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Review

Cancer Research

# Chemoprevention of Breast Cancer by Fish Oil in Preclinical Models: Trials and Tribulations

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## Abstract

Despite the perception that omega-3 fatty acids (*n*-3 FA) protect against breast cancer, epidemiologic studies have yielded inconsistent results. Although preclinical data have been, in general, more supportive of a protective effect of *n*-3 FA on breast cancer, inconsistencies still remain, which preclude definite conclusions or in-depth mechanistic investigations despite 30 years of research in this area. In this review, we discuss key variables that may account for inconsistencies of results across preclinical studies and provide recommendations for future experiments testing the chemopreventive effect of *n*-3 FAs in breast cancer, as part of a multiagent approach under rigorously controlled conditions. *Cancer Res; 71(19); 6091–6. ©2011 AACR.*

## Introduction

The role of diet in breast cancer development remains controversial. The contribution to mammary carcinogenesis of the specific fatty acid (FA) composition of the diet has received considerable attention in the literature. Among the FAs, omega-3 (*n*-3) and omega-6 (*n*-6) FA have been suggested to decrease and increase breast cancer risk, respectively (1). Evidence accumulated from numerous experimental systems indicates that *n*-3 FAs may exert an antitumor action by altering the cell-membrane phospholipid composition and, consequently, affecting the expression and function of numerous receptors, proteins, and lipid-derived signaling molecules, briefly summarized in Fig. 1. This process eventually leads to the inhibition of cell proliferation and increased cell death. Sources of *n*-3 FAs include cold-water fish [containing eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6)], certain seeds (flax) and nuts (walnuts), and some vegetable oils (soy bean). Plant sources of *n*-3 FA contain α-linolenic acid (ALA; 18:3). Sources of *n*-6 FA are vegetable oils, such as corn oil or safflower oil [containing linoleic acid (LA); 18:2].

Epidemiologic studies have been inconclusive relative to the protective effects of *n*-3 FAs against breast cancer development. The European Prospective Investigation into Cancer and Nutrition (EPIC), a large multicenter prospective study (2), reported a marginally significant positive association ($P = 0.10$) only in the highest quintile for fatty fish intake [hazard ratio 1.13, 95% confidence interval (CI), 1.01–1.26]. Another review of prospective cohort studies showed that *n*-3 FA intake was not associated with breast cancer risk in 7 studies, whereas it was associated with decreased risk in 3 [incidence risk ratios (RR), 0.68–0.72] and increased risk in 1 (RR 1.47; 95% CI, 1.10–1.98; ref. 3). Consequently, on the basis of these inconsistent observations, no recommendations can be offered to women about *n*-3 FA ingestion for reduction of breast cancer risk.

For more than 30 years, numerous preclinical studies have attempted to establish whether there is a causal relationship between *n*-3 FA ingestion and reduction in mammary carcinogenesis. Although, in general, the results have supported a protective effect from *n*-3 FAs, definitive conclusions cannot be drawn because of inconsistencies due to experimental variability, which does not allow reliable comparisons across studies. Establishing a causal role of *n*-3 FAs in breast cancer prevention would have a major translational impact because these nutrients may provide additional health benefits, such as reduction in cardiovascular risk. In addition, using them in combination with other agents with complementary antitumor action may improve their efficacy in breast cancer prevention.

The goals of this review are to analyze the confounding elements present in preclinical trials that may affect the accuracy of their results and provide recommendations for improved future studies. We strongly believe that, in addition to employing more rigorously defined experimental conditions, future studies should include a multitargeted approach, whereby *n*-3 FAs are administered together with other safe and health-promoting adjuncts with different and/or complementary mechanisms of antitumor action.

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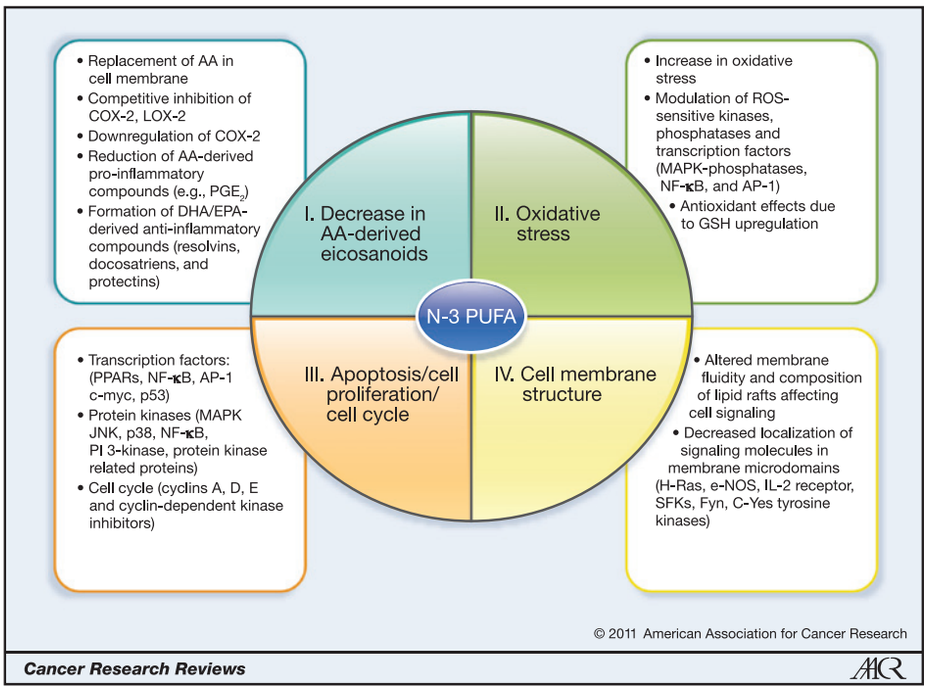


**Figure 1.** Simplified scheme of the multiple potential mechanisms of breast cancer prevention by *n*-3 FAs. *n*-3 Polyunsaturated fatty acids (PUFA) influence multiple cellular mechanisms, potentially mediating mammary carcinogenesis by affecting eicosanoid metabolism, oxidative stress, cell-membrane structure, and proliferation and apoptosis. AA, arachidonic acid; COX-2, cylcooxygenase-2; GSH, glutathione; IL-2, interleukin 2; JNK, c-*jun* NH, kinase; LOX, lipooxygenase; SFK, Src-family kinase; MAPK, mitogen-activated protein kinase; PI, phosphatidylinositol; PGE2, prostaglandin E2; ROS, reactive oxygen species.

## Preclinical Studies Tend to Support a Protective Effect of *n*-3 Fatty Acids in Breast Cancer Prevention, but Significant Inconsistencies Remain

Preclinical studies should provide more controlled conditions that facilitate examination of the causal links between *n*-3 FAs and inhibition of mammary carcinogenesis. To determine whether this expectation was achieved, a review was undertaken of preclinical studies using different carcinogenesis models. PubMed searches were conducted for the terms "fish oil mammary tumorigenesis" and "fish oil breast cancer." Carcinogenesis models used in the identified studies were *N*-methyl-*N*-nitrosourea (MNU; refs. 4–9), 7,12-dimethylbenz[*a*]anthracene (DMBA; refs. 10–23), 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhiP; ref. 24), and a *Her*-2/transgenic mouse model (25). Some studies did not include any carcinogenic agent but simply evaluated the effect of diet on normal mammary gland biomarkers (26, 27).

Out of the 24 rodent studies identified, the majority reported *n*-3 FAs had a protective effect on mammary carcinogenesis (5–9, 11, 13, 15–19, 21–25, 27). Some studies showed no protection with increasing *n*-3 FA intake (4, 5), and some reported promotion of mammary carcinogenesis by fish oil (10, 12, 13, 26).

Despite the prevailing hypothesis that the ratio of *n*-3/*n*-6 may be important for chemoprevention, this ratio was provided only in 11 of these preclinical studies. The studies that provided ratios showed protective effects at varying *n*-3/*n*-6 ratios: 0.16 (11), 0.33 to 0.55 (4, 13, 21), 1 (5), 1.2 (15), 2.3 (when combined with tamoxifen; ref. 6), 3.1 (23), 7 (14), and 10 (27). Promotion of carcinogenesis was observed with an *n*-3/*n*-6 ratio of 0.33 to 0.5 in a high-fat diet (39% calories from fat), whereas protection was observed with the same ratio in the presence of a low-fat diet (16% calories from fat; ref. 13). Promotion of carcinogenesis was observed by Sasaki and colleagues with increasing *n*-3/*n*-6 ratios (ranging from 0.01 to 7.84) within a low-fat diet (10). On the basis of these studies, no clear ratio has been detected as being protective.

In summary, most, but not all, preclinical studies have shown prevention of breast cancer by *n*-3 FA intake. However, the experimental conditions under which *n*-3 FAs exert their protective effect have been variable from study to study, preventing unifying conclusions.

## Confounding Factors That May Contribute to Variability Seen in Preclinical Studies

### Variability in *n*-3 fatty acid content of the diet

In studies using menhaden oil as the main source of *n*-3 FA, the oil was obtained from suppliers in Japan and in the United States. Other sources of *n*-3 FAs used were cod liver oil, sardine oil, purified DHA/EPA esters, and fish oil supplements. This variability in the source of *n*-3 FAs is likely to have introduced significant experimental variability among studies, because *n*-3 FA levels differ among fish species, as well as within the same species, owing to their developmental age, the season, and their diet at time of harvest, thus making it difficult to compare them to one another (28). Only 2 studies (4, 22) verified the chemical composition of the diet. Most studies reported the composition information provided to them by their fish oil supplier (6, 7, 16, 24–26), which may vary, as suggested by the reported range of concentrations of individual FA expected to be present in a batch of fish oil. Such

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variation may be biologically important if the beneficial effect of fish oil is restricted to a narrow *n*-3/*n*-6 ratio or to specific FAs. Other studies verified the chemical composition of the oil prior to adding it to the diet but not of the diet fed to the animals (5, 9, 10, 12, 14, 15). In 4 studies (17–20), the authors gave their rats fish oil supplement (Maxepa) intragastrically, instead of mixing it in the diet. Such bolus administration could change the biologic effect of *n*-3 FAs. Some studies did not provide information on the composition of the diet or cited a prior study for the diet composition (8, 11, 13, 21, 23, 27). Because of this variability, it is essential that the specific FA chemical composition of the diets used in carcinogenesis experiments be determined. In the absence of this information, comparison and interpretation of results across studies is impossible.

### *n*-3/*n*-6 Fatty acid ratio

The *n*-3/*n*-6 ratio is hypothesized to be an important factor in *n*-3 FA chemopreventive effectiveness, not only because the ratio affects the conversion of ALA to EPA and DHA but also because *n*-3 and *n*-6 series eicosanoids compete for the same enzymes that are involved in their metabolism. *In vivo* studies suggest that the modulation of eicosanoid biosynthesis depends on the ratio rather than the absolute levels of *n*-3 and *n*-6 FAs (29). On the basis of the above discussion, an accurate global *n*-3/*n*-6 ratio can only be determined if the chemical composition of diet samples are analyzed. More importantly, without specific FA composition data, the ratio of specific *n*-3 FAs and *n*-6 FAs cannot be calculated, a major limitation because various FAs are known to exert different biologic activities. Instead, most of the studies provided a calculated *n*-3/*n*-6 ratio on the basis of the information provided by the supplier or reported the percentage of fish oil (out of the total fat intake) fed to the animals. Therefore, in these studies it is difficult to establish the actual ratio of *n*-3 FAs to *n*-6 FAs fed to the animals.

### Type and bioavailability of *n*-3 fatty acids

Although most studies used fish oil as the source of *n*-3 FAs, others used purified EPA alone, DHA alone, or both combined. This variability in experimental approach can lead to different biologic effects because fish oil causes a more global change in FA composition of the diet compared with administering individual *n*-3 FAs, which, in turn, can differ significantly among one another in biologic activity. Manipulation of fish oil, which may occur in preparation of diets, may also alter efficacy of *n*-3 FAs, because it increases their susceptibility to oxidation (30). *n*-3 FAs processed into supplement form compared with those derived directly from the fish differ in their FA position on the triglyceride molecule, which has been shown to affect absorption (30). A triglyceride consists of a glycerol molecule with 3 FA chains, denoted often as *sn*-1, *sn*-2, and *sn*-3. In fish oil supplements, DHA is always located at the *sn*-2 position of the triglyceride backbone, whereas EPA can be in any of the 3 triglyceride backbones (*sn*-1, *sn*-2, *sn*-3). In contrast, seal fat EPA and DHA are usually located in the *sn*-1 and *sn*-3 positions only. Positioning on *sn*-1 or *sn*-3 allows easier release by pancreatic lipase and, therefore, improved absorption (30). Analysis of plasma and mammary tissue FAs would reflect the influence of the experimental diet on circulating and target tissue FA composition. Out of the 24 studies reviewed, only 6 reported serum FA analysis (4, 6, 7, 11, 14, 22), and 7 reported mammary tumor FA analysis (5, 7–9, 11, 12, 22). Again, this factor severely limits the ability to interpret results or to make cross-study comparisons.

### Influence of the percentage of total calorie intake from fat and specific fat composition of the diet

The overall percentage of calories from fat, as well as the specific *n*-3 FA and *n*-6 FA composition of the diet, including other FAs such as monounsaturated (MUFA) and saturated FA (SFA), are likely to be important factors in the promotion versus inhibition of mammary carcinogenesis. The American Dietetic Association recommends that 20% to 35% of calories should come from fat. An equal percentage of calories (~10%) should come from SFA, MUFA, and polyunsaturated FA (PUFA). In our analysis, the majority of the previous studies did not follow this dietary recommendation.

The importance of the percentage of caloric intake from fat on the effect of fish oil is illustrated by Olivo and colleagues (13). These investigators reported increased tumor incidence when *n*-3 FA was added to a high-fat diet (39% of calories), whereas a protective effect was observed when it was added to a low-fat diet (16% of calories).

The importance of the specific FA composition of the diet other than *n*-3 FA is suggested by Hopkins and colleagues (12). These investigators found that administration of even a small amount of fish oil (3%) to a high-SFA diet promoted carcinogenesis to a greater extent than did a diet high in SFA alone. Sasaki and colleagues (10) also found that increasing *n*-3 FA promoted carcinogenesis. However, to maintain the PUFA/SFA ratio constant, they mixed different proportions of coconut and safflower oil, which could have influenced the procarcinogenic effect of *n*-3 FAs. In the aggregate, these findings suggest that recommendations about fish oil ingestion need to take into account the composition of the rest of the FAs in the diet.

### Genetic variability

Genetic variability is prevalent in the metabolism of *n*-3 FAs and *n*-6 FAs, which may interfere with the effectiveness of *n*-3 FA supplementation. The plasma levels of both FAs are based not only on dietary intake but also on endogenous metabolism of their precursors (ALA and LA) by desaturase and elongase enzymes. The gene cluster of fatty acid desaturases (FADS1 and FADS2) is polymorphic and involved in the metabolism of the LA (*n*-6) and ALA (*n*-3) series leading to arachidonic acid (AA) and EPA, respectively. Differences in the level of activities of these enzymes could significantly influence the *n*-3/*n*-6 ratio when rats (or humans) are exposed to diets rich in both FAs. This factor is particularly important when *n*-3 FAs are derived from plants (rich in ALA) as opposed to marine fish oils, which are rich in the more distal FAs, such as EPA and DHA. The use of appropriate transgenic and knockout mouse models in future

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studies may offer an opportunity to test the influence of genetic variability in FA metabolism on mammary carcinogenesis.

### Timing of diet

Timing of the diet, both with regard to the rodent's life cycle (prepubertal versus adult) and carcinogen administration (before or after initiation of diet), is also a factor that adds variability to the studies, making them difficult to compare with one another. Epidemiologic evidence in humans suggests that dietary changes early in life influence the risk of breast cancer susceptibility. Olivo and colleagues (13) specifically looked at prepubertal exposure to fish oil prior to carcinogen administration. Therefore, the conclusions from this report cannot be extrapolated to the rest of the studies in which fish oil was administered to pubertal rats. The *n*-3 FAs were administered sometimes before and sometimes after the carcinogen for the duration of the experiment. This factor may also introduce a major confounding variable in comparing studies because some studies may examine fish oil effect on initiation and others on promotion of carcinogenesis.

## Recommendations

### Controlled experimental conditions

Our review is unique in that it represents the first attempt to systematically analyze the possible confounding variables responsible for the inconsistent effects of fish oil on mammary carcinogenesis reported in the literature. On the basis of our analysis, we propose the following recommendations for the design of future preclinical studies testing the chemopreventive efficacy of *n*-3 FAs on mammary carcinogenesis:

(i) Use translationally relevant diets so that protective effects can be better extrapolated for use in humans; for instance, using a diet with 20% to 35% of calories from fat or one that adheres to the recommended percentage of calories from SFA and MUFA (10% each), according to the American Dietetic Association. Using diets containing extremes of calories from fat would generate conclusions that are not directly applicable to humans. Keeping these dietary components constant across studies will make it possible to better evaluate the specific effects of *n*-3 FAs and *n*-6 FAs on mammary carcinogenesis, without the confounding effects of variable amounts of SFA and MUFA. Furthermore, the effects of *n*-3 FAs can be evaluated within the context of an overall healthy diet.

(ii) Experimentally verify the FA composition of the diets used in view of the multifactorial variability of *n*-3 FA sources and bioavailability. Performing a diet analysis makes it possible to determine an actual (instead of calculated) *n*-3/*n*-6 ratio, thus allowing us to establish if there is a ratio that consistently provides benefits.

(iii) Perform FA analysis in the plasma and within the target tissues to allow better comparison of results across studies. This will allow us to establish whether differences among studies using experimentally verified similar diets are due to differences in systemic or tissue-specific metabolism of FA.

(iv) Test the influence of FADS1 and FADS2 on *n*-3 FA effect on mammary carcinogenesis by doing chemoprevention studies in transgenic and knockout mice in which the activity of these enzymes has been genetically manipulated. This is a translationally important issue because genetic polymorphism of FADS1 and FADS2 has been reported in humans.

### Combination strategies

Breast cancer development requires the coordinated activation of multiple cellular mechanisms. To optimally inhibit mammary carcinogenesis, we need to adopt a multitargeted approach. In addition, to be applicable to a healthy population of women, a prevention strategy needs to be safe and easy to implement. The *n*-3 FAs are a class of compounds that could meet both of these criteria if the optimal conditions for their administration can be determined. From a mechanistic point of view, *n*-3 FAs are particularly attractive, as they have the potential of affecting multiple cellular pathways involved in tumor biology (Fig. 1). Elucidation of which of these mechanisms are specifically involved in mammary carcinogenesis should be a major focus of future research. Furthermore, combinations with other agents with complementary mechanisms of action that may enhance the antitumor effects of *n*-3 FA should be tested.

A multitargeted approach tested by Chatterjee and colleagues (20) evaluated the combination of vitamin D with Maxepa (a fish oil supplement) in inhibiting DMBA-induced carcinogenesis. The authors observed that the combination strategy was twice as effective as the individual treatments in reducing tumor incidence and multiplicity.

Our laboratories have tested a novel approach to breast cancer prevention by combining antiestrogens with an *n*-3 FA–rich diet. We have observed that the combination of tamoxifen and a fish oil–rich diet inhibited MNU-induced rat mammary tumor formation and multiplicity to a greater extent than the individual interventions (6). In an ongoing parallel clinical trial conducted in healthy postmenopausal women (NCT00723398), we are testing the potential superiority of the combination of the antiestrogen raloxifene and the U.S. Food and Drug Administration–approved *n*-3 FA preparation Lovaza (GlaxoSmithKline) in reducing mammographic breast density, a risk factor for breast cancer. Of interest, 2 clinical trials (NCT00612560 and NCT00635908) are testing the combination of the aromatase inhibitor anastrozole and flaxseed (a source of *n*-3 FAs) for treatment of breast cancer.

In summary, we believe that *n*-3-FAs play an important role in breast cancer prevention, provided that they are administered under optimal conditions, which have not been experimentally determined despite multiple studies for more than 30 years. From a mechanistic perspective, a strong rationale exists for the significant potential of *n*-3 FAs to inhibit

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carcinogenesis, especially when they are combined with other agents that exert different mechanisms of action. However, complex dietary interactions can occur among dietary lipids that can modulate the activity of *n*-3 FAs. To take advantage of this potential, a new paradigm is needed through which the dietary conditions that maximize protective activity can be determined.

Based on our review of the literature, we have presented here some suggestions for more rigorously controlled future studies that may be able to test whether there is, indeed, a causal relationship between *n*-3 FA ingestion and reduced breast cancer risk. If these studies are conducted in a translationally relevant fashion, their results will help to properly design clinical trials, eventually leading to evidence-based recommendations for women.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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