Review Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.2023104323-330

Effects of Supplementation with Omega-3 Polyunsaturated Fatty Acids as an Adjuvant Therapy in the Treatment of Patients with Breast Cancer: A Systematic Review

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ARTICLE INFO

Received:
4 July 2023
Revised:
4 September 2023
Accepted:
8 September 2023

Keywords:
Breast cancer, omega-3 polyunsaturated fatty acids, supplementation, docosahexaenoic acid

ABSTRACT

Background: Since Omega-3 (*n*-3) polyunsaturated fatty acid (PUFA) supplementation plays a significant role in the treatment of cancer, decreases the adverse effects of medications, and helps in preserving lean mass and weight control, there is a good correlation between it and the prognosis for patients with breast cancer (BC). The objective of this study was to examine the effects of *n*-3 PUFA supplementation as an adjuvant therapy in the treatment of patients with BC.

Methods: The following databases were searched electronically: Embase, PubMed, Web of Science, and Google Scholar. The selection criteria were based on relevance of the topic, which was mentioned as a certain stage of BC and the usage of *n*-3 PUFA. The first search yielded 62 papers in total; afterwards, 55 publications that did not meet our eligibility requirements were removed, and eight articles were selected.

Results: n-3 PUFA supplementation ranged from 1 to 4.3 g/day in the studies. When n-3 PUFA was added to the BC treatment regimen, tumor growth was inhibited and vascular endothelial growth factor and Ki-67 levels decreased, leading to an improvement in longevity. Many side effects of BC therapies have been studied, and it may be feasible to reduce these negative effects by taking n-3 PUFA supplements.

Conclusion: In addition to being an antioxidant, *n*-3 PUFA supplements have been shown to help patients with BC in other ways, such as by increasing their chance of survival, lowering side effects (like xerostomia and bone reabsorption), improving their lipid profile, and increasing breast density.

INTRODUCTION

Sedentarism, mutagenic agents, radiation, eating patterns, alcohol consumption, and obesity are clinically relevant conditions that have an impact on the development and progression of breast cancer (BC).[1] Therefore, oncological patients often experience changes in body composition, such as an increase in fat tissue, a decrease in lean mass, and the development of metabolic changes.[2] These characteristics make the disease more aggressive and have more complications in its prognosis, making it ideal for treatment.

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From the precise diagnosis to the conclusion of the stage, the type of treatment administered can be determined. The most fundamental types of heterogeneity in BC result from alterations in the transcriptome, proteome, genome, and epigenome levels, which manifest in both spatial and temporal dimensions. Different cancer therapies exist where it is feasible to direct cancer cells to undergo apoptosis, which also results in the death of healthy tissue despite considerable breakthroughs in heterogeneous tailored therapy for BC.[3] The primary methods of treatment include radiation therapy, chemotherapy (CT), hormone therapy, and surgery, which involves removing the tumor entirely or partially. Radiation and medication are used to kill cancer cells, and these treatments can be combined, used as a neoadjuvant, or used as the primary course of treatment.[4]

Treatments can affect the body and cause loss of appetite, lean mass, nausea, and fatigue.[5,6,7] Therefore, it is necessary to examine the role of nutrients in nutritional therapy to improve cancer prognosis and other impacts. Omega-3 (*n*-3) polyunsaturated fatty acids (PUFA) are one of the nutrients that are being studied as adjuvant management in the treatment of BC. These PUFAs are a group of long-chain PUFAs, the main types of which are alpha-linolenic acid, which comes from vegetables (soy, canola, and flaxseed), and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in fish and marine crustaceans.[8, 9]

Since *n*-3 PUFA supplementation plays a significant role in the treatment of cancer, decreases the adverse effects of medications, and helps preserve lean mass and weight control, there is a good correlation between it and the prognosis for patients with BC.[8] The objective of this study was to examine the effects of *n*-3 PUFA supplementation as an adjuvant therapy in the treatment of patients with BC.

METHODS

The PRISMA guidelines were followed in conducting this systematic review.[10] This systematic review was carried out using a search technique that includes the following eligibility criteria: 1) Original articles and case reports (multicenter, randomized, double-blind, controlled trial, and randomized longitudinal study); 2) Patients with BC, regardless of gender or race; type of treatment and use of n-3 PUFA; 4) The intervention studied must be supplementation with n-3 PUFAs; and 5) Articles published in English until May 10, 2023, within the last ten years.

Articles discussing BC post-treatment, prevention of BC, and other nutrients besides *n*-3 PUFA associated with another nutrient that could not be independently examined were not included. These did not include books, monographs, dissertations, theses, reviews, or preliminary *in vitro* or *in vivo* research.

The following databases were searched electronically: Embase, PubMed, Web of Science, and Google Scholar. This systematic review's search keywords, including ‘breast cancer’, ‘breast neoplasms’, ‘omega-3 fatty acids’, ‘eicosapentaenoic acid’, ‘docosahexaenoic acid’, and ‘cancer’, were obtained from the MeSH words through PubMed.

A specific stage of BC and the use of n-3 PUFA were identified as relevant topics for the selection criteria. Articles were chosen after their titles were read to ensure they were appropriate and an abstract was read to confirm that they were relevant to the subject. Using the flow diagram depicted in Figure 1, the papers satisfying these criteria were thoroughly examined and incorporated into the study.

Three authors (FA, HG, and AB) independently performed the search and excluded duplicate articles. The first search yielded 62 papers in total; afterwards, 55 publications that did not meet our eligibility requirements were removed, and eight articles were selected. Independent reviewers conducted the data extraction procedure and used an established format to gather the data from the selected publications. In the event of a difference of opinion or dispute, the writers had already agreed to include the work and submit it for review by an unbiased advisor before deciding on its final inclusion through discussion and consensus.

RESULTS

Overall, 5–250 participants, ages ranging from 18 to 80, were enrolled in the seven studies that were identified for the study of *n*-3 PUFA supplementation in BC treatment. Table 1 shows that the therapies examined included CT, hormone therapy, and surgery. *n*-3 PUFA supplementation ranged from 1 to 4.3 g/day in the studies. The duration of the therapy varied from 1–24 months. Unsaturated fatty acid accessibility was linked to cancer growth, patient survival, inflammatory markers, antioxidant effect, lymphocyte count, arthralgia, lipid profile, body composition, BMI, breast density, and side effects of treatment (xerostomia, bone reabsorption, toxicity, and quality of life).

When *n*-3 PUFA was added to the BC treatment regimen, tumor growth was inhibited and vascular endothelial growth factor and Ki-67 levels decreased, leading to an improvement in longevity.[11,12] With the results of the oxygen radical absorption test, the antioxidant enzymes superoxide dismutase, catalase, and glutathione reductase increased. This shows that *n*-3 PUFA supplementation has strong antioxidant

potential. The lack of variation in prostaglandin E2 blood levels was reported in the Spanish study, which could have been attributed to variations in timing or kind of supplementation.[12]

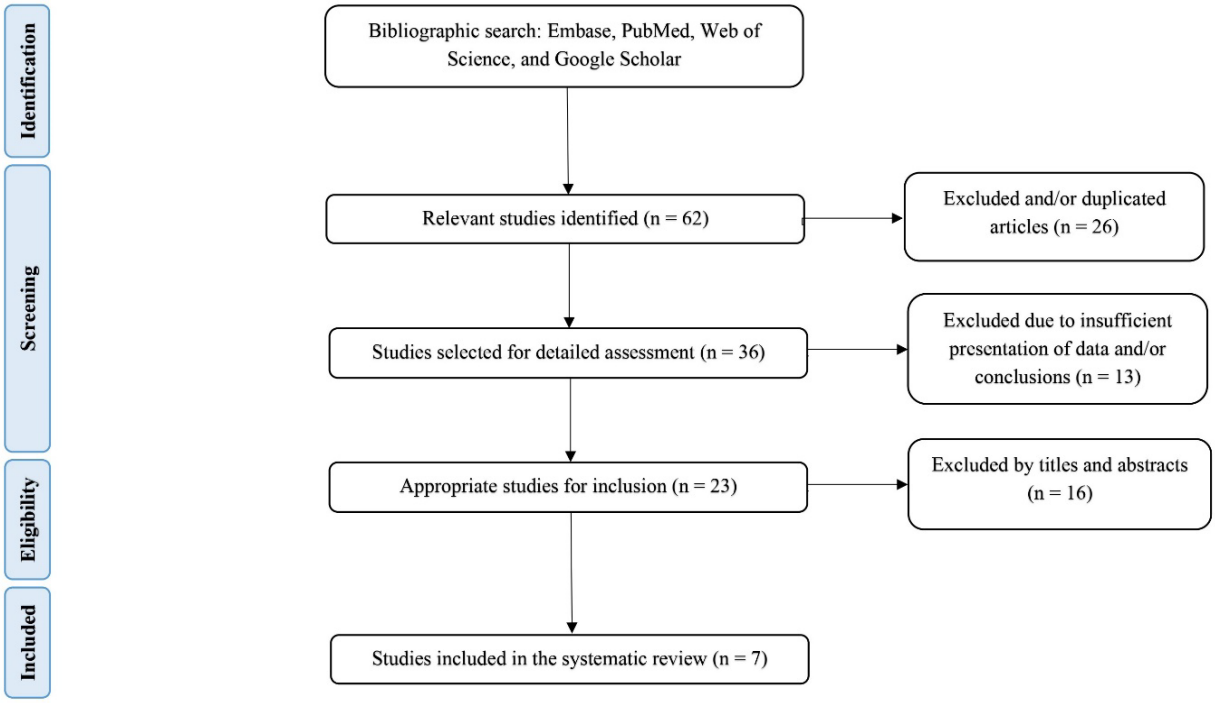

Figure 1. Flow diagram of literature search and study of selection for systematic review (PRISMA flow chart)

Studies on the immune system in Spain and the United States found no changes in inflammatory markers, blood levels of pro-inflammatory cytokines, or prostaglandin E2.[12,13] Helper T cell counts and high-sensitivity C-reactive protein (hsCRP) increased in the supplement-taking group but decreased in the placebo-taking group. Although the American study reported reduced stomach discomfort, pain increases and developments can occur with aromatase inhibitor (AI) drugs.[14] In an American clinical trial, arthralgia improved in both groups according to the Brief Pain Inventory, as did average pain in women taking supplements.[15]

Many side effects of BC therapies have been studied, and it may be feasible to reduce these negative effects by taking *n*-3 PUFA supplements. Studies conducted in the United States and Brazil indicated that dietary supplements can, respectively, lower xerostomy, lessen bone reabsorption, and enhance general health.[13,16] Neoadjuvant CT therapy did not result in a reduction in therapeutic toxicity.

In studies that examined how *n*-3 PUFA supplementation affected lipid profiles, triglycerides went down, high-density lipoproteins (HDL) went up, short-term therapy worked better, and EPA and DHA levels went up. Arachidonic acid levels were also shown to be lower in the supplemented groups in the American trial, which is beneficial for the treatment of BC.[12] Both the Brazilian clinical trial and the Spanish study reported that the use of *n*-3 PUFA had no effect on body composition in the BC treatment.[11,13] Women with a BMI greater than 29 kg/m2 may benefit from supplementation to enhance their lipid profile or reduce DHA-induced breast density.[17]

DISCUSSION

Immunity is one of the factors that directly stops tumors from growing, becoming resistant, and spreading. In a Brazilian clinical trial, supplementing with *n*-3 PUFA kept the amounts of hsCRP and helper T cells in the blood about the same as they were at the start. Although the cytotoxic T-lymphocytes, even in the placebo group, did not alter, it is probable that they are compromised given the decline in helper T cells. In spite of this, *n*-3 PUFA supplementation seems to have a good impact on adaptive immunity, assisting in preventing immunosuppression carried on by surgery and lowering the risk of metastasis.[12]

n-3 PUFA is thought to be an anti-inflammatory agent because it affects the production of pro-inflammatory cytokines and decreases the production of interleukin-6 and tumor necrosis factor alpha.[16] However, in the American clinical trial, supplementation did not reduce the tumor necrosis factor-2 receptor and interfered little with interleukin-6.[18]

Table 1. Characteristics of selected studies on the effect of Omega-3 polyunsaturated fatty acid supplementation in the treatment of patients with breast cancer

Author, Year, Country	Type of study	Study population (N, Age, BMI)	Objective	Treatment	Supplementation Dose (Time)	Main results
Darwito et al., 2016, Indonesia	Randomized, double-blind, controlled	48, 25–60 years	The effect of *n*-3 PUFA supplementation on Ki-67, VEGF, and OS expression in patients with BC	Standard NeoCT, CAF and mastectomy	1 g/day of *n*-3 PUFA COP (For 51 days).	- Significant reduction in Ki-67 and VEGF expression in supplemented patients ($p<0.001$). - Improved OS and PFS ($p=0.048$ and $p=0.015$).
De la Rosa Oliva et al., 2019, Mexico	Randomized, double-blind trial	53, 18–80 years, majority obese	To assess the impact of *n*-3 PUFA on LABC women's toxicity, side effects, body composition, CP, and QOL.	NeoCT	2.4 g/day of *n*-3 PUFA EPA 1.6g and DHA 0.8 g (3-6 months).	- No change in body composition, CP, or NeoCT toxicity in the supplemented group. - Only xerostomia improved significantly after supplementation ($p=0.0001$).
Hershman et al., 2015, USA	Randomized double-blind multicenter study	249, post-menopausal	To investigate the effects of *n*-3 PUFA supplementation on pain and stiffness in women with early stage BC.	Hormonal adjuvant with AI	3.3 g/day of *n*-3 PUFA; 560 mg of EPA + DHA in a 40:20 ratio (For 24 weeks).	- Lower triglyceride levels ($p=0.01$) and higher HDL levels ($p=0.007$) in the supplemented group. - No significant difference in HDL levels between groups in the long term. - Improvement in arthralgia in both groups.
Hutchins-Wies et al., 2014, USA	Double-blind randomized pilot study	31, 48–84 years, 58% obese	To investigate the association between high-dose *n*-3 PUFA supplementation in BC patients with AI	Hormonal adjuvant with AI	7 capsules/day containing 2520 mg EPA, 1680 mg DHA (For 3	- Arachidonic acid and the *n*-6 PUFA/*n*-3 PUFA ratio reduced in the supplemented group ($P<0.05$).

			therapy and decreased bone resorption.		months).	- Inflammatory markers were unaffected; - Higher BMI was related with elevated hs-CRP (P=0.003). - Reduced bone resorption in the supplemented group compared to placebo (P<0.05).
Lustberg et al., 2017, USA	Randomized, double-blind, controlled	35, post-menopausal, mean 59.5 years	To determine *n*-3 PUFAs' anti-inflammatory actions and decrease of symptoms of AI decrease.	Hormonal adjuvant with AI	4.3 g/day of *n*-3 PUFA (For 24 weeks).	- Joint pain was similar in both groups at the start of therapy (p=0.79). - Increased Functional Well-Being after supplementation (p<0.05). - Significant increase in CBR in the supplemented group (p<0.001).
Sandhu et al., 2015, USA	Longitudinal randomized study	241, 35-75 Years, 50% obese	To determine if *n*-3 PUFAs have anti-inflammatory properties and may relieve AI symptoms.	Chemotherapy (Tamoxifen and Raloxifene)	1,860 mg EPA + 1,500 mg of DHA per day (For 24 months).	- DHA reduced absolute breast density in those with BMI >29 kg/m^2 (p=0.0076). - EPA had no effect on breast density.
Shen et al., 2018, USA	Multicenter randomized controlled trial	249, mean 59 years, mean BMI 28.8 kg/m^2	To analyze *n*-3 PUFA supplementation for AI arthralgia.	3.3 g/day; 560 mg EPA plus DHA in 40:20 ratio.	3.3 g/day; 560 mg EPA + DHA in 40:20 ratio (For 24 weeks).	- At 24 weeks, patients with BMI 30 kg/m^2 who were supplemented showed a significant decrease in most significant BPI pain, average pain, and interference (p=0.02; p=0.002; p=0.009). - There was no improvement at 12 weeks, even in the supplemented group.

AI: Aromatase Inhibitors; BMI: Body Mass Index; BC: Breast Cancer; BPI: Brief Pain Inventory; CP: Cardiometabolic Profile; CAF: Cyclophosphamide, adriamycin, and 5-fluorouracil; CAT: Catalase; CLO: Cod liver oil; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic acid; GRx: glutathione reductase; HDL: High-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; QOL: Quality of life; LABC: Locally advanced breast cancer; NeoCT: Neoadjuvant Chemotherapy; N: number; *n*-3 PUFAs: Omega-3 polyunsaturated fatty acids; *n*-6 PUFA: Omega-6 polyunsaturated fatty acids; OS: Overall Survival; PFS: Progression Free Survival; USA: United States of America; VEGF: Vascular Endothelial Growth Factor..

The increased inflammatory state can also be generated by CRP, which, according to a Brazilian clinical trial,[12] is commonly produced in the acute phase. In their study, the supplemented patients had more regulated CRP, which stayed close to the baseline level.

Diet is crucial for both prevention and treatment, in addition to playing a significant role in both. One of its features is the ability to control the side effects of therapy, metabolic and catabolic changes caused by cancer, and problems like oxidative stress and immune-inflammatory regulation. This is done to reduce complications, treatment time, and mortality.[19] Dietary supplements were used by survivors of BC to enhance and maintain their overall health, as well as to supplement their diets.[20]

Supplementation with *n*-3 PUFAs improved both groups with and without arthralgia; however, it is difficult to determine if treatment helps with this symptom. The pain response was the same in all groups, demonstrating that supplementation beyond a certain level does not give more benefits, even in a clinical trial in the United States using a larger dose than the earlier studies.[18]

In the American study, patients at high risk for fractures reported bone reabsorption within the first six months of AI therapy.[13] However, bone remodeling markers remained stable in the placebo group at the beginning of treatment, which was unexpected and may have been due to ineffective placebo use or calcium and vitamin D supplements provided to patients. Even when compared to the placebo group, high-dose *n*-3 PUFA supplementation over a three-month period was successful in reducing bone reabsorption.

Hematological toxicity is a prominent side effect of Neoadjuvant CT; therefore, in the Spanish study, consuming *n*-3 PUFAs during CT had no protective impact on toxicities but showed a substantial improvement in the Xerostomy of the supplemented group.[16] In the Indonesian study, supplementation with *n*-3 PUFAs was associated with an improvement in disease-free survival and overall survival based on Ki-67 index analyses, as well as in BC survival and treatment response, owing to a decrease in vascular endothelial growth factor.[11]

A significant reduction in triglyceride levels and an elevation in HDL were observed in the supplemented group in an American clinical trial, indicating patient adherence and the anticipated effect of *n*-3 PUFAs. The HDL levels in both groups were similar after 12 weeks. Since most of the group the study examined had an unfavorable lipid profile, further research on this long-term comorbidity in BC survivors is recommended. Triglycerides increased and HDL decreased in both groups in the Spanish study, suggesting the need for further studies on the effects of *n*-3 PUFAs and the ideal dose amount.[16] Before beginning CT, the majority of the patients studied in the Spanish study had a low muscle mass and a high body fat percentage.[16] Both the skeletal muscle index and lean mass increased in both groups over the course of treatment. The only groups whose fat mass decreased were those who took supplements. According to clinical practice recommendations, taking calcium and vitamin D supplements is advised for certain groups of patients with BC whose bone density may be affected by aromatase inhibitors, androgen deprivation treatment, or chemotherapy-induced menopause. The recommended dosages for calcium are 1,000–1,500 mg and for vitamin D, 10–25 μg.[21,22] Based on practice in non-cancer settings, it was expected that supplements would improve bone health and not harm patients with BC.

Triple-negative BC (TNBC) may benefit from the antitumor effects of DHA and its metabolite 4-OH-DHA.[23] *n*-3 PUFAs have a supplementary role in chemotherapy for patients with TNBC as they can make paclitaxel more effective.[24] The overall survival rate for TNBC patients has not increased after huge efforts in therapy. Patients with TNBC receiving therapy may benefit from taking supplements containing *n*-3 PUFAs due to their anti-tumor properties in the diet. For patients with TNBC, we presently recommend *n*-3 PUFAs supplementation as an alternative to DHA or EPA monotherapy. Due to the distinct modes of action of DHA and EPA, further studies are necessary to determine the optimum dosage and ratio of each to optimize their positive effects in TNBC.[25,26]

In the examined studies, a lack of clarity regarding the correct dosage of the supplement and the use of a placebo to reduce bias in data processing were identified as limitations. Furthermore, vital metabolic characteristics that may interact with *n*-3 PUFA but were not identified or evaluated in a number of studies include BMI, lipid profile, physical activity habits, and the patient's diet. Furthermore, studies were not carried out throughout the course of the treatment.

CONCLUSION

In addition to being an antioxidant, *n*-3 PUFA supplements have been shown to help patients with BC in other ways, such as by increasing their chance of survival, lowering side effects (like xerostomy and bone reabsorption), improving their lipid profile, and increasing breast density. The analysis of supplementation in AI treatment was found to be a common goal across some studies. All studies involved 24 weeks of therapy for the improvement of arthralgia; the only variation was the dose, which

varied between the studies (4.3 g/day in one and 3.3 g/day in the others), and the outcomes were inconsistent.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENT

None.

FUNDING

None.

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How to Cite This Article

Vityala S, Kanteli KP, Vityala Y, Zhumabekova A, Vipin. Effects of Supplementation with Omega-3 Polyunsaturated Fatty Acids as an Adjuvant Therapy in the Treatment of Patients with Breast Cancer: A Systematic Review. Arch Breast Cancer. 2023; 10(4):323-30.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/765