty acid intake. Long chain n-3 PUFAs, such as EPA (C20:5) and DHA (C22:6), were inversely associated with prostate cancer risk in two studies [34,40], but not in the other studies [29,35,38,39]. ALA (C18:3 n-3) was also positively related to cancer in the two studies only [35,39]. Findings on linoleic acid (C18:2 n-6) were equally inconsistent, with inverse associations in three studies [29,34,37] and positive associations in two studies [38,39]. No other n-6 fatty acid, including arachidonic acid, was related to prostate cancer risk in any of these studies.

One of the possible reasons that many studies failed to find an association between n-3 PUFAs and prostate cancer risk is a low range of dietary intake in the study populations [24]. EPA and DHA concentrations are lower in warm water fish than in cold water fish [24]. Indeed, median intake of n-3 PUFAs in male participants in the Multiethnic Cohort living in Hawaii and California was 1.8 g/day [19], which is relatively low when compared to 2.6 g/day among men in a prospective study in Sweden [16] where fatty fish consumption is greater than in the US [24]. However, mean compositions of these PUFAs in erythrocyte membranes among the current study participants were higher compared to other studies conducted in different areas in the US; mean EPA and DHA values in controls were 0.67% and 6.84% of total fatty acids, respectively in the current study, while 0.59% and 5.23% in a study in North Carolina [38], and 0.61% and 4.17% in Washington [39].

Only a few investigations have been conducted for the relation between saturated fatty acids in blood and prostate cancer risk. While the Physicians' Health Study found no association for saturated fatty acids [41], a nested case-control study in Norway showed a positive association for myristic acid (C14:0) and palmitic acid (C16:0) [35]. Also, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study observed a positive association for myristic acid (C14:0) [29]. In our study, we examined palmitic and stearic but not myristic acid. The only positive findings were for palmitic acid (C16:0) in Japanese Americans. Major food sources of palmitic acid (C16:0) are meat, fish, milk, and cheese [42]. However, in our previous papers, we found no association between consumption of these foods and prostate cancer risk in Japanese Americans, or in the overall cohort [19,43].

Most participants in the previous biomarker studies were Whites. When the current analysis was restricted to Whites, the ratio of n-3/n-6 fatty acids was associated with an increased risk of prostate cancer. This finding is opposite to the hypothesis that n-3 fatty acids may suppress and n-6 fatty acids may promote carcinogenesis [4]. However, heterogeneity across ethnic groups was not statistically significant, so these results may be due to chance, especially given the small number ($n = 50$) of cases among Whites.

There are several strengths to our study. The prospective design minimizes the possibility that the disease process affected fatty acid levels. In order to further confirm this, when we excluded controls with high PSA values, some of whom may have had prostate cancer, the results were unchanged. Erythrocyte membrane fatty acid composition is a valid biomarker of relative dietary levels of fatty acids and reflects usual diet over a period of months, while plasma or serum fatty acids reflect short term (hours) intake and adipose tissue reflects even longer term (years) intake [18,44]. Godley et al. [45] reported that fatty acids in erythrocyte membranes was a reasonable substitute for adipose tissue as a biomarker of essential fatty acid consumption

given their reasonably high correlations with consumption over the previous year (correlation coefficient = 0.44 for EPA and 0.41 for DHA), and the fact that adipose tissue is more difficult to obtain and analyze than blood. In the present study, fatty acid composition in erythrocyte membranes was significantly correlated with dietary intake measured by a quantitative food frequency questionnaire (QFFQ) at baseline (correlation coefficient = 0.23 for EPA and 0.39 for DHA, $p < 0.001$), despite a substantial time gap between baseline and blood collection (6.8 ± 2.3 years). Also, we had information on several potential confounding factors and were able to evaluate whether they affected the fatty acid-prostate cancer associations.

Although we examined the relationship of fatty acids and prostate cancer risk by tumor stage, ethnicity, BMI, and smoking status, the number of cases was not large enough to thoroughly assess the associations in subgroup analyses. In particular, EPA and total PUFA showed a nonsignificant positive trend for advanced or high grade prostate cancer. In the unconditional logistic models adjusting for matching criteria and using all controls to gain more power, ORs for EPA were 1.00, 1.15, and 1.36 (p for trend = 0.26), which is still nonsignificant, while those for total PUFA were 1.00, 1.44, and 2.51 with a significant positive trend (p for trend < 0.001). Therefore, we cannot rule out a weak positive effect, especially for the trend of total PUFA.

Because the follow-up period in our study was relatively short (average follow-up period = 1.9 years), it is possible that a longer follow-up could lead to a different conclusion. Since the follow-up period from the baseline QFFQ, where the dietary intake of fatty acids was assessed, was longer (average follow-up period = 8.7 years), we combined the dietary and biomarker data to look at long-term effects indirectly. We defined high (above the median) dietary intake/high biomarker, high intake/low (below the median) biomarker, low intake/high biomarker, and low intake/low biomarker groups. However, we did not see any difference in the risk of prostate cancer between the four groups: for DHA, the respective proportions of the four groups are 30.8%, 19.3%, 19.2%, and 30.7%, and the ORs of prostate cancer were 0.94 (0.67–1.30), 0.96 (0.66–1.39), 0.88 (0.60–1.28), and 1.00 (ref.), respectively. This provides some evidence that the null results would persist over a longer term.

Although there was a suggestion of ethnic specific associations with some fatty acids, our overall findings do not support a role for fatty acids in prostate carcinogenesis.

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Table 1

Characteristics of prostate cancer cases and controls

	Cases	Controls
Number of participants	376	729
Age at blood draw (years) ^a	68.6 ± 7.1 ^b	68.5 ± 7.2
Fasting hours prior to blood draw ^c	13.5 ± 2.9	13.6 ± 3.0
Years of education	13.8 ± 2.9	13.8 ± 2.9
Body mass index (kg/m ²)	26.1 ± 4.0	26.4 ± 4.2
METS of activity per day	1.6 ± 0.3	1.6 ± 0.3
Alcohol consumption (% total energy)	3.9 ± 7.5	4.0 ± 7.3
Family history of prostate cancer (%)	12.5	7.1
Ethnicity (%) ^d		
African Americans	43.1	42.9
Native Hawaiians	3.5	3.3
Japanese Americans	21.3	21.5
Latinos	18.9	18.7
Whites	13.3	13.6
Fatty acids in erythrocyte membranes (% total fatty acids)		
Palmitic acid, C16:0	29.87 ± 2.36	29.81 ± 1.78
Palmitoleic acid, C16:1	0.49 ± 0.54	0.51 ± 1.17
Stearic acid, C18:0	21.95 ± 1.80	22.07 ± 1.79
Oleic acid, C18:1	16.41 ± 2.25	16.36 ± 2.11
Linoleic acid, C18:2 n-6	12.24 ± 1.77	12.29 ± 1.74
α-Linolenic acid, C18:3 n-3	0.58 ± 0.51	0.55 ± 0.40
Eicosadienoic acid, C20:2 n-6	0.42 ± 0.31	0.43 ± 0.34
Arachidonic acid, C20:4 n-6	8.82 ± 1.43	8.88 ± 1.22
Eicosapentaenoic acid, C20:5 n-3	0.70 ± 0.48	0.67 ± 0.53
Docosapentanoic acid, C22:5 n-3	1.60 ± 0.48	1.60 ± 0.48
Docosahexaenoic acid, C22:6 n-3	6.93 ± 2.02	6.84 ± 1.91
n-3 fatty acids	9.80 ± 2.50	9.66 ± 2.42
n-6 fatty acids	21.48 ± 2.25	21.60 ± 2.07
n-3/n-6 ratio	0.47 ± 0.15	0.46 ± 0.15
Polyunsaturated fatty acid (PUFA)	31.28 ± 2.54	31.25 ± 2.36
Monounsaturated fatty acid (MUFA)	16.90 ± 2.31	16.86 ± 2.31
Saturated fatty acid (SFA)	51.82 ± 2.69	51.88 ± 2.53
PUFA/SFA ratio	0.61 ± 0.08	0.61 ± 0.07

^a Age at blood draw was matched within ±1 year^b Mean ± SD^c Fasting hours prior to blood draw was matched within the following categories: 0 to <6, 6 to <8, 8 to <10, and 10+ h^d Ethnicity was a matching criterion

Table 2

Odds ratios (ORs) and 95% confidence interval (CIs)^a of prostate cancer by quartiles of fatty acid composition in erythrocyte membranes

	Q1	Q2	Q3	Q4	p for trend ^b
<i>Saturated fatty acids (SFA)</i>					
Palmitic acid, C16:0	≤28.63 91/186	28.63 to ≤29.89 97/178	29.89 to ≤31.03 87/190	>31.03 101/175	0.57
Cases/controls					
OR (95% CI)	1.00	1.13 (0.77–1.66)	0.88 (0.58–1.35)	1.21 (0.78–1.88)	
Stearic acid, C18:0	≤21.04 101/176	21.04 to ≤22.03 88/188	22.03 to ≤23.11 102/174	>23.11 85/191	0.60
Cases/controls					
OR (95% CI)	1.00	0.92 (0.62–1.37)	1.14 (0.75–1.74)	0.81 (0.49–1.35)	
Total SFA	≤50.31 99/178	50.31 to ≤51.95 90/186	51.95 to ≤53.53 89/187	>53.53 98/178	0.90
Cases/controls					
OR (95% CI)	1.00	0.86 (0.57–1.30)	0.82 (0.52–1.29)	1.08 (0.64–1.83)	
<i>Monounsaturated fatty acids (MUFA)</i>					
Palmitoleic acid, C16:1	≤0.29 97/179	0.29 to ≤0.39 92/184	0.39 to ≤0.52 93/184	>0.52 94/182	0.73
Cases/controls					
OR (95% CI)	1.00	0.90 (0.60–1.36)	0.89 (0.58–1.37)	0.90 (0.58–1.41)	
Oleic acid, C18:1	≤14.88 89/188	14.88 to ≤16.19 101/174	16.19 to ≤17.54 90/187	>17.54 96/180	0.49
Cases/controls					
OR (95% CI)	1.00	1.28 (0.88–1.86)	1.05 (0.69–1.58)	1.25 (0.78–2.00)	
Total MUFA	≤15.34 86/190	15.34 to ≤16.66 102/175	16.66 to ≤18.03 87/189	>18.03 101/175	0.20
Cases/controls					
OR (95% CI)	1.00	1.39 (0.94–2.04)	1.08 (0.72–1.64)	1.47 (0.92–2.34)	
<i>n-3 polyunsaturated fatty acids (n-3 PUFA)</i>					
α-Linolenic acid, C18:3 n-3	≤0.33 102/175	0.33 to ≤0.47 84/191	0.47 to ≤0.69 93/184	>0.69 97/179	0.81
Cases/controls					
OR (95% CI)	1.00	0.67 (0.41–1.09)	0.71 (0.42–1.20)	0.94 (0.50–1.75)	
Eicosapentaenoic acid, C20:5 n-3	≤0.41 96/180	0.41 to ≤0.55 86/191	0.55 to ≤0.77 91/185	>0.77 103/173	0.30
Cases/controls					
OR (95% CI)	1.00	0.80 (0.55–1.16)	0.85 (0.58–1.26)	1.11 (0.73–1.67)	
Docosapentaenoic acid, C22:5 n-3	≤1.25 102/175	1.25 to ≤1.53 86/190	1.53 to ≤1.92 93/183	>1.92 95/181	0.62
Cases/controls					
OR (95% CI)	1.00	0.63 (0.41–0.96)	0.74 (0.45–1.21)	0.78 (0.43–1.41)	

	Q1	Q2	Q3	Q4	p for trend ^b
Docosahexaenoic acid, C22:6 n-3	≤5.50	5.50 to ≤6.55	6.55 to ≤8.00	>8.00	0.65
Cases/controls	96/181	93/182	85/191	102/175	
OR (95% CI)	1.00	1.00 (0.69–1.45)	0.87 (0.58–1.29)	1.11 (0.73–1.69)	
Total n-3 PUFA	≤8.00	8.00 to ≤9.35	9.35 to ≤10.96	>10.96	0.46
Cases/controls	93/184	91/184	93/184	99/177	
OR (95% CI)	1.00	1.02 (0.70–1.50)	1.04 (0.69–1.56)	1.17 (0.76–1.80)	
<i>n-6 polyunsaturated fatty acids (n-6 PUFA)</i>					
Linoleic acid, C18:2 n-6	≤11.12	11.12 to ≤12.22	12.22 to ≤13.36	>13.36	0.84
Cases/controls	103/173	83/194	91/184	99/178	
OR (95% CI)	1.00	0.70 (0.48–1.02)	0.81 (0.55–1.18)	0.91 (0.62–1.33)	
Eicosadienoic acid, C20:2 n-6	≤0.33	0.33 to ≤0.39	0.39 to ≤0.46	>0.46	0.20
Cases/controls	96/180	103/174	91/185	86/190	
OR (95% CI)	1.00	1.00 (0.66–1.51)	0.86 (0.53–1.37)	0.74 (0.45–1.25)	
Arachidonic acid, C20:4 n-6	≤8.09	8.09 to ≤8.88	8.88 to ≤9.63	>9.63	0.29
Cases/controls	99/177	98/178	87/190	92/184	
OR (95% CI)	1.00	1.02 (0.71–1.45)	0.80 (0.54–1.18)	0.82 (0.54–1.26)	
Total n-6 PUFA	≤20.20	20.20 to ≤21.52	21.52 to ≤22.93	>22.93	0.19
Cases/controls	101/175	94/182	90/187	91/185	
OR (95% CI)	1.00	0.88 (0.60–1.29)	0.80 (0.54–1.18)	0.76 (0.50–1.17)	
<i>Other fatty acid measures</i>					
Total PUFA	≤29.62	29.62 to ≤31.13	31.13 to ≤32.67	>32.67	0.19
Cases/controls	100/177	98/177	82/194	96/181	
OR (95% CI)	1.00	0.96 (0.66–1.39)	0.66 (0.43–0.99)	0.80 (0.51–1.27)	
n-3/n-6 ratio	≤0.36	0.36 to ≤0.43	0.43 to ≤0.53	>0.53	0.30
Cases/controls	96/181	83/196	96/180	101/175	
OR (95% CI)	1.00	0.87 (0.60–1.27)	1.07 (0.72–1.58)	1.16 (0.77–1.76)	
PUFA/SFA ratio	≤0.56	0.56 to ≤0.60	0.60 to ≤0.65	>0.65	0.24
Cases/controls	96/180	99/177	87/189	94/183	
OR (95% CI)	1.00	0.97 (0.67–1.41)	0.71 (0.46–1.11)	0.77 (0.48–1.24)	

^a Matching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (± 1 year), date of blood draw (± 6 months), time of blood draw (± 2 h), and fasting hours (0 to <6 , 6 to <8 , 8 to <10 , and 10+ h). The models were adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables, as well as family history of prostate cancer, BMI, and education

^b The p for trend is based on the Wald statistic for a trend variable assigned the median values within the appropriate quartiles of composition

Table 3

Odds ratios (ORs) and 95% confidence interval (CIs)^a of advanced or high grade prostate cancer by tertiles of fatty acid composition in erythrocyte membranes

	Q1	Q2	Q3	p for trend ^b
<i>Saturated fatty acids (SFA)</i>				
Palmitic acid, C16:0	≤29.14	29.14 to ≤30.68	>30.68	0.96
Cases/controls	32/62	32/63	38/69	
OR (95% CI)	1.00	0.99 (0.48–2.04)	1.02 (0.48–2.15)	
Stearic acid, C18:0	≤21.39	21.39 to ≤22.70	>22.70	0.23
Cases/controls	44/76	36/63	22/55	
OR (95% CI)	1.00	1.07 (0.59–1.96)	0.49 (0.20–1.23)	
Total SFA	≤50.93	50.93 to ≤52.96	>52.96	0.99
Cases/controls	34/67	35/67	33/60	
OR (95% CI)	1.00	0.85 (0.42–1.72)	1.01 (0.43–2.39)	
<i>Monounsaturated fatty acids (MUFA)</i>				
Palmitoleic acid, C16:1	≤0.32	0.32 to ≤0.47	>0.47	0.78
Cases/controls	29/46	27/61	46/87	
OR (95% CI)	1.00	0.55 (0.25–1.23)	0.72 (0.31–1.71)	
Oleic acid, C18:1	≤15.33	15.33 to ≤17.04	>17.04	0.61
Cases/controls	44/89	38/65	20/40	
OR (95% CI)	1.00	1.05 (0.58–1.90)	1.27 (0.54–3.01)	
Total MUFA	≤15.81	15.81 to ≤17.54	>17.54	0.81
Cases/controls	41/80	37/66	24/48	
OR (95% CI)	1.00	0.97 (0.53–1.78)	1.14 (0.48–2.68)	
<i>n-3 polyunsaturated fatty acids (n-3 PUFA)</i>				
α-Linolenic acid, C18:3 n-3	≤0.38	0.38 to ≤0.59	>0.59	0.39
Cases/controls	59/104	23/51	20/39	
OR (95% CI)	1.00	0.59 (0.25–1.41)	0.60 (0.17–2.14)	
Eicosapentaenoic acid, C20:5 n-3	≤0.46	0.46 to ≤0.66	>0.66	0.23
Cases/controls	29/69	35/62	38/63	
OR (95% CI)	1.00	1.44 (0.75–2.76)	1.61 (0.79–3.25)	
Docosapentaenoic acid, C22:5 n-3	≤1.33	1.33 to ≤1.78	>1.78	0.88
Cases/controls	25/51	27/47	50/96	

	Q1	Q2	Q3	p for trend ^b
OR (95% CI)	1.00	1.18 (0.48–2.91)	1.13 (0.33–3.82)	
Docosahexaenoic acid, C22:6 n-3	≤5.93	5.93 to ≤7.41	>7.41	0.90
Cases/controls	39/75	34/61	29/58	
OR (95% CI)	1.00	1.03 (0.55–1.94)	1.05 (0.51–2.16)	
Total n-3 PUFA	≤8.49	8.49 to ≤10.36	>10.36	0.69
Cases/controls	38/73	32/63	32/58	
OR (95% CI)	1.00	1.09 (0.58–2.03)	1.16 (0.56–2.40)	
<i>n-6 polyunsaturated fatty acids (n-6 PUFA)</i>				
Linoleic acid, C18:2 n-6	≤11.46	11.46 to ≤12.95	>12.95	0.84
Cases/controls	27/51	26/59	49/84	
OR (95% CI)	1.00	0.75 (0.38–1.51)	1.02 (0.52–1.99)	
Eicosadienoic acid, C20:2 n-6	≤0.35	0.35 to ≤0.43	>0.43	0.34
Cases/controls	31/49	37/79	34/66	
OR (95% CI)	1.00	0.51 (0.22–1.16)	0.53 (0.20–1.36)	
Arachidonic acid, C20:4 n-6	≤8.38	8.38 to ≤9.38	>9.38	0.30
Cases/controls	23/42	41/71	38/81	
OR (95% CI)	1.00	1.17 (0.57–2.41)	0.72 (0.34–1.54)	
Total n-6 PUFA	≤20.66	20.66 to ≤22.40	>22.40	0.81
Cases/controls	25/37	25/71	52/86	
OR (95% CI)	1.00	0.55 (0.27–1.15)	0.80 (0.37–1.70)	
<i>Other fatty acid measure</i>				
Total PUFA	≤30.11	30.11 to ≤32.11	>32.11	0.22
Cases/controls	21/47	32/68	49/79	
OR (95% CI)	1.00	1.08 (0.49–2.40)	1.78 (0.67–4.68)	
n-3/n-6 ratio	≤0.38	0.38 to ≤0.49	>0.49	0.89
Cases/controls	39/74	36/71	27/49	
OR (95% CI)	1.00	1.02 (0.54–1.93)	1.05 (0.50–2.19)	
PUFA/SFA ratio	≤0.57	0.57 to ≤0.63	>0.63	0.69
Cases/controls	25/55	34/60	43/79	
OR (95% CI)	1.00	1.23 (0.56–2.70)	1.24 (0.49–3.13)	

^a Matching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (± 1 year), date of blood draw (± 6 months), time of blood draw (± 2 h), and fasting hours (0 to <6 , 6 to <8 , 8 to <10 , and 10+ h). The models were adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables, as well as family history of prostate cancer, BMI, and education

^b The p for trend is based on the Wald statistic for a trend variable assigned the median values within the appropriate tertiles of composition

Table 4
Odds ratios (ORs) and 95% confidence interval (CIs)^a of prostate cancer by tertiles of fatty acid composition in erythrocyte membranes and race/ethnicity

	African Americans		Japanese Americans		Latinos		Whites		<i>p</i> for interaction ^b
	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	
<i>Saturated fatty acid (SFA)</i>									
Palmitic acid, C16:0									
≤29.14	49/80	1.00	24/74	1.00	22/42	1.00	21/38	1.00	0.05
29.14 to ≤30.68	47/106	0.67 (0.37–1.23)	37/55	2.61 (1.26–5.42)	23/41	0.94 (0.40–2.21)	15/32	0.72 (0.30–1.73)	
>30.68	66/127	0.78 (0.43–1.44)	19/28	3.21 (1.21–8.53)	26/53	0.90 (0.35–2.30)	14/29	0.81 (0.31–2.13)	
<i>p</i> for trend ^c		0.55		0.009		0.82		0.62	
Stearic acid, C18:0									
≤21.39	39/77	1.00	38/61	1.00	33/60	1.00	17/29	1.00	0.87
21.39 to ≤22.70	65/109	1.37 (0.77–2.43)	19/49	0.55 (0.23–1.33)	23/43	1.05 (0.49–2.24)	15/35	0.70 (0.25–1.91)	
>22.70	58/127	1.03 (0.54–1.99)	23/47	0.60 (0.21–1.75)	15/33	0.79 (0.29–2.13)	18/35	1.14 (0.34–3.89)	
<i>p</i> for trend		0.99		0.39		0.70		0.88	
Total SFA									
≤50.93	43/68	1.00	34/77	1.00	23/45	1.00	16/39	1.00	0.84
50.93 to ≤52.96	50/118	0.62 (0.34–1.13)	27/41	2.16 (0.90–5.19)	28/53	0.90 (0.38–2.15)	19/30	1.96 (0.73–5.27)	
>52.96	69/127	0.94 (0.47–1.88)	19/39	1.73 (0.56–5.32)	20/38	0.91 (0.31–2.65)	15/30	1.69 (0.54–5.27)	
<i>p</i> for trend		0.92		0.32		0.86		0.35	
<i>Monounsaturated fatty acids (MUFA)</i>									
Palmitoleic acid, C16:1									
≤0.32	70/133	1.00	21/52	1.00	18/27	1.00	11/23	1.00	0.78
0.32 to ≤0.47	50/100	0.88 (0.51–1.52)	36/59	1.78 (0.81–3.92)	19/43	0.67 (0.26–1.70)	19/32	1.11 (0.41–3.02)	
>0.47	42/80	1.04 (0.58–1.87)	23/46	1.31 (0.54–3.14)	34/66	0.62 (0.23–1.65)	20/44	0.83 (0.29–2.37)	
<i>p</i> for trend		0.82		0.75		0.41		0.60	
Oleic acid, C18:1									
≤15.33	71/149	1.00	22/39	1.00	17/34	1.00	8/14	1.00	0.99
15.33 to ≤17.04	50/87	1.10 (0.65–1.86)	28/68	0.65 (0.30–1.43)	30/52	1.08 (0.47–2.48)	13/32	0.75 (0.25–2.24)	
>17.04	41/77	1.14 (0.62–2.10)	30/50	1.04 (0.44–2.45)	24/50	0.95 (0.32–2.84)	29/53	0.99 (0.32–3.13)	
<i>p</i> for trend		0.67		0.66		0.89		0.84	
Total MUFA									

	African Americans		Japanese Americans		Latinos		Whites		<i>p</i> for interaction ^b
	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	
≤15.81	73/151	1.00	22/40	1.00	15/33	1.00	8/13	1.00	0.99
15.81 to ≤17.54	49/87	1.15 (0.69–1.91)	28/67	0.79 (0.38–1.65)	30/49	1.19 (0.50–2.84)	14/36	0.68 (0.24–1.96)	
>17.54	40/75	1.16 (0.64–2.12)	30/50	1.20 (0.51–2.87)	26/54	0.96 (0.34–2.70)	28/50	0.94 (0.30–2.92)	
<i>p</i> for trend		0.60		0.64		0.84		0.89	
<i>n-3 polyunsaturated fatty acids (n-3 PUFA)</i>									
<i>α</i> -Linolenic acid, C18:3 n-3									
≤0.38	70/117	1.00	22/47	1.00	30/51	1.00	6/15	1.00	0.09
0.38 to ≤0.59	51/109	0.50 (0.26–0.95)	33/52	1.59 (0.64–3.99)	17/36	0.40 (0.11–1.48)	17/43	0.93 (0.24–3.63)	
>0.59	41/87	0.45 (0.18–1.10)	25/58	0.69 (0.21–2.34)	24/49	0.37 (0.07–1.99)	27/41	2.20 (0.51–9.41)	
<i>p</i> for trend		0.09		0.48		0.37		0.11	
Eicosapentaenoic acid, C20:5 n-3									
≤0.46	61/118	1.00	18/27	1.00	27/55	1.00	17/36	1.00	0.95
0.46 to ≤0.66	63/127	0.91 (0.56–1.48)	12/41	0.48 (0.20–1.15)	22/44	0.93 (0.41–2.12)	16/31	1.02 (0.40–2.63)	
>0.66	38/68	0.95 (0.52–1.75)	50/89	0.89 (0.44–1.80)	22/37	1.35 (0.60–3.05)	17/32	1.16 (0.45–3.01)	
<i>p</i> for trend		0.90		0.67		0.41		0.72	
Docosapentaenoic acid, C22:5 n-3									
≤1.33	66/118	1.00	30/54	1.00	15/26	1.00	11/27	1.00	0.31
1.33 to ≤1.78	53/106	0.73 (0.39–1.39)	28/53	0.83 (0.37–1.83)	19/45	0.79 (0.27–2.32)	19/40	1.73 (0.55–5.45)	
>1.78	43/89	0.64 (0.27–1.51)	22/50	0.60 (0.19–1.87)	37/65	0.99 (0.26–3.78)	20/32	2.90 (0.69–12.21)	
<i>p</i> for trend		0.34		0.38		0.92		0.15	
Docosahexaenoic acid, C22:6 n-3									
≤5.93	61/110	1.00	6/14	1.00	37/73	1.00	18/40	1.00	0.34
5.93 to ≤7.41	60/121	0.77 (0.48–1.25)	20/36	1.09 (0.33–3.58)	21/39	1.15 (0.55–2.43)	16/39	1.12 (0.49–2.54)	
>7.41	41/82	0.76 (0.43–1.35)	54/107	1.05 (0.35–3.15)	13/24	1.47 (0.60–3.60)	16/20	2.10 (0.79–5.61)	
<i>p</i> for trend		0.34		0.99		0.40		0.14	
Total n-3 PUFA									
≤8.49	65/120	1.00	6/13	1.00	33/69	1.00	14/41	1.00	0.12
8.49 to ≤10.36	57/114	0.87 (0.54–1.41)	22/44	0.88 (0.27–2.83)	21/40	1.16 (0.53–2.55)	18/37	1.63 (0.67–3.96)	
>10.36	40/79	0.77 (0.43–1.37)	52/100	0.92 (0.31–2.76)	17/27	1.64 (0.71–3.80)	18/21	2.77 (1.04–7.39)	
<i>p</i> for trend		0.37		0.99		0.25		0.04	

	African Americans		Japanese Americans		Latinos		Whites		<i>p</i> for interaction ^b
	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	
<i>n-6 polyunsaturated fatty acids (n-6 PUFA)</i>									
Linoleic acid, C18:2 n-6									
≤11.46	50/97	1.00	37/70	1.00	13/27	1.00	25/38	1.00	0.25
11.46 to ≤12.95	48/109	0.84 (0.50–1.42)	23/54	0.86 (0.43–1.72)	28/45	1.37 (0.57–3.31)	17/35	0.63 (0.28–1.42)	
>12.95	64/107	1.23 (0.75–2.01)	20/33	1.14 (0.55–2.35)	30/64	0.84 (0.36–1.98)	8/26	0.42 (0.15–1.17)	
<i>p</i> for trend		0.38		0.78		0.53		0.09	
Eicosadienoic acid, C20:2 n-6									
≤0.35	71/129	1.00	17/37	1.00	17/31	1.00	19/32	1.00	0.94
0.35 to ≤0.43	54/115	0.79 (0.45–1.39)	26/42	1.24 (0.54–2.81)	29/53	0.92 (0.37–2.32)	12/28	0.69 (0.26–1.86)	
>0.43	37/69	1.05 (0.51–2.18)	37/78	1.03 (0.39–2.74)	25/52	0.79 (0.29–2.14)	19/39	0.79 (0.25–2.49)	
<i>p</i> for trend		0.87		0.95		0.60		0.73	
Arachidonic acid, C20:4 n-6									
≤8.38	35/49	1.00	57/97	1.00	18/43	1.00	16/35	1.00	0.29
8.38 to ≤9.38	52/109	0.65 (0.35–1.19)	19/45	0.73 (0.37–1.42)	30/48	1.77 (0.85–3.71)	21/36	1.32 (0.56–3.13)	
>9.38	75/155	0.57 (0.30–1.08)	4/15	0.43 (0.12–1.50)	23/45	1.20 (0.51–2.80)	13/28	1.16 (0.38–3.50)	
<i>p</i> for trend		0.11		0.13		0.59		0.78	
Total n-6 PUFA									
≤20.66	36/78	1.00	54/90	1.00	15/25	1.00	25/35	1.00	0.27
20.66 to ≤22.40	53/97	1.29 (0.73–2.30)	19/50	0.62 (0.31–1.23)	26/52	0.75 (0.32–1.74)	15/39	0.49 (0.21–1.17)	
>22.40	73/138	1.26 (0.71–2.23)	7/17	0.57 (0.21–1.58)	30/59	0.72 (0.28–1.87)	10/25	0.55 (0.20–1.48)	
<i>p</i> for trend		0.53		0.13		0.54		0.17	
<i>Other fatty acid measures</i>									
Total PUFA									
≤30.11	53/98	1.00	19/34	1.00	23/51	1.00	28/50	1.00	0.50
30.11 to ≤32.11	56/113	0.69 (0.39–1.19)	28/58	0.95 (0.45–2.03)	23/46	1.52 (0.61–3.83)	12/27	0.78 (0.33–1.86)	
>32.11	53/102	0.75 (0.40–1.41)	33/65	0.92 (0.38–2.18)	25/39	2.23 (0.78–6.40)	10/22	0.80 (0.30–2.16)	
<i>p</i> for trend		0.41		0.84		0.14		0.62	
n-3/n-6 ratio									
≤0.38	64/124	1.00	9/11	1.00	32/72	1.00	14/34	1.00	0.09
0.38 to ≤0.49	67/121	1.01 (0.61–1.67)	15/40	0.39 (0.12–1.29)	23/37	1.69 (0.74–3.82)	13/36	1.10 (0.46–2.61)	

	African Americans		Japanese Americans		Latinos		Whites		<i>p</i> for interaction ^b
	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	Cases /controls	OR (95% CI)	
>0.49	31/68	0.70 (0.38–1.28)	56/106	0.56 (0.20–1.56)	16/27	1.57 (0.71–3.51)	23/29	2.92 (1.01–8.47)	
<i>p</i> for trend		0.24		0.82		0.30		0.04	
PUFA/SFA ratio									
≤0.57	63/113	1.00	21/35	1.00	21/46	1.00	20/40	1.00	0.63
0.57 to ≤0.63	54/111	0.66 (0.38–1.15)	23/48	0.72 (0.29–1.79)	25/48	1.22 (0.50–3.00)	19/33	1.10 (0.47–2.59)	
>0.63	45/89	0.68 (0.35–1.33)	36/74	0.62 (0.22–1.79)	25/42	1.78 (0.62–5.12)	11/26	0.87 (0.33–2.27)	
<i>p</i> for trend		0.27		0.42		0.29		0.77	

^aMatching criteria were accounted for by conditional logistic regression: geographic location (Hawaii or California), race/ethnicity, birth year (±1 year), date of blood draw (±6 months), time of blood draw (±2 h), and fasting hours (0 to <6, 6 to <8, 8 to <10, and 10+ h). The models were adjusted for age at blood draw and fasting hours prior to blood draw as continuous variables, as well as family history of prostate cancer, BMI, and education

^bThe *p* for interaction between fatty acid composition and ethnicity is based on the likelihood ratio test

^cThe *p* for trend is based on the Wald statistic for a trend variable assigned the median values within the appropriate tertiles of composition