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# Multi-targeted Therapy of Cancer by Omega-3 Fatty Acids

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## Abstract

Omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) are essential fatty acids necessary for human health. Currently, the Western diet contains a disproportionally high amount of n-6 PUFAs and low amount of n-3 PUFAs, and the resulting high n-6/n-3 ratio is thought to contribute to cardiovascular disease, inflammation, and cancer. Studies in human populations have linked high consumption of fish or fish oil to reduced risk of colon, prostate and breast cancer, although other studies failed to find a significant association. Nonetheless, the available epidemiological evidence, combined with the demonstrated effects of n-3 PUFAs on cancer in animal and cell culture models, has motivated the development of clinical interventions using n-3 PUFAs in the prevention and treatment of cancer, as well as for nutritional support of cancer patients to reduce weight loss and modulate the immune system. In this review, we discuss the rationale for using long-chain n-3 PUFAs in cancer prevention and treatment and the challenges that such approaches pose in the design of clinical trials.

## Introduction

Cardiovascular disease, cancer, obesity and diabetes collectively are responsible for more than 80% of the disease-related mortality in the US. Lipids play critical roles in all of these diseases, and the relative amounts and the types of dietary lipids consumed are believed to be of critical importance. Total fat intake and the ratio of n-6 to n-3 PUFAs in the Western diet have increased significantly since the Industrial Revolution (1,2). Thus, today's standard diet differs from the diet on which human beings have evolved, with profound implication on health. A preventive effect of n-3 PUFAs on cardiovascular disease, cancer as well as metabolic syndromes such as obesity and diabetes has been investigated extensively, and these studies were critically assessed in several Evidence Reports commissioned by the US Department of Health & Human Services (3,4,5,6) and discussed in some recent reviews (7,8,9,10,11). An aspect that is not well understood to date is the importance of gene-environment and in particular gene-diet interaction in human health. Indeed, the amount and content of dietary fat can have a drastic impact on the health of animals with an identical genetic background as well as the health of genetically predisposed populations.

The purpose of this review is to highlight recent progress in our understanding of the molecular mechanisms of action of n-3 PUFAs, with an emphasis on their multi-targeted effects, and discuss clinical trials investigating the role of n-3 PUFAs in cancer prevention and treatment.

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## Dietary sources and metabolism of polyunsaturated fatty acids

### Dietary sources of n-3 and n-6 fatty acids

Saturated and monounsaturated fatty acids can be synthesized *de novo* and obtained from the diet. However, mammals lack the desaturases necessary for synthesizing n-3 and n-6 PUFAs, therefore these essential fatty acids must be obtained from the diet. Terrestrial plants synthesize the first member of the n-6 series, linoleic acid (LA; 18:2n-6). LA is abundant in nearly all commonly available vegetable oils, including corn, sunflower, safflower and olive oil. Plants can also synthesize the first member of the n-3 PUFA series, alpha linolenic acid (α-LNA; 18:3n-3). Sources of this fatty acid include soybeans, walnuts, dark green leafy vegetables such as kale, spinach, broccoli and Brussels sprouts, and seeds or their oils such as flaxseed, mustard seed and rapeseed (canola); however, the majority of these oils are also rich in LA. Dietary long-chain n-3 PUFAs are found primarily in cold-water fish in forms of eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). Fish ingest EPA and DHA from phytoplankton and zooplankton (12). It is important to note that the content of marine n-3 fatty acids varies greatly according to the species of fish, the total fat content of the fish and the geographical location of waters they inhabit (13). Even within a species, the n-3 fatty acids vary from Atlantic to Pacific Ocean. As a general rule, deep water fish such as mackerel, tuna and salmon from colder temperatures have the highest content of EPA and DHA. Fish farming may have a marked influence on fatty acid composition according to diets supplied to the fish (12).

### Conversion of LA to AA and of α-LNA to EPA and DHA in animals and humans

While mammals cannot synthesize n-3 or -6 PUFAs *de novo*, mammalian cells can interconvert PUFAs within each series by elongation, desaturation and retroconversion (14). After ingestion, LA is metabolized by a series of alternating oxidative desaturation and elongation steps principally to arachidonic acid (AA; 20:4n-6). The main metabolic pathways for conversion of PUFAs are shown in Figure 1. The Δ6 pathway is responsible for conversion of LA to AA, and α-LNA to EPA, occurring primarily in the endoplasmic reticulum of liver cells. The Δ8 pathway, founded in plants, can also generate AA and EPA. Unlike α-LNA to EPA, the conversion from EPA to DHA is somewhat controversial. EPA may be converted to DHA through the Δ4 pathway (15). However, the existence of Δ4 fatty acid desaturation in the biosynthesis of DHA had been questioned for years, until a Δ4 fatty acid desaturase was characterized in vegetative organisms (16). Nevertheless, the existence of such desaturation for DHA synthesis in mammals is still unclear. Meanwhile, evidence suggests that the conversion to DHA occurs through the Sprecher pathway, namely elongation of docosapentaenoic acid (DPA; 22:5n-3) to tetracosahexaenoic acid (THA; 24:6n-3) and translocation to peroxisomes, a 2-carbon removal by β-oxidation, and translocation of DHA back to the endoplasmic reticulum (17).

The conversion of α-LNA to DHA in humans is very inefficient and since the same enzymes are involved in n-3 and n-6 pathways, the background diet may have a significant impact. Both α-LNA-feeding studies and stable isotope studies have consistently demonstrated that increased consumption of α-LNA does not result in increased DHA in plasma or cell lipids [reviewed in (18)]. In the first place most of the α-LNA is β-oxidized to provide energy and less than 10% of ingested α-LNA is converted to EPA. There is some evidence of gender differences in efficiency of the elongation-desaturation pathway suggesting that sex hormones may play a regulatory role, but this has not been widely studied (18). One study indicated that supplementing women with flaxseed oil (α-LNA) does not increase DHA (19). From kinetic analyses of fatty acid conversion, it was estimated that overall efficiency of conversion of α-LNA may be as low as 0.2% to EPA, 0.13% to DPA, and 0.05% to DHA (20). These data suggest that Δ-6 desaturase, the first enzyme in the bioconversion sequence, is the rate limiting

step of the pathway. Recently, it was proposed that the limited conversion of α-LNA to DHA in HepG2 cells was due to a competition of α-LNA and tetracosapentaenoic acid (TPA; 24:5n-3) for Δ-6 desaturase (21). Alternatively, there is evidence for two different Δ-6 desaturase activities for these two steps (22). Moreover, studies by Park and Harris (23) have shown that human intake of 4 grams of EPA/day for a 4-month period did not result in a detectable increase in plasma DHA, indicating that even in the absence of high α-LNA, the EPA to DHA conversion is an inefficient process. Our own *in vitro* studies have shown that human breast and prostate cancer cell lines can effectively convert EPA to DPA but have little ability to proceed to any subsequent step (Edwards *et al.* unpublished). Despite the lack of understanding of many details in this pathway to guide nutritional formulations and recommendations, a consensus has emerged that the most effective way to increase plasma and tissue concentrations of a particular n-3 fatty acid is to feed that specific fatty acid (24). In addition, this also implies that the source and nature of n-3 PUFAs under investigation in any preclinical or clinical setting should be considered carefully in both the design and interpretation of the study.

## Observational human studies linking PUFA intake and cancer risk

Epidemiological literature on the association of n-3 PUFAs and cancer, including correlational studies and migrational studies, suggests a protective effect of n-3 PUFAs and a promoting effect of n-6 PUFAs on cancer. However, the results of such studies are mixed, and many fail to demonstrate a statistically significant association between n-3 PUFAs and reduced cancer risk. Several recent reviews have been published on this topic (2,11,13,25,26,27). Here, we will limit ourselves to a brief overview of observational studies that have been published since our last review (11) and discuss limitations inherent to the observational human studies. Recent studies supporting a protective role of n-3 PUFAs in cancer include case-control studies performed in Japan (28) and Scotland (29). In the Japanese study, there was a trend for an inverse relationship between the risk of colorectal cancer and n-3 PUFA consumption, but this association was only statistically significant for distal colon cancer. In the Scottish study, significant dose-dependant reductions in colon cancer risk were associated with increased intake of total n-3 PUFAs as well as EPA or DHA taken separately. An additional case-control study with measurement of blood fatty acid levels showed an inverse relationship between long-chain n-3 fatty acids and overall prostate cancer risk (30); interestingly, LA levels were also inversely correlated with prostate cancer risk, but LA metabolites were directly correlated with cancer risk. However, in a study of Jamaican men undergoing prostate biopsy for elevated PSA levels, a positive correlation was observed between the LA-to-DHA ratio measured in erythrocyte membranes and prostate tumor volume (31).

Several confounding factors could account for the inconsistent results obtained in epidemiological data investigating the association between n-3 PUFAs and cancer risk. First, there are wide variations in the amount and source of n-3 PUFAs consumed in each study. Population and ecological studies mainly rely on data from self reported dietary fatty acid intakes or from estimates based on national consumption, and these assessments correlate poorly with direct measurements of fatty acids in individual patient samples. In some studies, the actual intake in n-3 PUFAs may be too low for a protective effect, or the protective effect may be mitigated by contaminants or other dietary components. Second, the ratio of n-6 to n-3 may be more important than the absolute amount of n-3 PUFAs, as suggested by animal and human studies (2,32,33). Our results in prostate-specific Pten knockout mice indicated that a ratio of n-6:n-3 lower than 5 was effective in slowing cancer progression (33). Because individuals consume different amounts of n-6 PUFAs and may have genetic or epigenetic differences in enzymes responsible for lipid metabolism, the amount of n-3 intake has to be individualized in order to achieve an effective ratio. Third, it is possible that results will depend upon the type (α-LNA, EPA or DHA) and even the form (triglyceride or ester) of n-3 PUFAs

used in various cancers. As mentioned earlier, it is still unclear whether different dietary n-3 PUFAs are equally effective in tumor suppression, and the conversion of α-LNA to EPA or DHA in humans is poor. Finally, the effects of n-3 PUFAs on cancer risk in an individual may be influenced by genetic factors, such as polymorphism in modifier genes. For instance, studies suggest a possible interaction between dietary intake of PUFAs and polymorphisms in cyclooxygenase (COX) and lipoxygenase (LOX) genes in determining cancer risk (34,35, 36). As discussed in the next section, COX and LOX families of enzymes can metabolize both n-3 and -6 PUFAs to eicosanoids with different biological effects that could modulate cancer risk.

## Molecular targets of PUFA

A number of biological effects that could contribute to cancer promotion by n-6 PUFAs and cancer suppression by n-3 PUFAs have been suggested (13,37). These effects include alterations in the properties of cancer cells (proliferation, invasion, metastasis and apoptosis) as well as those of host cells (inflammation, immune response and angiogenesis). The molecular mechanisms which account for these biological effects are not completely understood. Some of the proposed molecular targets are discussed below.

### Antagonism between n-3 and -6 PUFAs

The most widely studied effects of PUFAs are those that relate to eicosanoid biosynthesis and function. Eicosanoids are biologically active lipids with chain lengths of 20 carbon atoms which collectively modulate cell growth and differentiation, inflammation, immunity, platelet aggregation and angiogenesis. Dietary n-6 and n-3 PUFAs can be metabolized to prostaglandins (PG), thromboxanes (TX), hydroxyeicosatetraenoic acids (HETE) and leukotrienes (LT) by the enzymatic activity of COXs and LOXs. Generally speaking, eicosanoids derived from n-6 PUFAs have pro-inflammatory whereas those derived from n-3 precursors have anti-inflammatory effects (38). Likewise, eicosanoids derived from these two series have opposing effects in cancer cell growth (39,40), invasion (41) and angiogenesis (42,43). Besides eicosanoids, marine n-3 PUFAs can also be metabolized to resolvins and protectins (44,45). These compounds possess potent anti-inflammatory and immunoregulatory actions (46). Mounting evidence suggests that inflammation may play a critical role in the development of human cancer (47,48,49). Therefore, one of the possible mechanisms for inhibition of tumors by n-3 PUFAs is by suppression of inflammation through resolvins.

In addition to the biological effects of eicosanoids and other metabolites, n-3 PUFAs are also thought to exert indirect effects by inhibiting n-6 series eicosanoid biosynthesis. n-3 PUFAs become incorporated into membrane phospholipids, where they partially replace AA and reduce the pool of available AA. They compete with n-6 PUFAs for desaturases, elongases, COXs and LOXs, so that the biosynthesis of n-6 series eicosanoids is reduced. For instance, the high binding affinity and poor substrate properties of EPA for COX-1 interferes with AA oxygenation by this enzyme (50,51). Inhibition of tumor cell growth and invasion by n-3 PUFAs in a xenograft animal model was associated with decreased COX-2 and $PGE_2$ levels (32). Thus n-3 PUFAs may act as a natural COX “inhibitor”.

### Differential effects on signaling pathway, transcription and translation

A number of signaling pathways that are relevant to carcinogenesis and tumor progression are differentially affected by n-3 and -6 PUFAs. For instance, n-6 PUFA products were reported to upregulate and activate cellular signaling mediators including protein kinase C (42,52), ras (53,54), ERK 1/2 (55) and NF-κB (56) whereas n-3 PUFA products had the opposite effect. In Fat-1 transgenic mice, which convert endogenous n-6 to n-3 PUFAs, EPA and DHA activated the Jak2/Stat5 pathway in mammary cells, leading to cell differentiation (57). For

the most part, signaling pathways converge in the nucleus to regulate transcription factor function, leading to alterations in gene expression. The pleiotropic nature of transcriptional changes induced by n-3 and -6 PUFAs was illustrated by studies where global gene expression patterns were determined by microarray analysis *in vitro* (58) or *in vivo* (59). Several hundreds of genes participating in a number of biological processes are differentially regulated by n-3 and -6 PUFAs, underlining the complexity of the transcriptional changes induced - directly or indirectly - by these fatty acids.

The exact molecular mechanism of these signaling and transcriptional effects is not clear. Changes in lipid composition of the plasma membrane may affect the membrane fluidity and the way growth factors, cytokines and hormones interact with their receptors, and the resulting signal transduction through secondary messengers. One site of particular interest within the plasma membrane is the lipid raft, a microdomain thought to play important roles in signaling (60). EPA and DHA were shown to alter the lipid raft composition in MDA-MB-231 breast cancer cells, leading to sustained phosphorylation of epidermal growth factor receptor and downstream signaling pathways, but paradoxically reducing cell growth (61).

A second type of mechanism through which n-3 fatty acids may alter cellular signaling is by acting directly as ligands for nuclear receptors, including peroxisome proliferators-activated receptors (PPARs) (62) or retinoid X receptor alpha (63). These nuclear transcription factors bind lipid ligands to regulate gene expression, thereby mediating biological functions ranging from lipid metabolism and homeostasis to cell differentiation and cell death. DHA was shown to induce cell apoptosis through activation of PPARγ (64) Edwards *et al*, unpublished). The levels of nuclear receptor expressed in cells may also be modulated by PUFAs (63,65).

n-3 PUFAs may also regulate the translation machinery. EPA has been reported to affect intracellular homeostasis: EPA induced a $Ca^{++}$ release from the intracellular $Ca^{++}$ stores and simultaneously inhibited $Ca^{++}$ influx through store-operated $Ca^{++}$ channels in the plasma membrane, resulting in a depletion of the intracellular $Ca^{++}$ stores. Such $Ca^{++}$ depletion activated eIF2α kinase, inhibited translation initiation, and preferentially down-regulated oncogenes and G1 cyclins (66). It is unclear if other n-3 PUFAs, namely α-LNA and DHA, have similar effects.

Recent data suggested that Bcl-2 family proteins may play a key role in n-3 PUFA-induced cell death. We found that n-3 fatty acids reduced prostate tumor growth, slowed histopathological progression and increased survival of Pten knockout mice, whereas n-6 fatty acids had opposite effects. Tumors from mice on an n-3-enriched diet had lower proportions of phosphorylated Bad and higher apoptotic indexes compared to those on an n-6-rich diet. Knockdown of Bad eliminated n-3-induced cell death, and introduction of exogenous Bad restored the sensitivity to n-3 fatty acids (33). Furthermore, knockout of Bad abolished the tumor suppressive effect of n-3 fatty acids *in vivo* (Chen *et al.*, unpublished). Our data suggest that modulation of prostate cancer development by PUFAs is mediated in part through Bad-dependent apoptosis.

## Role of lipid peroxidation in PUFA-induced cytotoxicity

The ability of long-chain n-3 PUFAs to induce apoptosis in tumor cells has been attributed to the increased susceptibility of these cells to lipid peroxidation (62,67). In support of this mechanism, the ability of fatty acid preparations to induce cell death was linked to their ability to increases the level of secondary products of lipid peroxidation. In addition, the tumor suppressive effect of n-3 PUFAs in human breast and colon cancer cell lines was blocked in the presence of antioxidants. As n-6 PUFAs are also susceptible to undergo auto-oxidation, it is possible that peroxidized products of n-3 and n-6 PUFAs have different biological properties.

## Animal studies supporting a protective role of n-3 PUFAs on cancer development

The strongest data supporting a tumor protective role for n-3 PUFAs is provided by animal studies. Here, we will briefly outline some of the evidence obtained in animal models of prostate, breast and colon cancer.

### Models of prostate cancer

Early studies showed that growth of human prostate cancer cell xenografts in nude mice was significantly inhibited by a fish oil diet (68,69). More recently, a xenograft study using severe combined immunodeficiency mice demonstrated that tumor growth rate, final tumor volume, and serum PSA levels were all reduced by n-3 dietary supplementation (32). Decreased cyclooxygenase-2 (COX-2) and prostaglandin $E_2$ were measured in tumor tissues from n-3-fed animals. In our own studies we have used prostate-specific Pten knock out mice that have the advantage of being an immune competent, orthotopic model with similarities in tumor development to human prostate cancer (70). In these animals an n-3 fatty acid-enriched diet reduced tumor growth, retarded histopathologic progression and extended lifespan, whereas n-6 fatty acid supplementation had the opposite effect (33). In addition, tumor growth was also retarded in this model by introduction of the fat-1 omega-3 desaturase which converts n-6 to n-3 fatty acids (33).

### Models of breast cancer

A number of studies have shown n-3 fatty acid protection in rodent models of breast cancer. These include dietary supplementation of mouse transplantable tumors (71) and human cell xenograft models (72,73) as well as chemically induced tumors in rats (74,75,76). A recent report showed that dietary DHA-induced reduction in mammary tumors in a rat model was accompanied by a 60% increase in BRCA1 tumor suppressor protein (77). Interestingly, n-3 fatty acid-enriched diets enhanced the efficiency of doxorubicin (78) and mitomycin C (79) in inhibiting tumor growth and strengthened the inhibitory effect of tamoxifen in estrogen-dependent xenografts (80). These studies point to a potential value of n-3 fatty acids as adjuvant to standard chemotherapy (81).

### Models of colon cancer

As in prostate and breast cancer, efficacy of n-3 fatty acids protection in colon cancer is well supported by animal studies. These include mouse models with transplantable tumors (82,83, 84,85,86), as well as rats with chemically-induced colon cancer (87,88,89,90,91). In addition to primary tumor growth suppression, effective inhibition of metastases was also seen with n-3 enriched diets (83,92,93). Several studies with colon cancer models have emphasized a critical role of the COX pathway in the protective effects of n-3 fatty acids (86,87). However, tumor formation was inhibited in both COX-2 deficient as well as COX-2 over expressing colon cancer xenografts, suggesting the existence of a COX-2 independent pathway for n-3 fatty acid protection (85).

Although the tumor suppressive effect of marine n-3 PUFAs (EPA and DHA) is consistently observed, the effect of botanical n-3 PUFAs (α-LNA) is more controversial. Although a number of studies have indicated that flaxseed oil had anti-colon cancer activity in animal models (94,95,96), only EPA and DHA, but not α-LNA, reduced tumorigenesis in $Apc^{Min/+}$ mice (97). Importantly, some evidence suggested that the level of α-LNA was positively associated with cancer risk in human prostate cancer patients (98,99). This inconsistency, together with the fact that there is little conversion of α-LNA to EPA or DHA in humans, warrants further investigation.

## Clinical trials using n-3 PUFAs for cancer prevention and treatment

The tantalizing epidemiological data obtained to date, combined with the demonstrated effects of n-3 PUFAs on cancer in animal and cell culture models, has motivated the development of clinical intervention trials using fish oil or n-3 PUFAs in the prevention and treatment of cancer, as well as for nutritional support of cancer patients to reduce weight loss and modulate the immune system. Table I summarizes ongoing or recently completed clinical trials listed in the ClinicalTrials.gov database (http://clinicaltrials.gov/) as of January 2008 with dietary interventions including n-3 PUFA supplements. The majority of these trials have not yet been published. Published trials include NCT00031707 (100), NCT 00003077 (101) and NCT00558155 (102). In addition, the methodology of trial NCT 00094562 and the issues affecting dietary studies design were discussed (103).

### Nutritional support of cancer patients with n-3 PUFA supplements

Several trials address the possibility that nutritional supplements containing n-3 PUFAs are beneficial to reduce cancer-associated weight loss (cachexia) for patients with advanced malignancies. Initial clinical trials suggested that n-3 PUFAs could stabilize weight loss or lead to weight gain in advanced cancer patients with cachexia (104,105,106,107). The results of larger trials have been mixed, due in part to problems with tolerability of the dietary supplements (100,101,108,109). A recent review of the literature failed to find sufficient evidence to support the use of oral EPA in treatment of cancer cachexia (110). However, when patients were able to consume high doses of the dietary supplement, weight stabilization or weight gains could be achieved (101,109). This suggests that n-3 PUFAs may have a role in nutritional support of cancer patients if they can be administered in such a way that high doses can be achieved for prolonged periods of time with limited gastrointestinal side effects. Several additional trials listed in Table I are investigating the possible role of n-3 dietary supplements in improving nutritional status of patients with colorectal cancer, head-and-neck cancer, and other cancer types. Interestingly, synthetic COX-2 inhibitors such as celecoxib may also be beneficial for cachexic cancer patients, alone or in combination with n-3 PUFAs (111,112).

Nutritional supplements enriched in n-3 PUFAs have also been tested in clinical trials for their ability to improve the outcome of other cancer treatments. A particular area of emphasis has been placed on immunomodulatory effects of n-3 PUFAs, owing to their ability to reduce infection and inflammation (102,113,114). Administration of n-3 PUFAs either before or after major abdominal surgery for cancer was shown to reduce inflammatory cytokines (113,115) and improve liver and pancreas function (116). Patients receiving parenteral immunonutrition with a nutritional supplement containing glutamine or n-3 PUFAs had reduced incidence of infectious complications and improved immune function compared to patients who received a nutritional supplement without glutamine or n-3 PUFAs (102). Bougnoux et al. reported that dietary supplementation of breast cancer patients with DHA during anthracyclin chemotherapy had beneficial effects on time to progression, overall survival, and tolerance of side effects, particularly in a group of patients with high incorporation of DHA as measured in the plasma (117). Ongoing studies listed in Table I include several additional trials to examine the ability of n-3 supplements to reduce postoperative complications after surgery in patients with colorectal, gastric and pancreatic cancer, and on reducing inflammation in patients with head-and-neck, esophageal, hematologic malignancies and other cancer types. In addition, a phase IV trial is under way to assess the effectiveness of n-3 supplements in improving tolerance to chemotherapy in patients with colon cancer.

### Cancer prevention and treatment with n-3 PUFA supplements

Some evidence suggests that COX inhibitors, which primarily block the metabolism of AA, are beneficial in the prevention of colon (118) and prostate (119) cancer. However, the

cardiovascular toxicity of COX-2 inhibitors (120) has jeopardized the clinical utility of these drugs. Reducing the intake of n-6 PUFAs and increasing the proportion of n-3 in our diet is an attractive approach to reduce the production of proinflammatory eicosanoids and prevent cancer. Prevention trials using n-3 supplements to reduce colorectal cancer risk have used cell proliferation in the colonic or rectal mucosa as an intermediate marker of cancer risk. A randomized double-blind trial found that administration of fish oil for 30 days to individuals with high risk for developing colon cancer reduced rectal mucosa proliferation to a level found in low risk population, with a concomitant increase in n-3 fatty acid and decrease in arachidonic acid in the rectal mucosa (121). A double-blind, crossover trial where healthy individuals were given a controlled basal diet supplemented with either fish oil or corn oil for 4 weeks showed that rectal cell proliferation, ornithine decarboxylase activity and $PGE_2$ release were significantly lower during the fish oil period than the corn oil period (122). However, when a similar trial was repeated in the context of a high-fat diet (50% of energy), no significant differences were found, suggesting that the n-6:n-3 ratio is crucial in determining the effects of fish oil on cancer risk (123). At least four additional colorectal cancer prevention trials are ongoing to further define the role of n-3 PUFAs in colorectal cell proliferation and/or apoptosis as well as inflammation (Table I).

A second cancer type with potential chemopreventive benefit for n-3 PUFAs is prostate cancer, due in part to the extended window of opportunity afforded by the relatively slow disease progression. Preliminary studies have shown that a 3-month intervention with a low-fat, fish oil-supplemented diet was able to increase the n-3:n-6 ratio in plasma and adipose tissue (124). Another pilot study suggested that a low-fat, flaxseed-supplemented diet decreased PSA and cholesterol levels as well as benign prostatic epithelial cell proliferation in biopsy specimen from patients that were schedule for a repeat prostate biopsy (125). A phase II randomized controlled trial by the same group (NCT00049309) was completed recently and, to our knowledge, has not yet been published. Another clinical trial of prostate cancer prevention by n-3 PUFAs (NCT00049309) chose to use fish oil in patients with prostatic intraepithelial neoplasia or who are otherwise at risk for prostate cancer. In the latter study, still in progress, the measured outcomes include cell proliferation and apoptosis as well as phospholipid membrane composition, fatty acid synthase and sterol regulatory element binding protein expression. In addition to the prevention trials cited above, three prostate cancer trials listed in Table I include n-3 PUFA supplements as part of the treatment protocol for patients with early adenocarcinoma.

Dietary interventions with n-3 PUFAs have been assessed for prevention and/or treatment of other cancer types, including breast, skin, and lymphoma. An ongoing breast cancer prevention trial (NCT00114296) investigates the effect of n-3 PUFAs on mammographic breast density, breast epithelial cell atypia in ductal lavage samples, hormones and lipid peroxidation of women with family history of breast cancer or BRCA1/BRCA2 mutations. A possible beneficial role of n-3 PUFAs in skin cancer prevention was found in a double-blind randomized study of healthy subjects who took EPA for 3 months (126). The skin EPA content increased 8-fold from baseline, and sunburn sensitivity was reduced with a concomitant decrease in UVR-induced skin p53 expression. An ongoing Phase II clinical trial (NCT 00455416) is investigating the role of a dietary intervention including n-3 PUFAs, selenium, and extracts from garlic, pomegranate, grapes and green tea on follicular lymphoma proliferation, apoptosis, and immune function.

## Conclusion

In recent history, the typical dietary composition in PUFAs has changed drastically, tipping the balance towards n-6 PUFAs, with negative consequences to human health. Restoring a healthier balance of n-3 to n-6 PUFAs is an attractive approach for cancer chemoprevention.

Indeed, unlike many other chemopreventive agents, n-3 PUFAs are essential nutrients with additional beneficial effects on cardiovascular and inflammatory diseases. Experiments in animal models and tissue culture overwhelmingly support a protective effect of n-3 PUFAs against colon, prostate and breast cancer, whereas human association studies have been less consistent. Perhaps one reason for this difference is that diet, environment and genetic background can be controlled much easier in animal models than in human populations. Published epidemiological studies differ substantially in the source of n-3 PUFAs consumed (fish oils, seed oils, purified PUFAs), and few have confirmed the amounts of n-3 PUFAs available in blood or tissue samples by direct measurements. Because the conversion of α-LNA to EPA or DHA in humans is poor, results are likely to depend on the type (α-LNA, EPA or DHA) and even the form (triglyceride or ester) of n-3 PUFAs consumed, as well as the ratio of n-6 to n-3 PUFAs achieved in individuals, which will be influenced by dietary as well as genetic factors. Therefore, clinical trials with dietary interventions aiming to prevent or treat cancer need to be designed carefully to overcome these limitations and provide an optimal ratio of n-3 to n-6 PUFAs.

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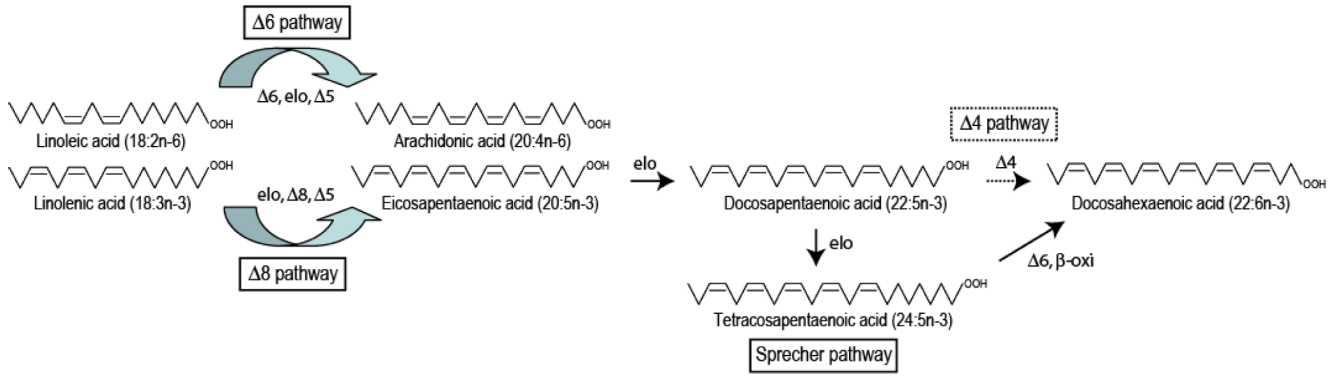


**Figure 1. Pathways for the synthesis of very long chain polyunsaturated fatty acids**

Linoleic acid (LA) and alpha-linolenic acid (α-LNA) are converted to arachidonic acid (AA) and eicosapentaenoic acid (EPA), respectively, through a sequential action of delta6 fatty acid desaturase (Δ6), elongase (elo) and delta5 fatty acid desaturase (Δ5). EPA may be elongated to docosapentaenoic acid (DPA) and then desaturated by delta4 fatty acid desaturase (Δ4) to docosahexaenoic acid (DHA). However, Sprecher *et al.* have demonstrated that EPA is likely elongated to DPA and to tetracosapentaenoic acid (TPA), desaturated to tetracosahexaenoic acid (THA) by Δ6 desaturase, translocated to peroxisomes, and β-oxidized (β-oxi) to docosahexaenoic acid (DHA).

**Table I**

Intervention trials with omega-3 PUFA for cancer prevention, treatment or patient support.

| Trial no. | Cancer type | Trial type | Title | Outcomes to be measured | Dates/Reference | Phase |
|---|---|---|---|---|---|---|
| NCT00114296 | Breast cancer | Prev. | Omega-3 Fatty Acids in Preventing Breast Cancer in Women at High Risk of Developing Breast Cancer | Mammographic breast density, atypia in ductal lavage, hormones, lipid peroxidation | 04/05-NS | NS |
| NCT00432913 | Colon cancer | Prev. | Effect of 2 Doses of EPA on Apoptosis and Cell Proliferation on Colon Mucosa | Proliferation and apoptosis in colonic mucosa, measure of tissue EPA, safety and tolerability | 10/06-05/08 | II/III |
| NCT00510692 | Colon cancer | Prev. | Chemoprevention Trial in Familial Adenomatous Polyposis Coli Using EPA | Number/ size of rectal polyps, apoptosis and cell proliferation in the rectal mucosa, EPA and FA uptake, tolerability | 11/06-03/08 | II/III |
| NCT00475722 | Colon cancer | Prev. | Healthy Eating for Colon Cancer Prevention | FA, carotenoids, inflammation mediators | 05/07-10/12 | NS |
| NCT00398333 | Colorectal cancer | Supp. | Study to Assess the Effectiveness of a Omega-3 Enriched Supplement on Chemotherapy Tolerance in Colon Cancer Patients | Tolerance to chemotherapy (QoL), nutritional status | 06/05-NS | IV |
| NCT00488904 | Colorectal cancer | Supp. | Omega-3 Fatty Acids and Postoperative Complications After Colorectal Surgery | Reduction in infectious complications, hospitalization time, mortality | 06/07-01/08 | IV |
| NCT00145015 | Colorectal cancer | Prev. | FishGastro Study: Fish Consumption and Gastro-Intestinal Health | Apoptosis, cell prolif., lymphocyte infiltration, cytokines, prostaglandins, gene expression | 12/04-01/08 | NS |
| NCT00168987 | Colorectal cancer, hepatocellular ca, cholangiocarcinoma | Supp. | Influence of an Oral Nutritional Supplement Rich in Omega-3 Fatty Acids on Functional State and Quality of Life in Malnourished Patients With Gastroenterological Tumors | Muscle function, cognitive functions, QoL, tolerance of nutritional supplement, nutritional state | 01/07-06/07 | IV |
| NCT00558155 | Gastric, pancreatic | Supp. | The Impact of Immunostimulating Nutrition on the Outcome of Surgery | Surgical and nonsurgical complications, overall morbidity/ mortality, hospital stay | 06/01-12/05 Klek et al, 2005 | IV |
| NCT00559156 | Head and neck | Supp. | Arginine/Omega-3 Fatty Acids/ Nucleotides Nutritional Supplement in Treating Patients With Stage III or Stage IV Head and Neck Cancer Undergoing Chemotherapy and Radiation Therapy | Immunomodulatory effect | 06/05-NS | II |
| NCT00333099 | Head and neck, esophageal | Supp. | INEC Study: Immuno-Modulating Enteral Nutrition in Cancer | Anti-inflammation (mucositis),complications, nutritional and immune status, QoL, cost | 05/06-04/09 | IV |
| NCT00533078 | Hematologic malignancies (AML) | Supp. | Lipid Use, Nutrition, and Colitis in Patients With Hematological Malignancies | Anti-inflammation (colitis) | 11/07-12/08 | II |
| NCT00003077 | Leukemia, Lymphoma, Multiple Myeloma, Plasma Cell Neoplasm | Supp., treat. | Omega-3 Fatty Acids in Treating Patients With Advanced Cancer Who Have Significant Weight Loss | Weight loss prevention, n-3 PUFA maximum tolerated dose, antitumor response | 10/95-NS Burns et al, 2004 | I/II |
| NCT00455416 | Lymphoma | Treat. | Dietary Intervention in Follicular Lymphoma | Tumor cell proliferation, apoptosis, immune cell infiltrate, cytokines | 04/07-12/09 | II |
| NCT00292279 | Multiple cancers | Supp. | The Impact of Fish Oil Emulsion on Clinical Outcome of Post-Operative Cancer Patients | Infection, inflammation, hosp. days, cost | 06/02-03/06 | III |

| Trial no. | Cancer type | Trial type | Title | Outcomes to be measured | Dates/Reference | Phase |
|---|---|---|---|---|---|---|
| NCT00031707 | Multiple cancers (excl. brain, breast, prostate, ovarian, endometrial) | Supp. | Comparison of Megestrol and/or Omega-3 Fatty Acid-Enriched Nutritional Supplement in Treating Patients With Cancer-Related Weight Loss and Lack of Appetite | Weight, appetite, nausea, vomiting, QoL, toxicity, overall survival, IL-6 | 03/00-NS Jatoi et al, 2004 | III |
| NCT00094562 | Multiple cancers and other diseases associated with cachexia | Supp. | A Fish Oil Supplement Maintain Body Weight Patients With Disease-Related Weight Loss | Body weight, lean body mass, QoL, anti-inflammatory, anticatabolic, anti-oxidant and anabolic actions | 06/04-09/06 | II |
| NCT00253643 | Prostate cancer | Prev. | Fish Oil in Preventing Prostate Cancer in Patients With Prostatic Intraepithelial Neoplasia or Who Are at for Developing Prostate Cancer | Proliferation, lipid metabolism: FASN, SREBP, apoptosis, bone loss | 07/05-NS | NS |
| NCT00049309 | Prostate cancer | Prev. | Low-Fat Diet and/or Flaxseed in Preventing Prostate Cancer | Proliferation, apoptosis, PSA and other biomarkers | 01/03-05/06 | II |
| NCT00402285 | Prostate cancer | Treat. | Lycopene or Omega-3 Fatty Acid Nutritional Supplements in Treating Patients With Stage I or Stage II Prostate Cancer | Gene expression pattern, correlation with diet, lack of progression | 04/03-NS | NS |
| NCT00458549 | Prostate cancer | Treat. | Polyunsaturated Fatty Acids in Treating Patients With Prostate Cancer Undergoing Prostate Biopsy and/or Surgery | eIF2α phosphorylation, relapse-free survival | 07/06-NS | NS |
| NCT00433797 | Prostate cancer | Treat. | Dietary Intervention With Phytochemicals and Polyunsaturated Fatty Acids in Prostate Cancer Patients | PSA, biomarkers of inflammation, antioxidant, oxidative stress, oxidative damage | 03/07-03/09 | I/II |

Prev.: prevention, Supp.: support, Treat.: treatment, NS: not specified, QoL: quality of life.