Published in final edited form as:
Curr Breast Cancer Rep. 2013 September 1; 5(3): 247–254. doi:10.1007/s12609-013-0112-1.

Omega-3 fatty acids for the prevention of breast cancer: an update and state of the science

Neil M. Iyengar, MD[1,2,3], **Clifford A. Hudis, MD**[1,2], and **Ayca Gucalp, MD**[1,2]

[1]Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center; New York, NY

[2]Department of Medicine, Weill Cornell Medical College; New York, NY

[3]The Rockefeller University; New York, NY

Abstract

The quantity and makeup of dietary fat intake are known to impact human health. Use of Omega-3 (ω-3) polyunsaturated fatty acid (PUFA) supplements has gained increasing attention for a variety of purported health benefits, including cancer prevention. Preclinical evidence has been encouraging and recent studies have expanded our understanding of the mechanisms by which ω-3 PUFAs may protect against breast cancer. However, epidemiologic studies have yielded mixed results. Recent population studies have attempted to delineate factors that may influence the effects of ω-3 PUFAs such as total fat intake and the ratio of ω-3 to ω-6 PUFA intake. Several clinical trials, including some currently ongoing, are investigating novel strategies that favorably alter endogenous fatty acid profiles in an effort to develop clinically feasible prevention methods. Identification of well-defined subpopulations that are most likely to benefit from a targeted prevention approach will likely be crucial in this effort.

Keywords

Breast cancer; fish oil; prevention; fatty acids; omega-3 polyunsaturated fatty acids; omega-6 polyunsaturated fatty acids; diet; metabolism; obesity; risk factors; inflammation; nutrition

Introduction/Background

Omega-3 (ω-3) and omega-6 (ω-6) polyunsaturated fatty acids (PUFAs) are essential fatty acids that have been shown to play an important role in several chronic illnesses [1]. Epidemiologic data suggest that changes in total fat intake and the shifted ratio favoring ω-6 over ω-3 PUFAs in the Western diet, have paralleled the rise of cardiovascular disease, obesity, diabetes, and other chronic diseases as leading contributors to morbidity and mortality rates [2]. Of its many clinical consequences, obesity is a well known risk factor for the development of several epithelial malignancies, and it is becoming increasingly apparent that inflammation may be a key mediator of this obesity-cancer link [3]. Partly for this reason, manipulating fatty acid composition has garnered increasing scientific attention as an attractive potential cancer prevention and adjunctive treatment strategy.

Dietary intake, predominantly from cold-water fish, is the most reliable source of the long-chain ω-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [1,4]. Data from several preclinical models suggest that these ω-3 PUFAs can exert an antitumor effect through various steric and molecular interactions that inhibit cellular proliferation and

Corresponding Author: Clifford A. Hudis, MD, 300 E 66th Street, New York, NY 10065, hudisc@mskcc.org.

promote cell death. DHA, for example, inserts into the phospholipid cell-membrane thereby altering permeability, cell elasticity, and the function of many membrane-embedded receptors and proteins. Additionally, attenuation of inflammatory pathways and activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ) have recently been implicated [5,6].

Epidemiologic data have been inconsistent relative to associations between ω-3 PUFA intake and cancer development. Observational studies suggest a protective effect of ω-3 PUFAs against colon, prostate, and other cancers [7,8]. However, the protective impact of ω-3 PUFAs on the risk of breast cancer (BC) development has been particularly controversial. Because of mixed epidemiologic observations, additional, larger population studies are needed to determine if there is an association consistent with an anti-cancer effect. At the same time, promising preclinical data have motivated a number of clinical prevention trials, which are currently ongoing. This review will provide an update on the advances made in recent years regarding the role of ω-3 PUFAs in the prevention of BC.

Population Studies

Despite numerous epidemiologic reports, conflicting data have hampered a consensus regarding a preventive effect of ω-3 PUFAs against the development of BC [9–12]. A large systemic review, reported in 2006, analyzed the findings of 38 studies that examined the effect of ω-3 PUFA intake on the incidence of various cancers in geographically heterogeneous populations [8]. Overall cancer risk was not affected by ω-3 PUFA intake. With respect to BC, some studies included in this review reported risk reductions while others reported an increased risk of cancer. Therefore, the authors concluded that the epidemiologic data, in aggregate, does not support an association between ω-3 PUFA consumption and BC incidence. Since this report, several additional population studies have been conducted and will be reviewed below.

In a large prospective study including over 35,000 postmenopausal women enrolled in the VITamins And Lifestyle (VITAL) Cohort, current use of fish oil supplements was associated with a decreased risk of localized invasive ductal carcinomas, but not lobular carcinomas or regional or distant disease (hazard ratio, HR 0.68, 95% confidence interval, CI 0.50–0.92; P=0.02) [13]. However, the specific type of ω-3 PUFA (i.e. DHA and/or EPA) was not reported. Inconsistent reporting of PUFA composition, background total fat intake, and ω-3 to ω-6 ratio may partly account for the conflicting findings of epidemiologic studies. To address this possibility, several studies have examined the specific makeup of consumed fatty acids.

In a case control study of a Korean population, 358 patients with BC and 360 healthy control subjects underwent dietary assessment by questionnaire and interview in order to determine amounts and types of fat intake [14]. Both pre- and postmenopausal women in the highest quartile of fatty fish intake had a lower incidence of BC (odds ratio, OR 0.23, 95% CI 0.13–0.42; P<0.001). Additionally, EPA and DHA intake was estimated by type of fish consumed. While no association was found between EPA and/or DHA intake with BC risk in premenopausal women, a protective effect was seen in postmenopausal women (EPA intake ≥ 0.101 g/day: OR 0.38, 95% CI 0.15–0.96; P=0.035; DHA intake ≥ 0.213 g/day: OR 0.32, 95% CI 0.13–0.82; P=0.010). Therefore, specific patient characteristics (i.e. menopausal status), in addition to the makeup of dietary fat intake, may be important considerations.

In contrast to the Korean study, a case-cohort study in a Danish population did not find any associations between total or specific ω-3 PUFA intake and BC risk [15]. Importantly, the Danish study quantified specific ω-3 PUFA levels in gluteal adipose tissue donated by

women who prospectively enrolled in the Diet, Cancer, and Health study during the 1990s. Tissue levels of total marine ω-3 PUFAs, EPA, and DHA were compared between women who went on to develop BC (n=463) and a subcohort of healthy subjects (n=1,098). However, total levels of marine ω-3 PUFAs were low in all subjects and may account for discrepancies between an ω-3 PUFA effect in this population versus populations that consume marine-rich diets. Interestingly, an earlier report from the same Danish study population found a higher rate of estrogen receptor (ER)-positive BC associated with higher fish consumption as determined by a detailed food frequency questionnaire [16]. This apparent discrepancy suggests that measurement of endogenous PUFA levels may be important in assessing a true effect.

Other population studies have addressed the interactions between ω-3 and ω-6 PUFAs. In general, ω-6 PUFAs are thought to have proinflammatory effects while ω-3 PUFAs are antiinflammatory. Therefore, quantifying the consumption of both fatty acids may be a critical step in isolating an ω-3 PUFA affect. In a French study population comprised of over 56,000 women followed for 8 years, no association was found between total ω-3 (or other) PUFA intake and BC risk [17]. However, increased ω-3 PUFA intake was protective against BC in women who consumed the highest amounts of ω-6 PUFAs (HR 0.62, 95% CI 0.44–0.86; *P interaction* = 0.042). Similarly, in the Shanghai Women's Study, which included over 72,000 women who were cancer-free at baseline and followed prospectively, there was no association between ω-3 PUFA intake and BC risk [18]. However, women who consumed the highest amounts of ω-6 PUFAs (> 7.28 g/day) and the least amounts of ω-3 PUFAs (≤ 0.045 g/day) were at the highest risk of developing BC (relative risk, RR 2.06, 95% CI 1.27–3.34; *P interaction* = 0.008) compared to women with the lowest ω-6 to ω-3 PUFA intake ratio. These findings were echoed in a case-control study including a cohort of Mexican women comprised of 1,000 patients with BC and 1,074 healthy subjects [19]. Importantly, increasing ω-3 PUFA intake was associated with decreased risk of BC in obese women defined as body mass index (BMI) ≥ 30 (OR 0.58, 95% CI 0.39–0.87; *P*=0.008). These population studies highlight the importance of investigating the interactions between dietary fats and specific patient characteristics, such as BMI and menopausal status, in order to better understand the complex relationships between ω-3 PUFAs and BC risk (Table 1). Additional studies that identify at-risk populations who may benefit from specific alterations in dietary fat intake via supplementation or lifestyle changes, as well as mechanistic studies that better elucidate the biologic underpinnings that mediate the relationship between ω-3 PUFAs and BC, will be critical in guiding clinical prevention trials.

Pre-clinical studies

Unlike the epidemiologic evidence to date, preclinical data derived from various experimental models are more promising with regard to a possible role for ω-3 PUFAs in the prevention of BC. In general, ω-3 PUFAs are thought to disrupt carcinogenesis by a variety of mechanisms leading to cell death and/or inhibition of cellular proliferation. These possible mechanisms include alteration of the phospholipid cell membrane and associated receptors, interruption of signal transduction pathways, anti-inflammatory effects, altered estrogen and insulin metabolisms, and the production of free radicals such as reactive oxygen species (ROS) [7]. Several studies that expand our mechanistic understanding of ω-3 PUFAs and BC are reviewed below.

Actions of ω-3 PUFAs in vitro

It has been well established that ω-3 PUFAs can suppress the development of cancers by inhibiting cellular proliferation and inducing cell death [7]. *In vitro* studies that elucidate the effects of ω-3 PUFAs on murine and human BC cells provide important insights into the mechanisms underlying this inhibition of tumorigenesis. Alteration of the lipid membrane

by ω-3 PUFAs and the related disruption of proinflammatory eicosanoid synthesis by the cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes has recently been demonstrated in mouse and human BC cell lines [20–23]. Additionally, treatment of ER-positive and ER-negative human BC cell lines with both EPA and DHA was found to induce apoptosis and decrease cell viability [24]. This was paralleled by decreased or absent expression of Bcl2 and increased procaspase-8 expression in the EPA and DHA treated versus control cells. Bcl2 is a key apoptosis regulator protein and its overexpression has been implicated in a number of cancers. Cleavage of pro-caspase 8 amplifies the caspase cascade thereby promoting apoptosis. Interestingly, Corsetto and colleagues also demonstrated inhibition of epidermal growth factor receptor (EGFR) activation by DHA and EPA, as well as a slight reduction in EGFR expression as a result of DHA exposure. EGFR is overexpressed in a number of malignancies, including those of the breast and lung, and promotes cell growth and migration via several downstream signaling proteins. Adding to these findings, the treatment of ER-negative human BC cells with DHA was shown to induce apoptosis via increased caspase-3 activity [25]. Additionally, DHA attenuated the migratory ability of these cells suggesting that DHA may also prevent tumor cell invasion.

DHA has also been shown to increase intracellular ROS in ER-positive BC cells [26]. Kang and colleagues demonstrated DHA-induced ROS accumulation leading to caspase-8 activation and resultant apoptotic cell death. This cytotoxic effect was abrogated by pharmacologic inhibition of specific caspases and knockdown of caspase-8 by siRNA transfection. Therefore, EPA and DHA appear to exert their anti-tumor effects via multiple mechanisms including disruption of the cell membrane and embedded receptors, alteration of signaling pathways that are involved in cellular proliferation and migration, dysregulation of apoptosis, and the production of cytotoxic oxidating molecules.

Animal models – in vivo effects of ω-3 PUFAs

Increasing dietary intake of ω-3 PUFAs in animal models has been shown to have significant anti-tumor effect. Yet, this effect has not been reflected well in the prevention of human carcinogenesis as demonstrated by epidemiologic data reviewed earlier. In an effort to better inform human clinical trials, more recent studies aimed to elucidate the mechanisms by which ω-3 PUFAs inhibit tumorigenesis in animals. In the study by Kang et al. discussed above, ER-positive breast cancer mouse xenografts were fed a fish oil supplemented diet in order to determine whether the *in vivo* effects of ω-3 PUFAs mirrored their findings *in vitro* [26]. At 6 weeks of feeding, plasma levels of DHA and EPA were significantly higher in mice fed a 5% fish oil diet. DHA and EPA levels increased several hundred-fold in both normal and tumorous mammary tissue. Significantly smaller tumors were observed in the mice receiving the fish oil supplemented diet compared to the control diet. As supported by the *in vitro* experiments, intracellular ROS levels were elevated in tumor tissue from the fish oil fed mice compared to control diet fed animals. Elevated apoptotic and diminished proliferative indices were also noted in the tumor tissue of the fish oil fed mice. Notably, little to no effect of ω-3 PUFAs was observed in ER-negative BC cells or xenografts. This suggests the anticancer effect of ω-3 PUFAs may be limited to certain tumor types. Indeed, decreased ERα and ERβ expression was observed in female rats that were fed a fish oil-rich diet [27]. Additionally, decreased mitosis and increased apoptosis were observed in the mammary gland and colon with increased fish oil feeding, pointing to a potential preventative, anti-neoplastic effect of ω-3 PUFAs.

An effect of ω-3 PUFAs on the development and progression of hormone insensitive tumors was explored in a series of studies by Manni and colleagues [28–30]. The investigators hypothesized that the combination of tamoxifen and ω-3 PUFAs, which are known PPAR agonists, would prevent the development of ER-negative tumors via suppression of synergistic interactions between the ER and PPARγ pathways. In a rat model of carcinogen-

induced mammary tumors, the combination of tamoxifen with an ω-3 PUFA rich diet profoundly inhibited mammary tumor development [28]. Importantly, the antitumor effect of fish oil in combination with tamoxifen was more pronounced than that seen with tamoxifen or ω-3 PUFAs alone. Additionally the administration of a fish oil-rich diet with suboptimal doses of tamoxifen was effective in curtailing the development of mammary tumors while suboptimal-dose tamoxifen alone had no protective effect. However, in a subsequent study utilizing a different animal model of ER-negative breast tumors, fish oil feeding did not provide an additive protective effect when combined with tamoxifen [29]. In order to better isolate a preventive effect, the investigators next examined the effect of tamoxifen and fish oil on pre-malignant, hyperplastic lesions in their carcinogen-induced rat mammary tumor model [30]. While fish oil-feeding significantly diminished the proliferative marker, Ki-67, in the hyperplastic lesions, the development of these preneoplastic lesions was not inhibited. Notably, in two of these three studies, tissue accumulation of ROS was observed in the fish oil-supplemented animals, pointing to increased oxidative stress as a potential anticancer mechanism. In the most recent study, tissue and plasma levels of arachidonic acid were suppressed by intake of ω-3 PUFAs, implicating alteration of COX and LOX pathways in the antitumor effect.

Population studies reporting the effect of ω-3 PUFA intake may often be confounded by changes in the ω-3 to ω-6 PUFA intake ratio. The effects of varying this ratio have subsequently been investigated in animal models. Exposure to high levels of ω-6 PUFAs in utero via increased maternal dietary intake, led to a greater propensity for the development of chemically-induced mammary tumors in female rats [31]. Adding fish oil to the maternal diet significantly protected against the ω-6 PUFA effect. In another rat model of chemically-induced mammary tumors, a high dietary ω-3 to ω-6 PUFA ratio was found to decrease cellular proliferation by 60% and increase apoptosis in the mammary carcinomas compared to a low ω-3 to ω-6 PUFA ratio [5]. Multiple complimentary mechanisms may explain this finding in the high ω-3 to ω-6 PUFA intake ratio group including attenuation inflammatory activation evidenced by diminished phosphorylation of nuclear factor kappa-B (NFκB), reduced lipid synthesis and metabolic alterations including decreased adiponectin levels and diminished insulin-like growth factor-1 (IGF-1) signaling, and alterations of signal transduction pathways such as activation of AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) suppression. Notably, a high ω-3 PUFA dose was used to achieve a high ω-3 to ω-6 PUFA intake ratio, which would not likely be achievable by fish intake alone. This study suggests that both dietary modification and ω-3 PUFA supplementation in combination may be a useful clinical strategy for the prevention of BC. Additionally, the heterogenous mechanisms underlying the anticancer activity of ω-3 PUFAs indicate the need to assess for a differential effect by BC molecular subtype.

Methods other than dietary supplementation have been shown to increase ω-3 PUFA levels in animal models. A calorie-controlled diet plus treadmill exercise lead to weight loss, diminished body fat, and altered epidermal phospholipid composition in mice [32]. Specifically, elevated DHA levels were found in the skin tissues of mice that were fed a calorie-consistent diet and underwent treadmill exercise compared to sedentary, *ad libitum*-fed and exercised alone mice. Taken together, the overwhelming majority of preclinical data has demonstrated anti-tumorigenic effects of increasing ω-3 PUFA levels via dietary intake and other methods. The recent animal studies described above have implicated multiple mechanisms that may contribute to a protective affect of ω-3 PUFAs against neoplastic transformation.

Clinical Trials

The encouraging animal data supporting a role for ω-3 PUFAs in the prevention of BC have led to a number of in-human trials. Additionally, the relatively innocuous side effect profile of ω-3 PUFA supplements has made this approach particularly attractive. As in animal models, dietary DHA and EPA supplementation in women increases serum and breast adipose tissue levels of these ω-3 PUFAs in a dose-dependent manner [33]. Rising BMI, however, attenuated dose responsiveness of DHA and EPA in serum and DHA in breast adipose tissue. Additionally, high doses of DHA and EPA (up to 7.56 g combined) were well tolerated with a high compliance rate (92.9% ± 9.2%). Also mirroring preclinical findings, methods other than dietary supplementation have been shown to increase endogenous ω-3 PUFA levels. In a pilot study including 40 women receiving chemotherapy for localized BC, diet and exercise counseling was associated with a rise in blood ω-3 PUFA levels [34]. All women in this study received written information and bimonthly newsletters on diet and exercise as well as a pedometer. Women randomized to the intervention arm additionally received telephone counseling with a registered dietician encouraging increased food and vegetable intake, decreased fat intake, and increased physical activity. Specific counseling regarding ω-3 or ω-6 PUFA intake was not provided. Over the 12-month study period, ω-3 PUFA levels increased in the blood, although there was no statistically significant difference between the control and intervention arm. Therefore, in addition to supplementation, diet and exercise can shift the ω-3 to ω-6 PUFA ratio in favor of ω-3 PUFAs. A multifaceted approach, then, including lifestyle and behavioral changes, as well as intake of ω-3 PUFA supplements, may be a more effective prevention strategy over supplementation alone.

Several studies have aimed to identify blood and urine based biomarkers that may be reflective of cancer risk and can be modified by altering the volume and composition of endogenous lipids through various interventions. The relationship between blood ω-3 PUFA levels, determined by the erythrocyte fatty acid level, and the development of benign fibrocystic conditions of the breast was explored in a case-control study in Shanghai [35]. Proliferative fibrocystic conditions of the breast are associated with an elevated risk of BC. Women with the highest EPA levels had a significantly reduced risk of BC as compared to proliferative fibrocystic conditions in relation to women with the lowest EPA concentrations (OR 0.51, 95% CI 0.27 – 0.94; P=0.003). These findings support the preventive role of EPA against the development of BC and also its protective effects against the progression of preneoplastic lesions to cancer. Furthermore, this study identifies the erythrocyte fatty acid level as a potential biomarker of fatty acid intake and composition, which may be a useful tool in diet and supplement interventions.

Identification of other blood-based biomarkers may be useful for future interventional trials. One such biomarker may be hepatic stearoyl-CoA desaturase-1 (SCD-1), a key regulator of endogenous saturated fatty acid composition. Epidemiologic studies have identified associations between decreased saturated fatty acid intake, characterized by lower SCD-1 levels, and improved BC risk [36]. Diets rich in PUFAs suppress SCD-1 expression, and therefore SCD-1 levels may be indicative of the anticancer activity of PUFAs, although this has yet to be investigated.

Several ongoing clinical trials of ω-3 PUFAs for BC prevention have aimed to disrupt the metabolic and inflammatory pathways implicated in carcinogenesis. The ubiquitous intercellular adhesion molecule-1 (ICAM-1) has also been investigated as a potential biomarker of BC risk and ω-3 PUFA response [37]. ICAM-1 is activated by several proinflammatory cytokines and has been associated with BC risk in epidemiologic studies [38,39]. In a nested case-control study including 408 subjects with cancer diagnosed

between 1994 and 2007, and 760 matched control subjects, elevated plasma ICAM-1 level was associated with increased BC risk in subjects with low ω-3 PUFA intake (OR 4.7, 95% CI 1.6–13.4; *P*=0.004) [37]. Prospective randomized trials are needed to validate ICAM-1 as a biomarker of BC risk and its utility in assessing for risk reductive effects of ω-3 PUFAs.

The addition of ω-3 PUFAs to endocrine chemoprevention strategies is also currently under investigation. Signori and colleagues reported preliminary data from an ongoing trial in which postmenopausal women at an elevated risk of BC based on increased breast density are randomized to receive no intervention, raloxifene 60 mg, raloxifene 30 mg, the ω-3 PUFA compound Lovaza 4g, or Lovaza 4g plus raloxifene 30 mg for 2 years [40]. The primary endpoint is reduction in breast density. After completing 1 year of the study (n=46), women in all arms tolerated the interventions well with high compliance rates. Raloxifene led to a dosedependent reduction in serum IGF-1 level as opposed to Lovaza, nor was an augmented IGF-1 effect observed with the addition of Lovaza to raloxifene. Additionally, levels of circulating inflammatory markers including C-reactive protein (CRP) and interleukin-6 were not affected by any of the treatment arms. The final results of this study are awaited.

Identifying an at-risk group most likely to benefit from a specific intervention will likely yield a more effective prevention strategy than seeking a singular approach for a diverse population. To this end, our group has been interested in identifying the mechanisms linking obesity, a known risk factor for the development of postmenopausal BC, and carcinogenesis [3,41].

Obesity is associated with systemic, subclinical inflammation and elevated levels of circulating proinflammatory cytokines [3,42]. Several of these cytokines are known to be elevated in BC patients and have been associated with BC development and progression [43,44]. We recently identified histologically evident inflammation of breast white adipose tissue, manifest as dead and dying adipocytes surrounded by a crown of infiltrating macrophages, now known as crown-like structures of the breast (CLS-B) [45]. The presence of these lesions in mouse models of obesity and in humans was associated with elevated levels of proinflammatory cytokines, NFκB activation, and increased aromatase activity [45,46]. Furthermore, elevated COX-2 and prostaglandin E_2 (PGE_2) levels in the inflamed breast tissue of obese patients was found to contribute to increased aromatase activity [47]. Disrupting this newly identified obesity→inflammation→aromatase axis would be a novel prevention strategy and the antiinflammatory properties associated with DHA make it an attractive agent to study in this high-risk group. Monitoring blood levels of proinflammatory cytokines associated with CLS-B, such as TNF-α, may be useful in assessing the benefit of investigational agents such as DHA in patients identified to have breast inflammation. Targeted strategies such as these, and others, are needed to identify more effective ways of preventing BC.

Conclusion

The role of ω-3 PUFAs in the reduction of BC risk remains unclear. Recent population studies have identified multiple factors, such as total fat intake and dietary fat composition that can modulate the endogenous effects of ω-3 PUFAs. Animal models and in vitro data have offered greater insights into the complex pathways involved in breast carcinogenesis and the points at which ω-3 PUFAs may be effective in interrupting this process. These preclinical findings are being translated into a new era of clinical prevention trials that utilize refined strategies that take into account the increasingly recognized complexities of fatty acid biology. Aiming to disrupt the links between distinct risk factors and the

development of malignancies in specifically defined populations could usher in the success of recent, so-called targeted treatments to the arena of cancer prevention.

Acknowledgments

This work was supported by the Breast Cancer Research Foundation and grant UL1TR000457 of the Clinical and Translational Science Center at Weill Cornell Medical College.

Conflict of Interest N.M. Iyengar, C.A. Hudis, and A. Gucalp disclose that they have received research support from National Institutes of Health, Sass Foundation, Metastases Research Center (Memorial Sloan-Kettering Cancer Center), and American Society of Clinical Oncology.

References

Recently published papers of particular interest have been highlighted as:

• Of importance

•• Of major importance

1. Berquin IM, Edwards IJ, Chen YQ. Multi-targeted therapy of cancer by omega-3 fatty acids. Cancer Lett. 2008; 269:363–377. [PubMed: 18479809]
2. Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr. 1999; 70:560S–569S. [PubMed: 10479232]
3. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev. 2009; 18:2569–2578. [PubMed: 19755644]
4. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr. 2006; 83:1467S–1476S. [PubMed: 16841856]
5. Jiang W, Zhu Z, McGinley JN, et al. Identification of a molecular signature underlying inhibition of mammary carcinoma growth by dietary N-3 fatty acids. Cancer Res. 2012; 72:3795–3806. [PubMed: 22651929] • In this animal study, rats who were fed a diet with a high ω-3:ω-6 PUFA ratio had lower proliferation rates in chemically-induced mammary tumors compared to rats fed a low ω-3:ω-6 PUFA ratio. • Notably, high doses of PUFAs were fed to rats, which would not be achievable by diet alone.
6. Chapkin RS, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. Prostaglandins Leukot Essent Fatty Acids. 2009; 81:187–191. [PubMed: 19502020]
7. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr. 2004; 79:935–945. [PubMed: 15159222]
8. MacLean CH, Newberry SJ, Mojica WA, et al. Effects of omega-3 fatty acids on cancer risk: a systematic review. JAMA. 2006; 295:403–415. [PubMed: 16434631]
9. Terry PD, Rohan TE, Wolk A. Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence. Am J Clin Nutr. 2003; 77:532–543. [PubMed: 12600840]
10. Terry PD, Terry JB, Rohan TE. Long-chain (n-3) fatty acid intake and risk of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. J Nutr. 2004; 134:3412S–3420S. [PubMed: 15570047]
11. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ. 2006; 332:752–760. [PubMed: 16565093]
12. Bougnoux P, Maillard V, Chajes V. Omega-6/omega-3 polyunsaturated fatty acids ratio and breast cancer. World Rev Nutr Diet. 2005; 94:158–165. [PubMed: 16145262]
13. Brasky TM, Lampe JW, Potter JD, et al. Specialty supplements and breast cancer risk in the VITamins And Lifestyle (VITAL) Cohort. Cancer Epidemiol Biomarkers Prev. 2010; 19:1696–1708. [PubMed: 20615886] • This is a prospective cohort study that followed over 35,000

postmenopausal women. • Current, but not past, use of fish oil supplements was associated with a decreased risk of developing invasive ductal carcinomas within the breast.

14. Kim J, Lim SY, Shin A, et al. Fatty fish and fish omega-3 fatty acid intakes decrease the breast cancer risk: a case-control study. BMC Cancer. 2009; 9:216. [PubMed: 19566923]
15. Witt PM, Christensen JH, Schmidt EB, et al. Marine n-3 polyunsaturated fatty acids in adipose tissue and breast cancer risk: a case-cohort study from Denmark. Cancer Causes Control. 2009; 20:1715–1721. [PubMed: 19711189]
16. Stripp C, Overvad K, Christensen J, et al. Fish intake is positively associated with breast cancer incidence rate. J Nutr. 2003; 133:3664–3669. [PubMed: 14608091]
17. Thiebaut AC, Chajes V, Gerber M, et al. Dietary intakes of omega-6 and omega-3 polyunsaturated fatty acids and the risk of breast cancer. Int J Cancer. 2009; 124:924–931. [PubMed: 19035453]
18. Murff HJ, Shu XO, Li H, et al. Dietary polyunsaturated fatty acids and breast cancer risk in Chinese women: a prospective cohort study. Int J Cancer. 2011; 128:1434–1441. [PubMed: 20878979] • This is the Shanghai Women's Study in which over 72,000 healthy women were followed prospectively. • While the amount of any indivual PUFA intake was not associated with breast cancer risk, low ω-3 PUFA intake by women who had the highest ω-6 PUFA intake was associated with elevated breast cancer risk.
19. Chajes V, Torres-Mejia G, Biessy C, et al. omega-3 and omega-6 Polyunsaturated fatty acid intakes and the risk of breast cancer in Mexican women: impact of obesity status. Cancer Epidemiol Biomarkers Prev. 2012; 21:319–326. [PubMed: 22194528] • This is a case-control study of Mexican women with and without breast cancer. • Higher levels of ω-3 PUFA intake in obese women, but not lean or overweight women, were protective against breast cancer.
20. Erickson KL, Hubbard NE. Fatty acids and breast cancer: the role of stem cells. Prostaglandins Leukot Essent Fatty Acids. 2010; 82:237–241. [PubMed: 20363115]
21. Pauwels EK, Kairemo K. Fatty acid facts, part II: role in the prevention of carcinogenesis, or, more fish on the dish? Drug News Perspect. 2008; 21:504–510. [PubMed: 19180268]
22. Tapiero H, Ba GN, Couvreur P, Tew KD. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed Pharmacother. 2002; 56:215–222. [PubMed: 12199620]
23. Kaur B, Jorgensen A, Duttaroy AK. Fatty acid uptake by breast cancer cells (MDA-MB-231): effects of insulin, leptin, adiponectin, and TNFalpha. Prostaglandins Leukot Essent Fatty Acids. 2009; 80:93–99. [PubMed: 19217762]
24. Corsetto PA, Montorfano G, Zava S, et al. Effects of n-3 PUFAs on breast cancer cells through their incorporation in plasma membrane. Lipids Health Dis. 2011; 10:73. [PubMed: 21569413] • Treatment of human breast cancer cell lines in vitro with EPA or DHA induced apoptosis and decreased cell viability in this study.
25. Blanckaert V, Ulmann L, Mimouni V, et al. Docosahexaenoic acid intake decreases proliferation, increases apoptosis and decreases the invasive potential of the human breast carcinoma cell line MDA-MB-231. Int J Oncol. 2010; 36:737–742. [PubMed: 20126994] • In this preclinical study, DHA activated the caspase cascade, thereby inducing apoptosis, in ER-negative human breast cancer cells.
26. Kang KS, Wang P, Yamabe N, et al. Docosahexaenoic acid induces apoptosis in MCF-7 cells in vitro and in vivo via reactive oxygen species formation and caspase 8 activation. PLoS One. 2010; 5:e10296. [PubMed: 20421971] • This study demonstrated that DHA induces apoptosis in breast cancer cells in vitro by increasing intracellular ROS accumulation.
27. Kramer F, Johnson IT, Doleman JF, Lund EK. A comparison of the effects of soya isoflavonoids and fish oil on cell proliferation, apoptosis and the expression of oestrogen receptors alpha and beta in the mammary gland and colon of the rat. Br J Nutr. 2009; 102:29–36. [PubMed: 19079816]
28. Manni A, Xu H, Washington S, et al. The impact of fish oil on the chemopreventive efficacy of tamoxifen against development of N-methyl-N-nitrosourea-induced rat mammary carcinogenesis. Cancer Prev Res (Phila). 2010; 3:322–330. [PubMed: 20179301] • In this rat model of chemically-induced mammary tumors, the combination of an ω-3 PUFA rich diet and tamoxifen had a great antitumor effect than either intervention alone.

29. Manni A, Xu H, Washington S, et al. The effects of Tamoxifen and fish oil on mammary carcinogenesis in polyoma middle T transgenic mice. Horm Cancer. 2011; 2:249–259. [PubMed: 21769696]
30. Manni A, Richie JP Jr, Xu H, et al. Effects of fish oil and Tamoxifen on preneoplastic lesion development and biomarkers of oxidative stress in the early stages of N-methyl-N-nitrosourea-induced rat mammary carcinogenesis. Int J Oncol. 2011; 39:1153–1164. [PubMed: 21892590]
31. Su HM, Hsieh PH, Chen HF. A maternal high n-6 fat diet with fish oil supplementation during pregnancy and lactation in rats decreases breast cancer risk in the female offspring. J Nutr Biochem. 2010; 21:1033–1037. [PubMed: 19954943]
32. Ouyang P, Jiang Y, Doan HM, et al. Weight Loss via exercise with controlled dietary intake may affect phospholipid profile for cancer prevention in murine skin tissues. Cancer Prev Res (Phila). 2010; 3:466–477. [PubMed: 20233900]
33. Yee LD, Lester JL, Cole RM, et al. Omega-3 fatty acid supplements in women at high risk of breast cancer have dose-dependent effects on breast adipose tissue fatty acid composition. Am J Clin Nutr. 2010; 91:1185–1194. [PubMed: 20335550]
34. Djuric Z, Ren J, Brown PR, et al. Lifestyle factors associated with serum N-3 fatty acid levels in breast cancer patients. Breast. 2012; 21:608–611. [PubMed: 22377591] • In this pilot study (n=40) of women with localized breast cancer receiving chemothearpy, diet and exercise counseling was associated with an increase in blood ω-3 PUFA levels.
35. Shannon J, King IB, Lampe JW, et al. Erythrocyte fatty acids and risk of proliferative and nonproliferative fibrocystic disease in women in Shanghai, China. Am J Clin Nutr. 2009; 89:265–276. [PubMed: 19056601]
36. Chajes V, Joulin V, Clavel-Chapelon F. The fatty acid desaturation index of blood lipids, as a biomarker of hepatic stearoyl-CoA desaturase expression, is a predictive factor of breast cancer risk. Curr Opin Lipidol. 2011; 22:6–10. [PubMed: 20935562]
37. Touvier M, Kesse-Guyot E, Andreeva VA, et al. Modulation of the association between plasma intercellular adhesion molecule-1 and cancer risk by n-3 PUFA intake: a nested case-control study. Am J Clin Nutr. 2012; 95:944–950. [PubMed: 22378736]
38. O'Hanlon DM, Fitzsimons H, Lynch J, et al. Soluble adhesion molecules (E-selectin, ICAM-1 and VCAM-1) in breast carcinoma. Eur J Cancer. 2002; 38:2252–2257. [PubMed: 12441261]
39. Basoglu M, Atamanalp SS, Yildirgan MI, et al. Correlation between the serum values of soluble intercellular adhesion molecule-1 and total sialic acid levels in patients with breast cancer. Eur Surg Res. 2007; 39:136–140. [PubMed: 17337890]
40. Signori C, DuBrock C, Richie JP, et al. Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: interim feasibility and biomarkers analysis from a clinical trial. Eur J Clin Nutr. 2012; 66:878–884. [PubMed: 22669332] • In this interim report of an ongoing trial of raloxifene and the ω-3 PUFA supplement, Lovaza, the combination of raloxifene and Lovaza was feasible and well tolerated. • The awaited primary endpoint in this trial is reduction in breast tissue density.
41. Cleary MP, Grossmann ME. Minireview: Obesity and breast cancer: the estrogen connection. Endocrinology. 2009; 150:2537–2542. [PubMed: 19372199]
42. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010; 72:219–246. [PubMed: 20148674]
43. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer. 2008; 8:887–899. [PubMed: 18846100]
44. Bachelot T, Ray-Coquard I, Menetrier-Caux C, et al. Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients. Br J Cancer. 2003; 88:1721–1726. [PubMed: 12771987]
45. Morris PG, Hudis CA, Giri D, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res (Phila). 2011; 4:1021–1029. [PubMed: 21622727]

46. Subbaramaiah K, Howe LR, Bhardwaj P, et al. Obesity is associated with inflammation and elevated aromatase expression in the mouse mammary gland. Cancer Prev Res (Phila). 2011; 4:329–346. [PubMed: 21372033]

47. Subbaramaiah K, Morris PG, Zhou XK, et al. Increased levels of COX-2 and prostaglandin E2 contribute to elevated aromatase expression in inflamed breast tissue of obese women. Cancer Discov. 2012; 2:356–365. [PubMed: 22576212]

Table 1

Selected recent population studies of ω-3 PUFAs and breast cancer risk.

Author	Subjects	Number	Instrument	Variable	Magnitude of effect	95% Confidence Interval	*P* value
Brasky [13]	Cohort	35,016	Questionnaire	Current fish oil supplement intake	0.68 *	0.50 – 0.92	0.02 +
Kim [14]	Case Control	358 360	Questionnaire	High fatty fish intake (≥15.39 g/day) vs. low intake (<3.42 g/day)	0.23 ^	0.13 – 0.42	<0.001
				High EPA intake (≥0.101 g/day) in postmenopausal women	0.38 ^	0.15 – 0.96	0.035
				High DHA intake (≥0.213 g/day) in postmenopausal women	0.32 ^	0.13 – 0.82	0.01
Witt [15]	Case Control	463 1,098	Adipose tissue biopsy	Adipose tissue levels (per 1% increase):			
				Total ω-3 PUFAs	1.00 *	0.95 – 1.05	n.s.
				DHA	1.00 *	0.91 – 1.10	n.s.
				EPA	0.94 *	0.73 – 1.21	n.s.
Thiebaut [17]	Cohort	56,007	Questionnaire	Highest vs. lowest quintile total ω-3 PUFA intake	0.99 *	0.84 – 1.15	n.s.
				Highest vs. lowest quintile long-chain ω-3 PUFA intake in women with highest ω-6 PUFA intake	0.62 *	0.44 – 0.86	0.04
Murff [18]	Cohort	72,571	Questionnaire	Highest (0.20 g/day) vs. lowest (0.02 g/day) marine ω-3 PUFA intake	0.74 ^^	0.52 – 1.06	n.s.
				Lowest (≤0.045 g/day) vs. highest (>0.10) ω-3 PUFA intake in women with highest ω-6 PUFA intake (>7.28 g/day)	2.06 ^^	1.27 – 3.34	0.008
Chajes [19]	Case Control	1,000 1,074	Interview & questionnaire	Highest vs. lowest tertile total ω-6 PUFA intake in premenopausal women	1.92 ^	1.13 – 3.26	0.02
				Highest vs. lowest tertile ω-3/ω-6 PUFA intake in obese premenopausal women	0.58 ^	0.39 – 0.87	0.008

+ Effect on risk of invasive ductal carcinoma not including other histologies;

* Hazard ratio;

^ Odds ratio;

^^ Relative risk;

n.s., not significant