

## Editorial

# Essential Fatty Acids and Prostate Cancer: An Emerging Hypothesis?

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Prostate cancer is the most common cancer in United States men, accounting for 41% of the newly diagnosed cases (1). It is estimated that in 1996, 317,100 new cases will be diagnosed and 41,400 men will die of this cancer (1). Despite the large numbers, age, race, and family history of prostate cancer are the only established risk factors. Ecological and analytic studies have suggested that environmental factors, and diet in particular, may play an important role in the development of prostate cancer (2). Most epidemiological studies have reported a positive association with total fat, animal fat, and red meat consumption (3), although results have not all been consistent. Few studies have investigated the role of individual fatty acids or essential fatty acids (fatty acids that cannot be synthesized by human tissue and have to be obtained through dietary sources), which are believed to be better markers of dietary fat intake (4).

In this issue of *Cancer Epidemiology, Biomarkers & Prevention*, Godley *et al.* (5), in a hospital-based case-control study conducted in North Carolina, report that levels of linoleic acid in both erythrocyte membranes and adipose tissue are associated with an increased risk of prostate cancer. Linoleic acid (c18:2n6) is an omega-6 polyunsaturated essential fatty acid that comes primarily from soybean and vegetable oils, mayonnaise, margarine, potato chips, salad dressings, peanut butter, French fries, lard, and red meat. No association was found for  $\alpha$ -linolenic acid (c18:3n3), a major essential fatty acid, the sources of which are similar to those of linoleic acid but with the addition of butter, or for the marine omega-3 fatty acids, eicosapentaenoic acid (c20:5n3) and docosahexaenoic acid (c22:6n3), which come mostly from fish oils. These results add to the already confusing data from four previous studies that have assessed plasma/serum or dietary fatty acid levels in relation to prostate cancer risk (6–9). For linoleic acid, a nonsignificant inverse association was found in two prospective studies, the Health Professionals Follow-up Study (6) and the Physicians' Health Study (7). A significant inverse association was found in a case-control study (8), whereas there were no clear risk patterns in the Washington County Cohort Study (9). For  $\alpha$ -linolenic acid, a positive association was found in the Health Professionals Follow-up Study (6) and the Physicians' Health Study (7). In the Washington County Cohort Study (9), although risk of prostate cancer was increased among subjects

whose serum levels of  $\alpha$ -linolenic acid were in the second and third tertiles, no significant trend was observed.

Caution is required in interpreting results in these studies. Differences in the type of biological samples obtained or in the timing of sample collection may partially explain the discrepancies. Godley *et al.* (5) measured levels of linoleic and  $\alpha$ -linolenic acids in both erythrocyte membranes and adipose tissue from cases at the time of diagnosis of prostate cancer. In contrast, these fatty acids were assessed in prediagnostic plasma/serum drawn within 6 years of diagnosis in the Physicians' Health Study and drawn over 6 years before diagnosis in the Washington County Cohort Study. In the Health Professionals Follow-up Study, linoleic and  $\alpha$ -linolenic acid indices were computed from a nutrient data base derived from a food frequency questionnaire. Of these four types of measurements, adipose fatty acid content probably is the best marker of long-term dietary intake of linoleic acid (fewer data are available for  $\alpha$ -linolenic acid), because the half-life of linoleic acid in adipose tissue has been estimated to be approximately 680 days (4), and the levels in adipose tissue correlate well with those from dietary records or food frequency questionnaires (10–12). Erythrocyte fatty acid levels, although less stable, are also relatively good markers for dietary fatty acid intake in epidemiological studies. They correlate well with both dietary fatty acids and adipose tissue levels, and the effect of storage after 12 months is minimal (13). Plasma levels of fatty acids, although they correlate with levels in red blood cell membranes, are affected by diet and metabolism and therefore represent a relatively short-term marker (4). The validity of fatty acid indices derived from a dietary questionnaire depends largely on the ability of the food items used to capture fatty acids in the diet.

With respect to timing, it is not clear whether the presence of prostate tumor can affect the intake or metabolism of fatty acids, thereby influencing the case-control comparison. If such an effect exists, results from Godley *et al.* (5) and the Physicians' Health Study would need to be interpreted with great caution. In the Washington County Cohort Study, although the disease effect on exposures is likely to be minimal, the numbers are too small to evaluate the small case-control differences with any certainty. Additional data from longer follow-up of these cohorts should help clarify these issues.

The findings for linoleic acid reported by Godley *et al.* (5) warrant additional investigation. Although little epidemiological data are available to evaluate this hypothesis, most laboratory and animal studies have shown that linoleic acid and, to some extent,  $\alpha$ -linolenic acid may promote prostate tumor growth in cell lines and in laboratory rodents and change membrane phospholipid composition, thereby affecting membrane permeability and nuclear receptor activity (14–16). Furthermore, in malignant prostatic tissue, increased metabolism of arachidonic acid (c20:4n6) has been reported (17, 18). Arachidonic acid is a metabolite of linoleic acid and a precursor for eicosanoids, such as prostaglandins E<sub>1</sub> and E<sub>2</sub> and leukotrienes, which have been shown to enhance prostate carcinogenesis (19). As with epidemiological data, laboratory findings

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are not entirely consistent. One study suggested that certain essential fatty acids have chemoprevention properties, because they may modulate androgen metabolism by inhibiting the activity of 5- $\alpha$  reductase, an enzyme that converts testosterone to dihydrotestosterone within the prostate gland (20). The difference in 5- $\alpha$  reductase activity across populations has been proposed as a possible explanation for the remarkable racial and ethnic disparities in clinical prostate cancer incidence (21). Of special interest is whether the difference in 5- $\alpha$  reductase activity is determined genetically by the gene 5- $\alpha$  reductase type II (*SRD5A2*) encoding for this enzyme or is subject to dietary modulation through gene-diet interactions.

Contrary to earlier reports (6, 7), Godley *et al.* (5) found no significant association with  $\alpha$ -linolenic acid, although risk estimates in all upper quartiles exceeded 1. In the Health Professionals Follow-up Study, Giovannucci *et al.* attributed the 2-fold risk associated with red meat to  $\alpha$ -linolenic acid, but more studies are needed (6). It is possible that other dietary components of red meat or chemicals generated by cooking contribute to the reported association. For example, in beef and pork, levels of linoleic acid are usually 2–10 times higher than those of  $\alpha$ -linolenic acid, depending on the location and the leanness of the meat, and levels of saturated fats (palmitic and stearic acids) and protein are also much higher than those of  $\alpha$ -linolenic acid (22). Accumulating data have shown that cooking meat at high temperature can produce large amounts of mutagens and carcinogens, including heterocyclic amines (23). Furthermore, although Godley *et al.* (5) found no protective effect for marine omega-3 fatty acids, laboratory studies have shown that these fatty acids inhibit prostate cancer cell growth (14, 15). Future studies are needed to clarify the role of red meat,  $\alpha$ -linolenic acid, and marine omega-3 fatty acids.

Despite the paucity of epidemiological data, given the preliminary data from laboratory studies and the very few leads available for prostate cancer etiology, essential fatty acids should be added to the list of promising working hypotheses, including hormones, dietary fat, physical activity, and body size. A potential common thread among these hypotheses is hormones, which appear to be involved in the origins of prostate cancer but modulated by the potential dietary and putative risk factors (24). A better understanding of the interrelationships among these epidemiological factors, circulating hormones and their metabolites, and dietary components such as fatty acids will provide new insights into the origins and progression of prostate cancer. Large-scale studies that combine a comprehensive dietary interview with collection of biological samples are needed to evaluate fully the role of dietary, hormonal, and genetic interactions involved in the etiology of prostate cancer. Interdisciplinary studies that take advantage of the substantial racial differences in prostate cancer risk may be equally informative.

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