Biomarkers of Essential Fatty Acid Consumption and Risk of Prostatic Carcinoma

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Abstract

Animal studies have suggested that omega-6 fatty acids found in vegetable oils may promote prostate cancer. Our goal was to use erythrocyte membrane and adipose tissue fatty acid composition as biomarkers to investigate whether essential fatty acids modulated prostate cancer risk.

An outpatient clinic-based study of 89 cases and 38 controls was conducted in North Carolina between July 1989 and December 1991. Cases were recruited from a university-based urology outpatient clinic. Eligible cases were more than 45 years of age and had histological confirmation of a prostate cancer diagnosis within 1 year of entry into the study. Controls were histologically confirmed free of prostate cancer. Erythrocyte membranes from venous blood and adipose tissue fatty acids from s.c. fat samples were analyzed in batches using capillary gas chromatography. Unconditional logistic regression analysis was used to calculate odds ratios for the association of each fatty acid with prostate cancer while controlling for potential confounders.

Linoleic acid consumption was positively associated with prostate cancer risk. The odds ratios comparing the first and fourth quartiles of linoleic acid consumption were 3.54 (95% confidence interval, 1.0–12.53) with P trend <0.04 for erythrocyte membranes, and 2.47 (95% confidence interval, 0.66–9.26) with P trend <0.08 for adipose tissue. These data suggest that linoleic acid consumption may increase prostate cancer risk, which is consistent with results from animal experiments. Linoleic acid is found in vegetable oils used in cooking and in cereals, snack foods, and baked goods. Our data failed to demonstrate consistently a protective effect of marine omega-3 fatty acids on prostate cancer.

Introduction

Among men in the United States, prostate cancer is the most commonly diagnosed non-skin malignancy and the second leading cause of cancer deaths (1). African Americans have the highest prostate cancer rate in the world, followed by white Americans (2). Despite the high incidence of prostate cancer, little is known definitively about its etiology. Epidemiological studies of environmental exposure, including dietary fat consumption, have yielded largely contradictory results (3–8), although recent studies have supported an increased risk of prostate cancer with consumption of saturated fats (9, 10).

Several epidemiological studies support an inverse relationship between fish consumption and prostate cancer (3, 11). Animal experiments support a protective effect of fish oils against prostate cancer and other cancers (12–20) and suggest a growth-enhancing effect of vegetable oils. Fish consumption may lower the risk of prostate cancer through the production of prostaglandins derived from omega-3 fatty acids. Seafood is the exclusive source of two polyunsaturated essential omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid (21). In contrast, omega-6 fatty acids such as linoleic acid are found in high concentrations in vegetable oils (22). Tissue fatty acid composition can act as a biomarker of relative consumption of these essential fatty acids (23–25).

We tested the hypothesis that omega-3 fatty acids from marine sources are protective against prostate cancer, and that omega-6 fatty acids promote prostate cancer, in an outpatient clinic-based unmatched case-control study using erythrocyte membrane and adipose tissue fatty acid composition as biomarkers of essential fatty acid consumption. We also investigated prostate cancer risk associated with the nonmarine omega-3 fatty acid α-linolenic acid, which has been associated with increased prostate cancer risk (26).

Materials and Methods

Participants. Subjects were men more than 45 years of age who were attending a university-based urology outpatient clinic in North Carolina between July 1989 and December 1991. Eligible subjects had undergone either a prostate biopsy or a prostatectomy. Patients with a history of a previous non-skin malignancy and the second leading cause of cancer deaths (1). African Americans have the highest prostate cancer rate in the world, followed by white Americans (2). Despite the high incidence of prostate cancer, little is known definitively about its etiology. Epidemiological studies of environmental exposure, including dietary fat consumption, have yielded largely contradictory results (3–8), although recent studies have supported an increased risk of prostate cancer with consumption of saturated fats (9, 10).

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Schools of Medicine and Public Health at the University of North Carolina approved both the consent form and the study design. Written, informed consent was obtained from each subject. A total of 147 patients was eligible for the study over the recruitment period. Twenty patients declined to participate, resulting in a response rate of 127/147 or 86%. Thirty-eight percent of the subjects (48/127) were assigned case or control status after enrolling in the study.

**Interview, Collection, and Preparation of Specimens.** Once the subjects gave informed consent to participate in the study, a trained research nurse conducted an interview and obtained demographic and dietary information. Information on fish consumption was obtained using a modified Block food frequency questionnaire described in a separate validation study, which used the same study population (27).

Total cholesterol measurement and erythrocyte membrane fatty acid analysis was performed on 7 cc of venous blood. A s.c. fat sample was obtained from one of three sites, the upper arm, the buttock, or the abdomen, using the technique described by Handelman et al. (28). A 25-gauge needle containing 1–2 ml of 2% lidocaine with epinephrine was used to infiltrate the aspiration site. A 15-gauge needle attached to a Vacutainer of 2% lidocaine with epinephrine was used to infiltrate the s.c. fat pad. The needle was moved in and out 1–2 cm to disrupt the fatty tissue, and a small fat sample was aspirated into an evacuated blood collection tube. The needle was withdrawn and pressure applied to the site. This technique resulted in a 5–10-mg fat sample. The sample was then flushed from the needle-holder with 0.9% saline into a plastic freezer tube.

**Laboratory Procedures.** The erythrocyte membranes were prepared for storage by centrifuging for 5 min at 1400–2000 rpm and pipetting off the buffy coat and supernatant. Erythrocyte ghosts were created by freezing the specimens at −70°C and lysing the erythrocyte membranes. The adipose specimens were also stored at −70°C and analyzed in batches.

The fatty acids were extracted from adipose tissue samples using a variation of the methods described by Folch et al. (29). The extract was saponified under nitrogen for 30 min at 70°C in 3 ml of ethanol containing 0.3 ml of 33% KOH. The nonsaponifiable lipids were extracted in 10 ml hexane and discarded. The aqueous sample was acidified with seven to eight drops of concentrated H2SO4 and the fatty acids extracted in 10 ml of hexane. The extract was transferred to a clean tube and blown dry under N2. The FAMEs were prepared under N2 in 1 ml 14% BF3 in methanol at 60°C for 20 min. After cooling, 10 ml of hexane was added. The solution was washed twice with 2 ml of saturated NaCl. The FAMEs were resuspended in 0.2 ml of undecane. Free fatty acid concentrations were assayed as methyl esters using capillary gas chromatography.

The fatty acids were extracted from erythrocyte membranes using a modification of the technique of Bligh and Dyer (30). One ml of chloroform was added to a 0.4-ml aliquot of erythrocyte suspension. The extract was washed with 1 ml of 0.9% NaCl after another 2 ml of chloroform were added. The phases were separated by centrifugation for 5 min at 600 × g. The chloroform phase was transferred to a clean tube and the extract blown down under N2 at 50°C.

Both adipose tissue and erythrocyte membrane samples were analyzed on a Perkin-Elmer Corp. (Norwalk, CT) Sigma 2000 gas chromatograph equipped with a flame ionization detector and a Perkin-Elmer AS 2000-B autosampler. FAMEs were separated on a 0.25 mm–internal diameter, 30 m-long SP2330 fused silica capillary column using helium as the carrier gas, with a split ratio of 1:30. The initial column temperature was 190°C. After 10 min, it was increased to 210°C at a rate of 2°C/min. The quantitation was performed with a flame ionization detector kept at 250°C. The peaks were quantified using a Shimadzu (Columbia, MD) CR601 integrator. Individual fatty acids were identified using the retention times of standard fatty acid preparations (Nu Check Prep, Elysian, MN).

Each specimen was divided in half, and the fatty acid composition was analyzed separately for each aliquot. The two independent analyses of the percentage of total fatty acids were averaged together for the final result.

**Statistical Analyses.** The Student’s t test was used to generate a P value for the descriptive information for cases and controls. ORs were produced by categorizing individuals into quartiles, which we determined by the distribution of each fatty acid in the control group only. Unconditional logistic regression analysis was used to calculate ORs with 95% confidence intervals for each fatty acid, using the lowest fatty acid consumption category as the reference group (31). The base model included race and age as covariates because of the strong correlations these factors have with prostate cancer. None of the variables were entered into the model. The analyses limited to white subjects were adjusted for age. The Mantel extension test was used to evaluate the ORs for a trend across quartiles (32, 33).

**Results**

During the study period, we enrolled 127 subjects for a participation rate of 86%. More than twice as many cases (89) as controls (38) were recruited into the study, reflecting the high prevalence of prostate cancer among urology clinic patients. African Americans represented 23 (26%) of these cases, and the remainder were white. Among the cases, 17 (19.1%) had low-grade tumors with a Gleason score of 2–4, 36 (40.4%) had Gleason scores of 5–6, and 33 (37.0%) had high-grade tumors with Gleason scores of 7–10 (34). The Gleason score was unknown in three subjects with pathological reports from outside institutions. The distribution of clinical staging was 9 (10.1%) stage A, 33 (37.1%) stage B, 30 (33.7%) stage C, and 15 (16.9%) stage D. The clinical stage was unknown in two (2.2%) subjects. The diagnosis of prostate cancer was made on needle biopsy in 61 (68.5%), transurethral prostatectomy in 9 (10.1%), and open prostatectomy in 16 (18.0%). In three patients, the method of diagnosis was not specified.

African Americans represented a smaller proportion of the control group; 6 (15.8%) were black, and 32 (84.2%) were white. Confirmation of control status was performed by needle biopsy in 16 (42.1%), transurethral prostatectomy in 18 (47.4%), and open prostatectomy in 2 (5.3%). The procedure was not specified in two subjects diagnosed at referring hospitals.

Descriptive statistics are presented in Table 1 by case-control status. Cases were slightly older than controls, and controls had marginally greater body mass and reported more total pack-years of smoking and more years of education. None of the case-control differences reached statistical significance.
In Table 5, linoleic acid demonstrates a significant increase in risk in whites with increasing quartile of consumption. However, a significant protective effect of eicosapentaenoic acid is also demonstrated, with the highest quartile of consumption having about one-third of the prostate cancer risk of the lowest quartile.

### Discussion

Men in the highest quartile of linoleic acid consumption had as much as a 5-fold increased risk of prostate cancer compared to men with low levels of consumption. The trend toward increased risk was more evident using erythrocyte membrane samples than adipose tissue specimens and in whites compared to all subjects. An anticipated protective effect of the omega-3 fatty acid, eicosapentaenoic acid, was found only in the adipose tissue fatty acid analysis using white subjects. The results did not change with adjustment for age, race, education, cholesterol level, smoking history, other fatty acids, or body mass index.

These results are consistent with two rodent feeding studies using implanted human prostate tumors and diets consisting either of omega-6 or omega-3 fatty acids (12, 35). The animals fed linoleic acid developed larger, heavier, and more numerous tumors than the animals who were fed fish oil, suggesting either a growth-stimulatory effect of linoleic acid, a protective effect of eicosapentaenoic acid, or both effects. Studies of prostate cancer cell lines have also reported that omega-6 fatty acids stimulated growth (36), although a recent study found concomitant inhibition of tumor cell growth by omega-3 fatty acids only at relatively high levels (37). A growth-stimulatory effect of linoleic acid is most consistent with the findings of this study, but an additional protective effect of eicosapentaenoic acid cannot be excluded. Although this study did not find evidence of an independent dose-response relationship between omega-3 fatty acids in tissue and risk of prostate cancer, the finding of lower ORs in the highest quartile of omega-3 fatty acid composition is interesting and warrants additional study with a larger sample size. The median erythrocyte membrane omega-3 fatty acid composition for each quartile in Tables 2 and 4 demonstrates an increase between the third and fourth quartile that is substantially greater than the increases among the lower quartiles. It is possible that a threshold effect exists such that a certain level of usual fish consumption is necessary for a protective effect of omega-3 fatty acid intake to occur.

The findings were not in complete agreement with findings from a prospective trial of fatty acids and prostate cancer risk by Gann et al. (26), which measured plasma-free fatty acids. Their results indicated that linoleic acid had a weakly protective effect, in contrast to our findings of a significant prostate cancer risk increase. The authors also reported a significant trend toward an increase in prostate cancer risk from the terrestrial omega-3 fatty acid α-linolenic acid, which is found in moderate concentrations in plant leaves, including spinach, legumes, citrus fruits, and starchy vegetables, with linseed (flaxseed) oil being the richest common source (38). Our study revealed increases in the ORs, but without a significant trend. One possible explanation for the differences between the studies is that the investigators did not indicate that they used fasting plasma specimens, which previous studies have shown to correlate with adipose tissue fatty acid composition (39–41). In contrast, there is substantial evidence for the validity of adipose tissue samples as a stable biomarker of past essential fatty acid consumption over a period of years (42–44). Supporting studies include a study documenting the prolonged decay of a labeled fatty acid in adipose tissue (45) and an
Omega-6 Fatty Acids and Prostate Cancer Risk

To investigate whether prostate cancer alters serum fatty acid biomarkers, Godley et al. (27) correlated erythrocyte membrane fatty acids with both food frequency questionnaires and 7-day diet records (41). The authors found no significant differences seen in fatty acid composition, and supports the use of fatty acid biomarkers in case-control studies of past diet. Recent weight loss among the cases is also an unlikely explanation for these findings, because at least one study found that a 20% weight loss did not affect adipose tissue eicosapentaenoic acid or docosahexaenoic acid levels (47), and the proportion of lean subjects among the case group (13.5%) and that among the control group (10.5%) are similar.

We attempted to minimize the recruitment of controls who were actually misclassified unsuspected prostate cancer cases, by including only those control subjects found to be free of prostate cancer by a prostate biopsy or resection. Autopsy series (48-50) and cystoprostatectomy studies (51-53) have documented a rate of unsuspected prostate cancers in males more than 50 years of age that ranges as high as 40%. To our knowledge, this is one of only a few studies that attempted to correlate erythrocyte membrane fatty acid composition, comparing adipose tissue eicosapentaenoic and docosahexaenoic acids, and a food frequency questionnaire. The correlations are similar to those reported by Hunter et al., comparing adipose tissue fatty acids with either food frequency questionnaires or 7-day diet records (41). The authors found no significant differences in the food frequency questionnaire/biomarker omega-3 fatty acid correlation between men with and without prostate cancer. This finding argues against the presence of prostate cancer or its treatment substantially accounting for the differences seen in fatty acid composition, and supports the use of fatty acid biomarkers in case-control studies of past diet.

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**Table 2** Prostate cancer risk by erythrocyte membrane fatty acid composition

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>ORs (95% confidence intervals)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 1 (Low)</td>
<td>Quartile 2</td>
</tr>
<tr>
<td>Eicosapentaenoic (20:5 omega-3)</td>
<td>1.00</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>(0.47-3.96)</td>
<td>(0.34-2.97)</td>
</tr>
<tr>
<td>Docosahexaenoic (22:6 omega-3)</td>
<td>1.00</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>(0.41-3.58)</td>
<td>(0.47-4.04)</td>
</tr>
<tr>
<td>α-Linolenic (18:3 omega-3)</td>
<td>1.00</td>
<td>3.02</td>
</tr>
<tr>
<td></td>
<td>(0.97-9.45)</td>
<td>(0.43-7.00)</td>
</tr>
<tr>
<td>Linoleic (18:2 omega-6)</td>
<td>1.00</td>
<td>3.16</td>
</tr>
<tr>
<td></td>
<td>(0.91-10.93)</td>
<td>(1.23-14.66)</td>
</tr>
</tbody>
</table>

* Fatty acids are independent variables in a logistic regression model with race and age as covariates.
* Median fatty acid peak for each quartile in controls: 0.29, 0.41, 0.54, and 0.90.
* Median fatty acid peak for each quartile in controls: 3.27, 4.23, 5.77, and 7.49.
* Median fatty acid peak for each quartile in controls: 0, 0.16, 0.19, and 0.24.
* Median fatty acid peak for each quartile in controls: 9.96, 11.83, 13.16, and 14.79.

**Table 3** Prostate cancer risk by adipose tissue fatty acid composition

<table>
<thead>
<tr>
<th>Fatty acid</th>
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<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quartile 1 (Low)</td>
<td>Quartile 2</td>
</tr>
<tr>
<td>Eicosapentaenoic (20:5 omega-3)</td>
<td>1.00</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>(0.22-2.29)</td>
<td>(0.50-15.57)</td>
</tr>
<tr>
<td>Docosahexaenoic (22:6 omega-3)</td>
<td>1.00</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td>(0.38-4.65)</td>
<td>(0.47-6.19)</td>
</tr>
<tr>
<td>α-Linolenic (18:3 omega-3)</td>
<td>1.00</td>
<td>3.73</td>
</tr>
<tr>
<td></td>
<td>(0.97-14.33)</td>
<td>(1.17-15.83)</td>
</tr>
<tr>
<td>Linoleic (18:2 omega-6)</td>
<td>1.00</td>
<td>2.04</td>
</tr>
<tr>
<td></td>
<td>(0.59-7.49)</td>
<td>(1.20-15.12)</td>
</tr>
</tbody>
</table>

* Fatty acids are independent variables in a logistic regression model with race and age as covariates.
* Median fatty acid peak for each quartile in controls: 0.01, 0.03, 0.04, and 0.05.
* Median fatty acid peak for each quartile in controls: 0.04, 0.08, 0.12, and 0.19.
* Median fatty acid peak for each quartile in controls: 0.46, 0.67, 0.82, and 1.06.
* Median fatty acid peak for each quartile in controls: 12.61, 16.65, 20.21, and 22.64.
We recruited cases with prostate cancer diagnosis within 12 months of study entry. The Gleason scores of the cases were intermediate, with 40% of the cases having a Gleason grade of 5 or 6, suggesting predominately moderately differentiated cancers. The clinical stages were almost evenly divided between early- and late-stage disease, a distribution that is consistent with reports of newly diagnosed prostate cancers prior to the increased consumption of linoleic acid found in vegetable oils were seen when using both erythrocyte membrane and adipose tissue biomarkers and are supported by the results of rodent feeding studies. These preliminary findings of a common dietary component that may increase prostate cancer risk could contribute to dietary recommendations that lower prostate cancer incidence rates or help identify men at high risk for the disease; however, these conclusions need to be confirmed by other studies. Linoleic acid, although found in vegetable seed oils such as safflower (75% of total fatty acids), walnut (60%), sunflower (54%), corn (53%), soybean (52%), cotton (49%), palm (8%), and coconut (2%), is not a major component of vegetables (67). Vegetables have not been found to be prostate cancer risk factors. Linoleic acid is found in high levels in vegetable oils, particularly breads, cereals, snack foods, and baked goods that are cooked in vegetable oils (68). If these findings were confirmed in other studies, the hypothetical reduction in prostate cancer risk derived from decreasing consumption of omega-6 fatty acids such as linoleic acid would have to be weighed against the known beneficial cardiovascular effects of substituting vegetable oils for animal fats.

Future investigations may improve on the ability of erythrocyte membrane fatty acid composition (whites only) to select a prostate cancer control group based on pathological evidence of lack of prostate cancer.

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rocyte membrane fatty acid composition to reflect accurately the relative consumption of fatty acids found in very low proportions in human tissue by examining the fatty acid composition of specific phospholipids. Phosphatidylcholine and phosphatidylethanolamine, for example, selectively incorporate omega-3 fatty acids, whereas phosphatidylcholinol esters tend to remain stable with dietary alterations (69, 70).

References


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