# Dietary Fatty Acids and Prevention of Hormone-Responsive Cancer (44172)

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*Abstract.* **The results from some, but not all, epidemiological studies indicate that the level of dietary fat intake and the nature of the constituent fatty acids influence both breast and prostate cancer risk, and disease progression. These observations derive support from the use of animal models, which demonstrate that polyunsaturated ω-6 fatty acids stimulate mammary carcinogenesis and tumor growth and metastasis, whereas long-chain ω-3 fatty acids exhibit inhibitory effects. While studies of prostate cancer are less advanced, the available data are in agreement with those designed to evaluate the associations between breast cancer and dietary fatty acids. In both cases, a multiplicity of biological actions of eicosanoids derived from tumor cell arachidonate metabolism appear to elicit responses, both in the tumor itself and in the host cells that subscribe to its microenvironment. This review concludes that clinical intervention trials designed to reduce total fat intake and increase the ratio of ω-3 to ω-6 fatty acids in the diet should be targeted at groups at a relatively high risk for breast or prostate cancer, and also at postsurgically treated cancer patients with the objective of preventing disease recurrence.** [P.S.E.B.M. 1997, Vol 216]

Breast cancer is the second most common cause of cancer-related death in American women, and prostate cancer occupies the same ranking among American men. It was estimated that 44,300 women and 41,400 men in the United States were expected to die of breast and prostate cancer, respectively, during 1996 (1). The management of prostatic carcinoma is particularly difficult because, in over half the cases, the tumor has spread beyond the prostate capsule at the time of diagnosis, and there is no curative treatment for the advanced disease. While early diagnosis combined with adjuvant chemohormonal therapy has resulted in a significant improvement in the outcome of breast cancer therapy (2), and progress along the same lines may be anticipated in prostate cancer (3, 4), the emphasis of current and future clinical trials is turning towards prevention.

Opportunities for cancer prevention occur at two levels. The first, termed primary prevention, involves the avoidance or inhibition of the process of carcinogenesis: an example is the development and implementation of smoking cessation programs. The second level is actually one in which an intervention is designed to suppress the progression of transformed cells to a state of clinically manifest cancer. The current breast cancer prevention trials in which the antiestrogen tamoxifen is being evaluated are conceptually studies of chemosuppression rather than chemoprevention, the objective being to inhibit the progression of very early neoplastic lesions in middle-aged, largely postmenopausal, symptom-free women (5). A similar approach is now being explored for the prevention of prostate cancer; here, the agent being tested in a National Cancer Institute–sponsored clinical trial is finasteride, a pharmacological inhibitor of the 5α-reductase that converts the androgen testosterone to the biologically potent dihydrotestosterone (6).

Despite their initial hormone dependence, both breast and prostate cancers will, if not successfully eradicated, eventually become autonomous and independent of their hormonal environment (7–9). This emergence of hormone independence is due to the selection of preexisting autonomous cells, together with the acquisition of those features, including cell membrane receptors for epidermal growth factor, which characterize the hormone-independent, typically biologically aggressive, phenotype (Fig. 1). One characteristic of this loss of dependence on steroid hormones for growth and metastasis is the establishment of autocrine and paracrine control by polypeptide growth factors (7, 10–12);

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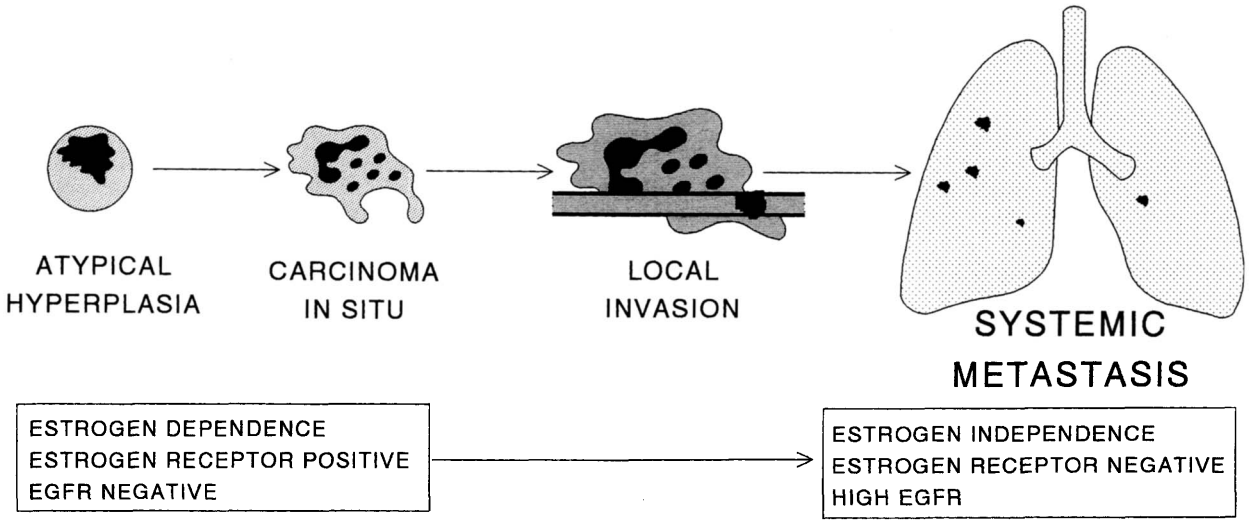


**Figure 1.** Progression of breast disease beyond the stage of preneoplastic atypical hyperplasia to noninvasive carcinoma *in situ,* invasion through basement membranes, and establishment of the invasive/metastatic phenotype. EGFR, epidermal growth factor receptor.

another appears to be responsiveness to the influence of dietary fatty acids (FAs).

In this review, we will be focusing on the effects that dietary FAs, specifically the unsaturated FAs, have on the biological characteristics of breast and prostate-cancer cells. The hypothesis will be developed that a dietary intervention which is based on the individual classes of polyunsaturated FAs, and monounsaturated FA, offers a plausible approach to the prevention of these two tumor types, and/or to the inhibition of cancer progression once neoplastic transformation has taken place.

## Targets for Primary and Secondary Prevention

**Benign Breast Disease.** Noncancerous breast disease in which there is an abnormal proliferation of the ductal epithelium is associated with an increased risk for breast cancer (13–16). Atypia describes a histological appearance in which the cells themselves show morphological abnormalities, prominent among which is an increase in the ratio of nuclear to cytoplasmic size. In its extreme form, it constitutes one element of ductal carcinoma *in situ.* In one study, subsequent breast cancer risk for women with proliferative benign breast disease without atypia was 1.9 times that of women with nonproliferative disease, but this risk increased to 5.3-fold if atypia was also present (13). There is also an interaction between atypical hyperplasia and a family history of breast cancer; in the study by Dupont and Page (13), the risk was found to be 11 times that of patients with nonproliferative lesions without a family history (mother, sister, daughter). Atypical hyperplasia constitutes a risk factor not only in countries, such as the United States and Britain, with high breast cancer incidence rates but also among Japanese women, who are at a relatively low risk for this type of cancer (16).

The growth of solid tumors requires the participation of cancer cell-induced blood vessel formation (17), and the extent of neovascularization, or angiogenesis, in primary breast cancers has been shown to correlate with prognosis (18, 19). This critical role for angiogenesis in cancer progression has prompted considerable interest in antiangiogenic agents as suppressors of growth and metastasis, but of particular interest in the present context are reports that a relationship exists between angiogenic activity in benign breast lesions and their likelihood of progression to malignant disease (20–22).

**Mammographic Patterns.** The relationship between the patterns of the breast parenchymal tissue detected by mammography and cancer risk was first described by Wolfe (23), and has been reviewed by Goodwin and Boyd (24). The Wolfe classification defines four categories: the risk is lowest in that designated N1, the parenchyma being composed largely of fat, and highest in the DY category, which is characterized by extensive nodular densities (''mammographic dysplasia''). An alternative to the Wolfe classification is to determine directly the proportion of the breast volume occupied by radiological densities (25). Using this technique, Boyd *et al.* (26) found that extensive mammographic densities in women aged 40–49 years predicted a 9.7-fold increase in the likelihood of developing atypical hyperplasia or breast carcinoma *in situ.*

**Breast Carcinoma *in Situ.*** Ductal carcinoma *in situ* is the common form of noninvasive breast cancer. It is characterized by the proliferation of cancerous epithelial cells, but these are restricted to the ducts, and there is no microscopic evidence of invasion through the basement membrane into the surrounding stroma. The distinction between ductal carcinoma *in situ* and the premalignant state of atypical hyperplasia is not always apparent, as the one merges into the other (27). Indeed a continuous spectrum exists between ductal hyperplasia and invasive breast cancer with metastasis (Fig. 1).

Several studies have assessed the risk of subsequent

invasive disease in patients in whom the diagnosis of ductal carcinoma *in situ* was missed, or who were not treated by mastectomy; these showed that 10%–30% developed invasive breast cancer in the same breast within 10–20 years (27, 28). Before the introduction of mammographic screening, ductal carcinoma *in situ* was an uncommon diagnosis, but now it is being recognized with increasing frequency. This has created a clinical dilemma because treatment by mastectomy, although previously the standard and acceptable approach, is difficult to justify, given the estimate that only about one-third of the small histopathological lesions are likely to progress to invasive breast cancer. As might be anticipated, neovascularization has been suggested as a predictor of subsequent invasive behavior in carcinoma *in situ* (22), as it has in atypical hyperplasia.

**Prostatic Carcinoma *in Situ* and Proliferative Intraepithelial Neoplasia.** As in the case of breast cancer, the populations with a high incidence of carcinoma of the prostate are those of northern Europe or of northern European origin; an exception to this generalization is the extremely high prostate cancer risk among African-Americans in the United States (29). The lowest prostate cancer incidence and mortality rates occur in the Asian countries, including highly industrialized Japan. However, despite the widely differing rates with which clinically manifest prostate cancer occurs, autopsy studies have shown that neoplastic lesions which are restricted to the prostate gland and have usually remained unrecognized throughout life (''latent'' prostate cancer) occur with much the same frequency among Japanese men as in white males in North America and Europe (29). Also, when Jackson *et al.* (30) performed a histopathological comparison of prostatic lesions in African-Americans and black Africans in Ibadan, Nigeria, they found that small, microscopically detected carcinomas of the prostate were present in approximately equal numbers, whereas invasive cancer was more common among the African-Americans.

A closer examination of the intraprostatic tumors indicates that there are differences in proliferative rates. One internationally based autopsy study compared the frequency and histopathological characteristics of latent prostate cancers in seven geographical areas (31). Small ''focal'' latent carcinomas occurred with approximately the same incidence in all locations, but larger, diffusely infiltrating cancers, while common in European men, were unusual in Chinese males residing in Hong Kong or Singapore. The death rate from prostate cancer among Japanese in Hawaii is closer to that of the white American population than it is in Japan, and when Akazaki and Stemmerman (32) performed a comparative study of latent prostatic carcinoma, larger, infiltrating tumors within the prostate were observed more frequently among the migrants to Hawaii than the native Japanese. Studies such as these suggest that diffuse latent carcinomas constitute progressive, potentially life-threatening tumors, whereas focal latent prostate cancers are either in a state of growth arrest or growing at a very slow rate.

We have suggested elsewhere that dietary FAs may be involved in the acquisition of biological characteristics which are essential for prostatic cancer cell progression, and the emergence of invasive disease from preexisting intraprostatic foci (33).

Prostatic intraepithelial neoplasia (PIN), or intraductal dysplasia, is a histologically recognized condition analogous to the merging of breast ductal atypical hyperplasia with ductal carcinoma *in situ*. There is a strong association between the most-advanced grade of PIN and invasive carcinoma, which has led to the proposal that PIN constitutes a common precursor lesion for clinically manifest prostatic cancer (34). Subsequent studies have lent support to this concept (35, 36) and have identified immunohistochemical markers for PIN and demonstrated a unique growth-regulating, platelet-derived growth factor–mediated autocrine loop (37). This premalignant condition is being diagnosed with increased frequency with the introduction of prostate cancer screening by serum prostate-specific antigen assay and ultrasonography.

## Dietary Fat and Fatty Acids: Breast Cancer

**Epidemiology.** International comparisons have consistently demonstrated a positive correlation between prostate cancer mortality rates and estimates of *per capita* fat intake (38–40). However, such studies may be criticized because of variability in the quality of the tumor registries and food consumption data in different countries, and the influence of other modifiers of breast cancer risk such as reproductive factors. Scientifically more stringent epidemiological investigations, based on a case-control or cohort design, have given inconsistent results (41) but, in general, do not support a relationship between total dietary fat intake and breast cancer causation (42–44). One difficulty in interpreting the findings of most of the published epidemiological studies is that they do not take account of the relative levels of the FAs which contributed to the total amount of fat consumed; indeed, in most instances the sensitivity of the instruments used to assess dietary intakes has not been adequate to provide such data. Nevertheless, some reports have described a positive association between ω-6 (n-6) polyunsaturated FA consumption and breast cancer (45–47).

While Japan is a country with relatively low breast cancer incidence and mortality rates, this is changing; it is calculated that within the next two decades breast cancer will become a major cause of cancer death in Japanese women (48). This shift in breast cancer risk is taking place largely in the urban centers of the country, and in several studies it has been associated with an increase in fat consumption (48–50). However, the changes in dietary patterns are more complex; they include an increase in the proportion of n-6 polyunsaturated FAs contained within the total fat consumed, as well as a reduction in long-chain n-3 FAs and hence a decrease in the n-3/n-6 FA ratio (51–53), and Kamano *et al.* (54) suggested that this change in relative

dietary FA intake may be related to the increasing breast cancer incidence in Japanese women.

Another difficulty that arises when attempting to evaluate the putative relationship between dietary fat and breast cancer is that the epidemiological studies have been largely population based, rather than targeting groups of women with a genetically and/or pathologically determined propensity for developing the disease (55). In this context, it is noteworthy that both proliferative benign breast disease (56, 57), and the "high-risk" Dy mammographic pattern (58, 59) have been associated with high fat intakes and, in one study, specifically with the n-6 FAs (59). While these observations require confirmation in independent, larger studies, if correct they point the way towards novel approaches to breast cancer prevention.

The long-chain n-3 FAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), occur in seafoods, with particularly high concentrations being present in some fish oils. In contrast to the n-6 FAs, they may exert a protective effect against breast cancer. Coastal- and rural-dwelling Japanese (60), and Eskimos (61–63), who traditionally consume large quantities of these n-3 FAs, have low breast cancer rates (64, 65), but once again dietary changes towards the typical Western diet are accompanied by adverse shifts in cancer risk (66).

**Animal Models: Mechanisms.** The enhancing effects of high-fat, n-6 FA–rich diets on experimental mammary carcinogenesis have been extensively covered in earlier reviews (67–69). Carroll and Hopkins (70) described the promotion of mammary tumor development by n-6 FA-containing corn oil and safflower oils in rats exposed to the indirect chemical carcinogen dimethylbenz[*a*]anthracene (DMBA), and Cohen *et al.* (71) reported a similar effect after exposure to the direct-acting carcinogen *N*-nitrosomethylurea (NMU). In both of these, and similar experimental studies, high intakes of saturated FA did not influence tumor development; indeed, in one experiment it was observed that saturated FAs reduced the incidence of spontaneous mammary tumors in high-risk C3H mice (72).

In contrast to the plethora of reports dealing with the influence of dietary FAs on chemically induced mammary carcinogenesis, relatively little has been published concerning the preneoplastic process. Linoleic acid (LA), a dietary n-6 FA, does stimulate the proliferation of mouse mammary epithelial cells *in vitro* (73), and a similar response occurs with nontransformed human breast epithelium (74). Welch *et al.* (75) showed that feeding a high-fat, LA-rich diet to female mice stimulated mammary epithelial cell proliferation. In an extension to this finding, Zhang *et al.* (76) demonstrated that the [$^3$H]thymidine-labeling index of the terminal ducts, the target for malignant transformation, was increased not only by a high-LA–containing diet, but also by feeding a high–saturated FA beef tallow diet, with 3% LA present to avoid essential FA deficiency. When a "Western-style" diet (high in total fat, LA and phosphate, but low in calcium and vitamin D) was fed to female mice for 14 or 20 weeks there was an increase in the actual number of terminal ducts, again enlarging the target for carcinogenic activity (77).

Telang and his colleagues have performed a series of elegant studies of the effects of FAs on the premalignant mammary alveolar lesions which form in organ cultures of tissues from the high–mammary cancer strain of RIII mice (78–80). Both LA and its metabolic derivative arachidonic acid stimulated the development of these lesions, as well as the expression of *ras* p21 (80); the enhanced incorporation of [$^3$H]thymidine into the cellular DNA of mammary alveolar lesion–containing glands was accompanied by increased prostaglandin synthesis (78).

In addition to their enhancement of the primary neoplastic process, n-6 FAs also stimulate mammary tumor progression once transformation has taken place. Hillyard and Abraham (81) showed that feeding a LA-rich diet increased the growth of a transplantable mouse mammary carcinoma, and in a series of studies from the author's laboratory a similar effect was demonstrated on both the growth and metastasis of human breast cancer cells when these were injected into the mammary fat pads of female athymic nude mice (82–84).

In keeping with their association with reduced human breast cancer risk, the long-chain n-3 FAs suppress mammary carcinogenesis and tumor progression in animal models. Thus, they inhibit the formation of mammary alveolar lesions in the preneoplastic explant culture model developed by Telang *et al.* (80), chemically induced rat mammary carcinogenesis (85), the progression of transplanted mammary carcinomas (86–88), and the growth and metastasis of human breast cancer cells in nude mice (89–91).

There is convincing evidence from tumor tissue assays, experiments *in vitro,* and the use of pharmacological inhibitors that the effects of dietary FA on breast carcinogenesis, and the subsequent behavior of the tumor cells involves the biosynthesis of eicosanoids (Fig. 2). In all probability, the products formed from arachidonic acid under the influence of both cyclooxygenase and lipoxygenase activities are involved, although not necessarily in modulating the same phases of tumor formation and progression.

The stimulation of alveolar lesion formation by arachidonic acid in explant cultures of RIII mouse mammary tissue was accompanied by increased prostaglandin $E_2$ production, and was blocked by indomethacin, a cyclooxygenase inhibitor (78). Likewise, indomethacin suppressed the stimulation of DMBA-induced rat mammary carcinoma development by dietary LA (92), although here the 5-lipoxygenase product leukotriene $B_4$ (Fig. 2) also appears to be involved in the carcinogenic process (93–95).

Recently, it has become evident that another product of arachidonic acid metabolism, 12-hydroxyeicosatetraenoic acid (12-HETE), has the potential for exerting an influence on breast cancer cell progression at several levels. This eicosanoid may enhance the expansion of tumor cell mass by suppressing the process of programed cell death (96, 97),

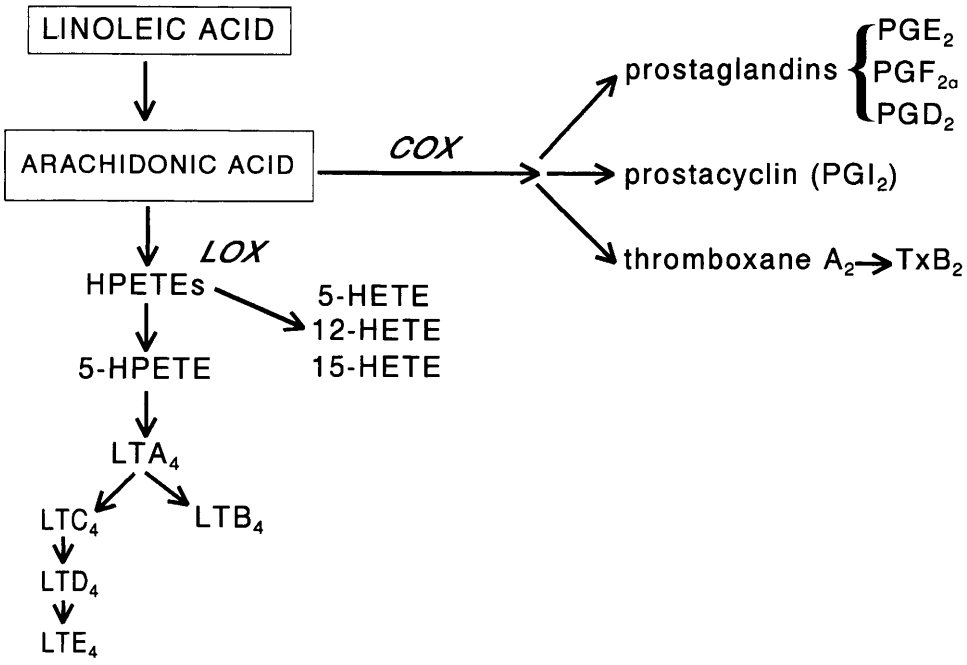


**Figure 2.** Metabolic pathways for the cyclooxygenase (*COX*)-mediated production of prostaglandins (PG) and thromboxanes, and lipoxygenase (*LOX*)-mediated synthesis of hydroxyeicosatetraenoic acids (HETE) and leukotrienes (LT). HPETE, hydroperoxyeicosatetraenoic acid.

and also by stimulating angiogenesis (98); in addition, 12-HETE promotes expression of the invasive phenotype, which it does at least in part by inducing the production and secretion of proteolytic enzymes which are essential for passage of tumor cells through the basement membrane (99, 100).

Inhibition of eicosanoid biosynthesis from arachidonic acid is most likely responsible, at least in part, for the suppressive effects of n-3 FAs on the experimental mammary carcinogenesis (93), and human breast cancer cell progression in nude mice (90). The phospholipid fraction in tumors from mice fed EPA or DHA contained reduced levels of arachidonate, and of both cyclooxygenase and lipoxygenase products, including prostaglandin $E_2$ and 12-HETE (90). However, several other mechanisms may also be involved, including alterations in the properties of tumor-cell membranes and consequently in polypeptide hormone and growth factor–binding sites (69), modulation of gene expression (80), modification of estrogen metabolism (101), and the formation of cytotoxic peroxidation products (102). The mechanisms by which the n-3 FAs may influence breast cancer development and progression, and so have a place as dietary preventive agents, are summarized in Table I.

**Dietary Fatty Acid–Based Intervention To Reduce Breast Cancer Risk.** The epidemiological, experimental, and mechanistic studies reviewed in the preceding sections of this article all support the concept that dietary modification based on a reduction in dietary n-6 FA and an increase in n-3 FA intakes will favorably influence breast cancer risk in women consuming a typical Western diet. The biological rationale rests heavily on the demonstrated effects of n-6 FA–derived eicosanoids on mammary carcinogenesis and breast cancer progression, and the opposing actions of the long-chain n-3 FAs.

In animal models, modulation of the dietary LA content alone has been shown to influence mammary carcinogenesis (70, 71), and human breast cancer cell progression in nude mice (83). It has also been argued that the high LA intake, which is typical of the Western diet, is undesirable because it would be expected to maintain correspondingly high levels of arachidonic acid in cell membranes, so promoting the "overproduction" of arachidonate-derived eicosanoids (51, 103). However, it is not clear that readily achievable, or desirable, reductions in LA intake, without an accompanying increase in n-3 FAs, will alter human eicosanoid production. Thus, in one study of adult males, feeding diets of equal fat content (35% total energy), but with a daily

**Table I.** ω-3 Fatty Acids and Breast Cancer Prevention: Mechanisms

| Mechanism | References |
|---|---|
| 1. Inhibition of eicosaniod synthesis from arachidonic acid (AA) | 90, 93 |
| a. Displacement of AA from cell membrance phospholipids | |
| b. Competition for $\Delta^6$ desaturase: inhibits AA production | |
| c. Inhibition of cyclooxygenase and lipoxygenase | |
| 2. Altered cell membrane hormone and growth factor receptor function | 69 |
| 3. Enhanced apoptosis[a] | |
| 4. Inhibition of angiogenesis[a] | |
| 5. Formation of cytostatic and cytotoxic peroxidation products | 102 |
| 6. Effects on oncogene expression | 80 |
| 7. Altered estrogen metabolism with reduction in 16α-hydroxyestrone production | 101 |

[a] By way of 12-HETE biosynthesis inhibition.

LA intake of 30 or 10 g, produced no change in the urinary prostaglandin E excretion (104).

Both animal and human experimental studies have stressed the importance of the ratio of n-3 to n-6 FA present in the diet. In rats, suppression of eicosanoid biosynthesis from arachidonic acid by n-3 FAs depended on a shift in the n-3/n-6 ratio from 0.3 to 0.6, rather than on the absolute amount of n-3 FA (105). There is little published data concerning the n-3/n-6 ratio and biological responses in the human, but it has been shown that the level of LA in the diet modulates the incorporation of n-3 from fish oil supplements into neutrophils (106). Also, the combined results from two studies in which fish oil supplements were fed to achieve suppressive effects on rectal epithelial cell proliferation and prostaglandin $E_2$ synthesis, indicated the need to obtain an n-3/n-6 ratio of 0.4 in the diet, as opposed to 0.25 (107, 108).

Dietary n-3 FAs have been evaluated in clinical trials for non-neoplastic diseases, and their efficacy in modifying eicosanoid metabolism without inducing toxic side effects is well documented (109–114). A reduction in dietary LA could readily be obtained by a partial substitution with olive oil, which is rich in the n-9 FA oleic acid. Several epidemiological studies have clearly associated high olive oil consumption with a relatively low breast cancer incidence rate (115–117); in the present context, it is of special interest to note that one of these studies, from Spain, also found that fish intake was also inversely correlated with breast cancer risk (115). Also, in an animal study comparing different vegetable oils, feeding a high-fat, but olive oil–rich diet, had no stimulatory effect on NMU-induced rat mammary carcinogenesis (71). James *et al.* (118) compared the effects of interactions among various vegetable oils and fish oil on rat leukocyte phospholipid FAs and leukotriene production, and found that EPA-rich dietary fish oil supplements achieved a greater reduction in leukotriene $B_4$ and 5-hydroxy FA synthesis when the LA content of the total fat intake approached that of olive oil rather than safflower or corn oil.

While a case could be made that a dietary modification of breast cancer risk should be effective in reducing the high overall incidence rates in North America and Northern Europe, such an approach is difficult to implement, and to evaluate in the context of a clinical trial. Rather, trials designed to evaluate efficacy should target defined high-risk groups of women, and associated intermediate biomarkers of response. Earlier, we discussed proliferative benign breast disease, ductal carcinoma *in situ*, and mammographic parenchymal patterns and densities as conditions constituting high risk for invasive breast cancer. End points in a dietary FA-based intervention targeting these high-risk groups of women might include not only a reduction in breast cancer incidence, a long-term undertaking, but also the rate of regression and/or progression of preneoplastic changes, and alteration in cellular or biochemical way stations (''intermediate biomarkers'') on the pathway to carcinogenesis and expression of the invasive phenotype (119).

## Dietary Fat and Fatty Acids in Prostate Cancer

**Epidemiology.** International comparisons show the same positive correlation between prostate cancer mortality rates and estimates of *per capita* fat intake as that described for breast cancer (33, 38, 40). However, in contrast to breast cancer, the results from case-control studies very largely support the association, and some have shown a dose response between estimates of fat intake and prostate cancer risk (reviewed in Ref. 33). Other epidemiological studies have emphasized a relationship between clinically more aggressive prostatic cancers and high fat consumption (120, 121). The prospective study by Giovannucci *et al.* (121) found that the association was due largely to animal fat, a result consistent with the observation from international comparisons that the estimated intake of animal fat, but not vegetable fat, is correlated with prostate cancer mortality rates (33).

The influence of individual classes of FAs on human prostate cancer risk is unclear. Giovannucci *et al.* (121) concluded that advanced disease was associated with high intakes of α-linolenic acid; in their analysis, red meat was a major source, and this was supported by a related study from the same group of investigators which found a corresponding association with high plasma levels of this metabolic precursor of the long-chain n-3 FAs (122). These findings appear difficult to reconcile with the observation that prostate cancer risk is low in populations that consume large amounts of EPA- and DHA-containing fish and seafood (64, 66, 123), and with a case-control study performed in England, which also demonstrated a protective effect of high fish consumption (124). However, more recently a case-control study from North Carolina found that the levels of LA, but not α-linolenic acid, in erythrocyte membranes and adipose tissues were associated with an increased risk of prostate cancer; only the highest level of EPA was related to a decreased risk (125).

**Animal Models.** In contrast to breast cancer, animal models have so far proven to be of limited value in advancing our understanding of the relationships between nutrition and prostatic carcinogenesis. From an earlier review of the literature (126), we concluded that the results from experiments utilizing chemically induced rat prostatic cancers provide little support for a role for dietary fat intake, although in part this may be due to deficiencies in the models. More success has been obtained using human prostate cancer cell xenografts in athymic nude mice, although much remains to be done.

The androgen-independent DU145 human prostate cancer cell line readily forms solid tumors when injected subcutaneously into male nude mice, and their growth is suppressed by feeding an n-3 FA–rich diet (127, 128). In culture, both DU145 and PC-3 prostate cancer cell growth was inhibited by EPA and DHA, but only PC-3 cells showed a

growth response to LA (129). Wang *et al.* (130) found that feeding a high-fat, high-calorie diet stimulated the growth of the androgen-responsive LNCaP human prostate cancer cell line. The fat source in this experiment was LA-rich corn oil, which was fed at five different levels, ranging from 2.3% to 40.5% of total energy intake. A dose effect of the fat intake was observed both in tumor growth over time, and the serum prostate-specific antigen levels at the termination of the experiment.

Thus, overall the limited data available from experiments with cell xenografts in nude mice, and cell culture experiments *in vitro,* support a role for dietary fat and FAs in prostate cancer progression, with n-6 FAs perhaps exerting stimulatory, and long-chain n-3 FAs inhibitory, effects.

**Dietary Intervention in Prostate Cancer.** The demonstration that high fat consumption not necessarily with consideration of the individual FAs involved, is associated with aggressive prostate cancer suggests that a reduction in intake to 15% of total calories be considered as a first approach to dietary intervention. Recently, a low-fat intervention trial, with or without nutritional supplementation, has been initiated for cancer patients who have undergone prostatectomy and whose serum prostate-specific antigen (PSA) becomes elevated during subsequent follow-up (131). An analogous situation exists in breast cancer, where the currently active Womens Intervention Nutrition Study (WINS) is recruiting postmenopausal patients after their surgical treatment, who, if clinically indicated, also receive adjuvant therapy with the antiestrogen tamoxifen. One limitation in the breast cancer study is that there is no appropriate biological marker, whereas PSA provides an index of prostate tumor volume.

Also as in the case of breast cancer, other suitable targets for early intervention suggest themselves, namely intraductal dysplasia (prostatic intraepithelial neoplasia) and prostatic carcinoma *in situ.*

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