Implications of dietary ω-3 and ω-6 polyunsaturated fatty acids in breast cancer (Review)

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Abstract. Breast cancer represents one of the most common forms of cancer in women worldwide, with an increase in the number of newly diagnosed patients in the last decade. The role of fatty acids, particularly of a diet rich in ω-3 and ω-6 polyunsaturated fatty acids (PUFAs), in breast cancer development is not fully understood and remains controversial due to their complex mechanism of action. However, a large number of animal models and cell culture studies have demonstrated that high levels of ω-3 PUFAs have an inhibitory role in the development and progression of breast cancer, compared to ω-6 PUFAs. The present review focused on recent studies regarding the correlation between dietary PUFAs and breast cancer development, and aimed to emphasize the main molecular mechanisms involved in the modification of cell membrane structure and function, modulation of signal transduction pathways, gene expression regulation, and antiangiogenic and antimetastatic effects. Furthermore, the anticancer role of ω-3 PUFAs through the modulation of microRNA expression levels was also reviewed.

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Contents

1. Introduction

Breast cancer is a highly prevalent cancer in women worldwide, with ~1.6 million new cases diagnosed in 2015 (1). Globally, the incidence of breast cancer appears higher in industrialized countries, with the majority of cases being observed in Western Europe, Australia and New Zeeland, and North America (2). According to the National Institute of Statistics, 90% of women have their disease diagnosed in an advanced form, which dramatically decreases their chances of survival and their quality of life (3-5).

Breast cancer incidence is further increased as a response to multiple toxic environmental exposures or the presence of certain environmental factors, including radiation, mutagens or carcinogens (6,7). Meanwhile, epigenetic and genetic alterations may occur due to an unbalanced diet (1). Mammary cancer development and progression is directly affected by dietary habits and environmental exposure (1,6,8,9). Advances in new generation technologies, particularly in the fields of transcriptomics and metabolomics (10,11), have markedly facilitated the pursuit to elucidate the influence of diet at the molecular level (12). This may eventually contribute to the health evaluation for particular nutritional components,

with the final purpose of developing novel functional food products (12,13).

Presently there are a broad range of ongoing nutrigenomics studies focusing on detecting the mechanisms on which nutrient and gene interactions are based. Such studies may lead to the identification of genetic variants used for the discovery and development of novel biomarkers for specific and personalized diet prescriptions for each patient (14,15). A classic example is related to the Mediterranean diet, which is associated with reduced mortality rates for a wide range of pathologies, such as cancer (8). According to this, the increased olive oil consumption in a Mediterranean diet is linked to a reduced risk of breast cancer (16-18), due to the beneficial actions of polyunsaturated fatty acids (PUFAs). The main PUFAs are presented in Fig. 1. Therefore, the favorable effects of PUFAs have been demonstrated by epidemiological and experimental studies worldwide. The purpose of the present review was to summarize these findings.

2. ω-3 and ω-6 fatty acid balance in a healthy diet

It is well known that modern society diets are dominated by processed foods and vegetable oils with high levels of ω-6 and low levels of ω-3 PUFAs (19). A proportion of 2:1 for the case of ω-6:ω-3 PUFAs is believed to have been present in our ancestors' diet, a ratio that today has been markedly altered to 10:1 because of unhealthy dietary habits (14). Overconsumption of ω-6 PUFAs, and an increased proportion of ω-6:ω-3 PUFA ratio observed in general in Western diets, leads to the activation of pathogenesis mechanisms for a wide range of pathologies (Fig. 2), including cardiovascular diseases, metabolic or immune pathologies, and cancer (14,20). Thus, the risk of cancer may be abridged by limiting the consumption of foods containing ω-3 fatty acids (21,22).

For elongation and desaturation reactions, there is a competition for the same enzymes between the two types of fatty acids. High levels of ω-6 PUFAs result in an inhibition of the elongation and desaturation of ω-3 PUFAs (20-22). This competition between ω-3 and ω-6 PUFAs reveals the importance of low ratios of ω-3:ω-6, compared to the individual fatty acid concentrations in human organisms (21-29).

3. Implication of ω-3 and ω-6 fatty acids in breast cancer

The role of a fatty acid-rich diet in the development and progression of breast cancer is not well understood and remains challenging, particularly since the information from human studies is limited. *In vitro* cell culture investigations or *in vivo* animal models have demonstrated the tumor suppressive role of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); however, the inhibitory role of ω-3 PUFAs in cancer is yet to be fully elucidated and requires further investigation (3,23,24).

PUFAs are essential nutrients, and include ω-6 fatty acids, such as linoleic and arachidonic acids (AA), as well as ω-3 fatty acids, including EPA and DHA acids. They have been demonstrated to have notable roles in modulating key cellular and molecular processes (Tables I and II) due to the fact that they are essential precursors of the cell membrane and interfere with other mediators of the inflammatory response (25,26). By adapting the fatty acid composition of the cells, a wide range of aspects related to cell metabolism may be controlled (24,25).

Despite their distinct physiologic and metabolic characteristics, ω-6 and ω-3 PUFAs cannot be endogenously produced by the human body, and thus must be obtained from the diet; however, these should preferably be obtained in the correct ratio (21). This has been supported by multiple epidemiological studies, where a reduced ratio of ω-6:ω-3 PUFAs has been indicated to have beneficial effects (25-27). Studies have also demonstrated that a modern diet is related to estrogen receptor (ER) negative breast cancer risk among taller women (≥160 cm tall) (28).

EPA and DHA are present in marine organisms, particularly in ocean fish. According to a 2011 United Nations report, global fish consumption increased with a yearly average of 17 kg/person (1,30-32). In the nutritional etiology of breast cancer, ω-3 fatty acids of fish origin have been demonstrated to have a significant role as protective factors, being associated with a 14% reduction in the risk of developing this malignancy (29-31). When comparing tumor and normal breast tissue in terms of their fatty acid content, higher levels of ω-6 PUFAs were observed in malignant tissues (33). The study conclusion was that an increased expression level of the enzyme Δ-6 desaturase is desired, as well as an abundance of ω-6 PUFA precursors (32).

Preclinical studies have offered a higher understanding of the effects of PUFAs, particularly in the etiology of breast cancer (Fig. 3). These studies have attempted to explain the cancer-related preventive activity of ω-3 PUFAs (Table I), and the association between ω-6 PUFAs and procarcinogenic effects (Table II) in breast malignancies (18), leading to the alteration of gene expression patterns, as well as dysregulations of microRNA (miRNA) sequences. PUFAs were demonstrated to have effects on the composition of the plasma membrane (18,33,34), increased cellular oxidative stress (14), gene expression modifications (35,36), alterations to intracellular signaling pathways (37,38), antiangiogenic and antimetastatic activity (39-43).

4. Modifications of cell membrane structure and function

Cell membrane integrity and alterations in signal transduction are important cellular processes in which ω-3 PUFAs are involved, and these cellular changes lead to reduced cell proliferation, the induction of apoptosis and an increased degree of unsaturation (38). Cell membrane structures, their fluidity and permeability, are affected in a notable manner by higher densities of ω-6 fatty acids (44).

High concentrations of ω-6 PUFAs have a potent effect on cell functions by damaging different ion transporters and channels, such as the ones for Ca^{2+} (38). Increased amounts of ω-6 PUFAs reduce the number of Ca^{2+} channels (45), which damages the fluidity of membranes and affects the function of specific integral and membrane-bound proteins (45-47).

The incorporation of ω-3 PUFAs, particularly EPA and DHA, is able to modify the degree of lipid peroxidation in cell membranes, altering the formation of lipid rafts and suppressing raft-associated cell signal transduction (37). The susceptibility to peroxidation is determined by the degree of unsaturation of the membrane phospholipid fatty acids. High unsaturation causes increased cell oxidative stress and disrupts

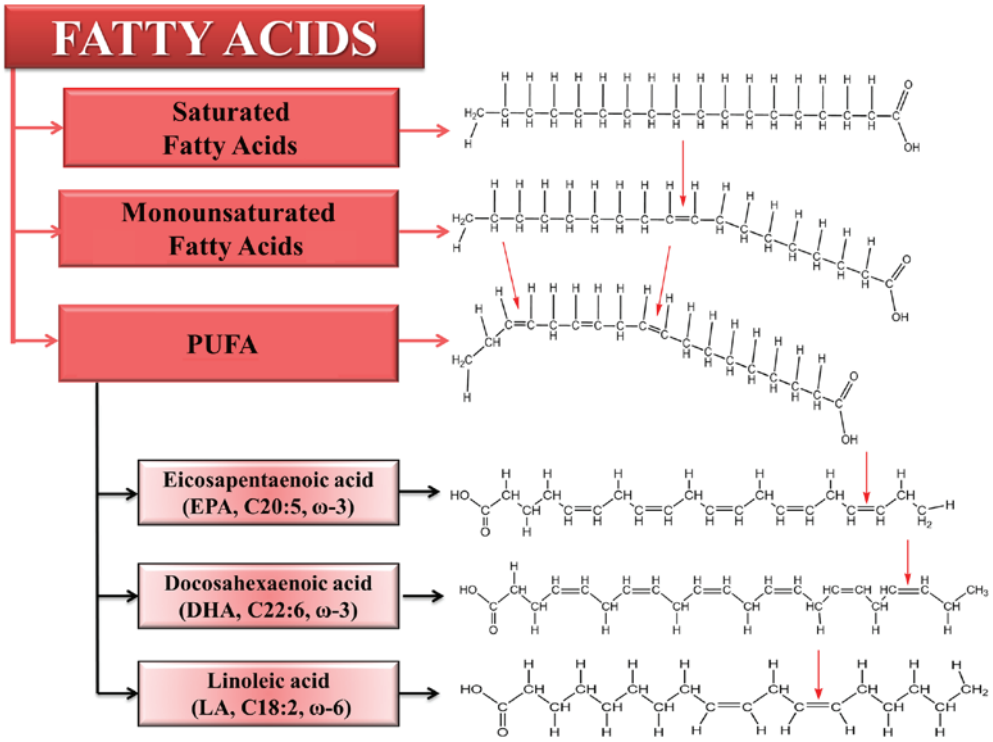

Figure 1. Types of fatty acids with emphasis on the main class of PUFAs. The difference between fatty acids is determined by the presence of double bonds. Eicosapentaenoic acid and docosahexaenoic acid are characterized by the double bond in three positions, also known as ω-3 PUFAs, while linoleic acid has the first double bond in position 6, also known as ω-6 PUFAs. PUFA, polyunsaturated fatty acid.

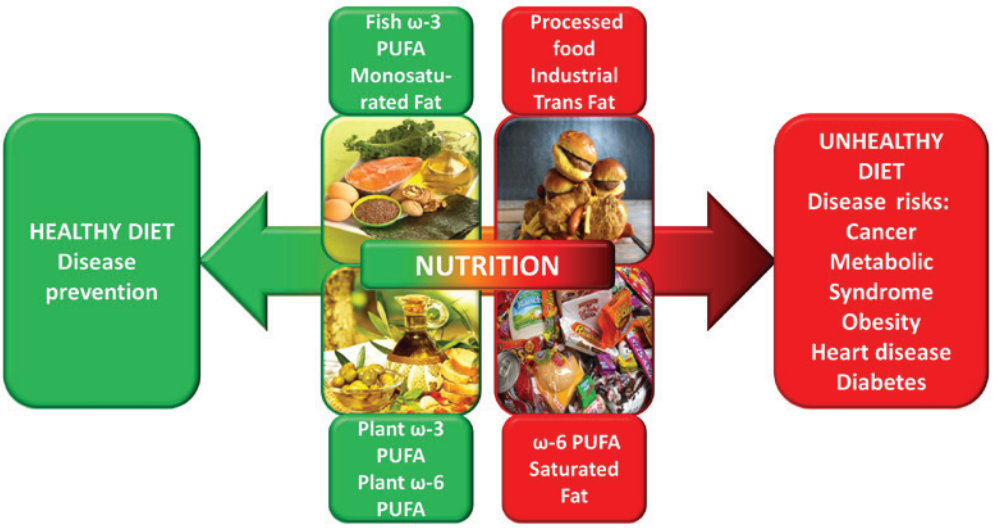

Figure 2. Impact of dietary PUFAs in disease prevention or risk. The diagram emphasizes the importance of a balanced diet to maintain a healthy condition. The human body is unable to synthesize ω-6 and ω-3 PUFAs and they may only be obtained from a balanced diet. The amounts and balance of PUFAs in the diet are important for maintenance of and improving health due to their role in the body's functions, including immune and inflammatory responses, blood lipid levels, blood pressure and blood clotting. PUFA, polyunsaturated fatty acid.

physiological signaling pathways by leading to malignant transformation (48,49).

5. Modulation of signal transduction pathways

A clinical study revealed that ω-3 and ω-6 PUFAs have similar biochemical activity and require the same elongase, desaturase, cyclooxygenase and lipoxygenase enzymes (50). Enzymatic conversion into eicosanoids, compounds with notable roles in cell differentiation and growth, is among the most important cellular functions of PUFAs (50-60). Studies have demonstrated that a diet rich in ω-6 PUFAs has strong promoting effects on breast cancer development (50-59). The carcinogenic effects of high levels of ω-6 PUFAs were correlated with increased ratios of eicosanoids (48). Studies have also indicated that eicosanoid compounds, including prostaglandins (PG), thromboxane (TX), leukotrienes (LT), hydroxyl fatty acids and lipoxins, are produced in higher quantities than

Table I. Principle mechanisms of ω-3 polyunsaturated fatty acids in breast cancer.

Mechanism	Key target/gene	(Refs.)
Changes of cell membrane properties	Bcl-2; procaspase-8	(18,37)
Modulation of intracellular signaling pathways	FAK, NF-κB, MAPK, COX-2	(33,82)
Regulation of gene expression	EGFR, Her-2, Erk 1/2, AKT PTEN, Bcl-2, PDCD4, NF-κB	(70,110-112)
Antimetastatic and antiangiogenic activity	EZH2, VEGF, E-cadherin	(36,103)
Regulation of miR expression	miR-21, miR-26a/b, miR19b, miR146b, miR183	(34,42,110)

Bcl-2, B-cell lymphoma 2; FAK, focal adhesion kinase; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; COX-2, cyclooxygenase 2; EGFR, epidermal growth factor receptor; Erk, extracellular signal-regulated kinase; PTEN, phosphatase and tensin homolog; PDCD4, programmed cell death 4; EZH2, enhancer of zeste 2; VEGF, vascular epithelial growth factor; miR, microRNA.

Table II. Principle mechanisms related to pro-carcinogenic effects of ω-6 polyunsaturated fatty acids in breast cancer.

Mechanism	Key/target gene	(Refs.)
Lipid peroxidation, DNA adducts	Redox-cycling of 4-hydroxyestradiol	(21,26,37)
Regulation of gene expression	p21WAF1/CIP1, MAPK, TGF-β, TLR	(21,42)
Antimetastatic and antiangiogenic activity	VEGF, FGF, HIF-α, E-cadherin	(21,41,122)
Regulation of miR expression	MiR19b, miR146b, miR1835p, let-7a, miR-23b, miR-27a/b, miR-21, let-7	(42,109)

MAPK, mitogen-activated protein kinase; TGF-β, transforming growth factor-β; TLR, toll-like receptor; VEGF, vascular epithelial growth factor; FGF, fibroblast growth factor; HIF-α, hypoxia-inducible factor-α; miR, microRNA.

those of ω-3 PUFAs, due to the high amounts of ω-6 PUFAs present in Western diets (20,51,52).

Eicosanoids derived from ω-6 PUFAs have been demonstrated to have pro-inflammatory and pro-carcinogenic effects as compared to ω-3 PUFA-derived lipid mediators (48,53). In obese individuals, ω-6 PUFA-derived eicosanoid levels were observed to be increased, which stimulated breast cancer initiation, invasion and metastasis (54).

Cyclooxygenase (COX)-2 is an enzyme that serves an active role in prostaglandin synthesis, and increased levels are associated with inflammation in all subtypes of breast cancer (55-57). The COX and lipoxygenase (LOX) enzymes are key factors for the enzymatic production of PG and LT (58). ω-3 fatty acids compete with ω-6 fatty acids for COXs for the production of eicosanoids, and a suppressive effect on COX-2 expression has been observed (59-62). COX enzymes produce two-series prostanoids, including PG and TX, and four-series LT, including LTC4, LTD4, LTE4 and LTF4, while LOX enzymes produce hydroxyeicosatetraenoic acids (48,63). In a transgenic mouse model expressing human epidermal growth factor receptor 2 (HER2)/neu, treatment with dietary ω-3 PUFAs inhibited breast tumor cell proliferation and upregulated COX-2 expression (64).

In breast tissue, the metabolites of the arachidonate 5-lipoxygenase pathway are able to induce tumorigenesis and sustain breast cancer progression (65-68). A study on LOX genetic variants combined with ω-6 PUFAs revealed a significant increase of breast cancer risk (14). According to a study on the breast cancer cell line MCF-7, DHA upregulated syndecan-1 (a component of the extracellular matrix) expression and promoted apoptosis via downregulation of MEK/extracellular signal-regulated kinases (Erk)/Bad signaling (69). Another study indicated that ω-3 PUFA treatment reduced the effect of E2 on epidermal growth factor receptor (EGFR), Erk1/2 and AKT, and upregulated G protein-coupled estrogen receptor 1 (GPER1)-cyclic adenosine 5'-phosphate (cAMP)-protein kinase A (PKA) signaling (70). In MDA-MB-231 breast cancer cells, linoleic acid (LA) induces focal adhesion kinase (FAK) activation and cell migration by modulating a FAK-dependent pathway (33).

6. Regulation of gene expression

Evidence-based preclinical studies and epidemiologic data consistently support the anticancer effect of ω-3 PUFAs based on their capacity to target key genes altered in breast cancer (71-78). EGFR and HER2 are cell surface receptor tyrosine kinases, representing key therapeutic targets in breast cancer management (39,79,80). ω-3 PUFAs may represent a dietary approach for controlling growth factor-mediated carcinogenesis, by activating tyrosine kinase transduction pathways, p38 mitogen-activated protein kinase activation and apoptosis induction (71). Restoring EGFR signaling was observed in many breast cancer cases as being correlated with dietary habits (72), while an apoptotic effect of DHA from marine sources was found by targeting EGFR pathways in malignant breast tissue (38). In MCF-7 and T47D cells, ω-3 PUFA treatment may initiate pro-apoptotic signaling of estrogen by increasing the GPER1-cAMP-PKA signaling response, and inhibiting EGFR, Erk1/2 and AKT activity (70).

Overexpression of the tyrosine kinase receptor, ErbB2/HER2/neu, occurs in 25-30% of invasive breast cancer cases with poor prognosis (73). HER2/neu is an oncogene that is overexpressed in many types of cancer, with an important role in development, progression and chemosensitivity of tumors; studies have demonstrated that it is downregulated by ω-3 PUFAs (73,74).

As described in previous studies, ω-3 PUFA effects are also observed at the translational and post-translational level. In mammary cancer cell lines (MCF10A, MCF7, T47D and MDA-MB-231), ω-3 PUFAs may modulate the protein expression of the transcription regulator enhancer of zeste 2 polycomb repressive complex 2 subunit (36), while the activation of peroxisome proliferator-activated receptors (PPAR) was induced in the same type of cancer cells (75). PPARs (PPARα, PPARγ and PPARβ/δ) are ligand-activated transcription factors of the nuclear hormone receptor superfamily involved in glucose and fatty acid metabolism (76). This PUFA-mediated PPAR activation exerts an effect on several molecular mechanisms, including apoptosis and autophagy (36,81-84). PPARβ expression was reduced by a ω-3 PUFA-rich diet in mammary tumors, while in other circumstances, the expression of other PPAR mRNA was modulated, leading to the inhibition of breast cancer cell growth (35). In MCF-7 breast cancer cells, ω-3 PUFA ethanolamides, docosahexaenoyl ethanolamine (DHEA) and eicosapentaenoyl ethanolamine (EPEA), augmented the expression of PPARγ, inducing autophagy (77). At the same time, in MCF-7 and MDA-MB-231 cells, AA decreased the Erk1/2 phosphorylation level, and positively modulated PPARγ and PPARα expression (78). In MCF-7 cells, DHEA and EPEA stimulated the expression of PPARγ as well as PPAR response element-dependent transcription by upregulating phosphatase and tensin homolog (PTEN) expression, while inhibiting the AKT-mechanistic target of the syntetic agent rapamycin via mTOR pathway (77). In another study, MCF-7 cells treated with DHA from a cultured microalga demonstrated increased apoptosis via the upregulation of the B-cell lymphoma 2 (Bcl-2)-associated X protein/Bcl-2 ratio, and inhibition of cell growth (79). In a rat model of breast cancer, dietary ω-3 PUFAs increased the apoptotic index in tumor cells (80,81).

AA induces nuclear factor (NF)κB-DNA binding activity through a phosphoinositide 3-kinase- and AKT-dependent pathway (82). ω-3 PUFAs were demonstrated to modulate total AKT expression (83). In contrast with ω-6 PUFAs, ω-3 PUFAs reduced COX-2 and NFκB expression, decreasing the level of cell invasiveness (84). LA induces FAK and NFκB activation, migration and invasion in MCF10A human mammary epithelial cells (85).

Another fundamental process related to carcinogenesis is cell proliferation. Ki-67 is a nuclear protein used as a prognostic or predictive marker in breast cancer (86). Treatment with α-linolenic acid (ALA)-rich flaxseed oil in rats induced a decrease in tumor size, together with decreased Ki-67 levels (87,88). Proliferating cell nuclear antigen (PCNA) is also considered by researchers to be a potential prognostic marker in breast cancer (89). It has been demonstrated that diets rich in ω-3 PUFAs reduce the percentage of proliferating tumor cells by decreasing the expression levels of PCNA (90).

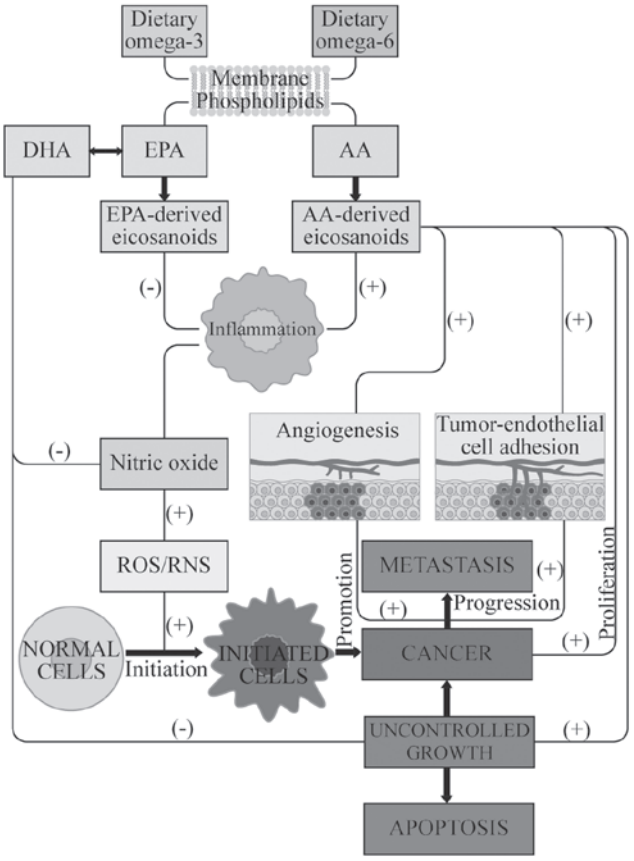

Figure 3. Potential mechanisms of action of ω-3 and ω-6 PUFAs in tumorigenesis, related to the activation of inflammation and production of ROS, which finally leads to the activation of cell proliferation, a predisposition for carcinogenesis and distant metastasis in breast cancer. PUFAs may stimulate (+) or suppress (-) pathways. Dietary ω-3 PUFAs suppress the inflammatory process, stimulate apoptosis, inhibit metastasis and tumor proliferation, and also upregulate the gene expression of antioxidant enzymes. In tumor cells, phospolipase A2, cyclooxygenase 2 and lipoxygenases are overexpressed and induce the overproduction of AA (20:4n-6)-derived eicosanoids, which lead to inflammatory processes. The production of nitric oxide is elevated in inflammation and is involved in the initiation and the progression of carcinogenesis. Nitric oxide may be responsible for tumor growth and metastasis due to its ability to stimulate tumor cell angiogenesis. ω-3 PUFAs reduce the desaturation and elongation of linoleic acid (18:2n-6) to AA. ROS, reactive oxygen species; PUFA, polyunsaturated fatty acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; RNS, reactive nitrogen species.

Studies have indicated that PUFAs have an effect on lipid metabolism in mammary tumors by modifying the expression levels of fatty acid binding protein 5, cluster of differentiation 36, FAS and ER genes (91). The alterations of gene expression levels were demonstrated to be time-dependent in MDA-MB-231 cells following ALA treatment, accompanied by low levels of ID1, and increased JUN, NME1 and thrombospondin 1 expression (92). A significant increase of Erk1/2 and AKT phosphorylation levels was observed in MCF-7 cells treated with a combination of tamoxifen and ω-3 PUFA, compared to ω-3 PUFA alone (93). Additionally, mammary tumor growth and Py230 cancer cell proliferation was inhibited by ω-3 PUFAs, independent of GPR120 signaling, suggesting that ω-3 PUFAs act in a Toll-like receptor 4-mediated fashion, or via peroxisome proliferator-activated receptors or other G protein-coupled receptors (94).

7. Antimetastatic and antiangiogenic activity

Different fatty acid compositions affect the affect the breast cancer carcinogenic mechanisms, in particular those associated with tumor growth, proangiogenic and metastatic capacities in breast cancer cells (95,96). In HT115 and MDA-MB-231, ω-6 PUFAs enhanced the expression of a metastasis-suppressor gene, nm-23 (97). Studies conducted on various animal models have demonstrated the effect of PUFAs in regards to cellular growth. A reduction in tumor growth and proliferative abilities caused by PUFAs was observed in an immunocompromised nude murine model of transplanted human breast cancer cells (98). A fish oil diet rich in EPA and DHA in a murine model of MDA-MB-231 human breast cancer cells led to the prevention of bone metastases (99).

The molecular mechanism by which the administration of PUFAs, alone or alongside other compounds, may affect the metastatic potential of tumors remains to be deciphered. The anti-proliferative and anti-invasion activity of DHA may be connected to alterations in the composition of fatty acids, which leads to damage to the membranes of tumor cells, and consequently reduction in metastatic potential (96,100,101).

A diet rich in fatty acids (DHA and EPA) of marine origin in patients with breast cancer was correlated with reduced mortality (102). ω-3 PUFAs lead to E-cadherin expression upregulation, while inhibiting the invasion mechanisms in mammary malignant cells (36), since the appropriate expression of E-cadherin is important in maintaining the integrity of intracellular adhesions (103).

In human breast tumor tissues, AA and cytosolic phospholipase A2 were demonstrated to be associated with the signaling activity of mTOR complex (C)1 and mTORC2, and with expression levels of vascular epithelial growth factor (68).

8. Regulation of miRNA expression

The mechanisms by which dietary factors modulate the expression of miRNA in breast cancer cells have not been completely elucidated (104-106). Experimental studies have suggested that some nutrients, including ω-3 PUFAs (107-109), have anticancer effects through the modulation of miRNA expression levels (110-113). Previous studies have demonstrated extensive interactions between ω-3 PUFAs and miRNA in cancer, lipid metabolism and inflammation (105). Recent findings indicated that DHA, which has anti-inflammatory and anticancer effects, is able to downregulate miRNA-21, causing an increase in tumor necrosis factor α mRNA expression levels and, subsequently, triggering apoptosis in human cancer cells (106,107). High expression of miRNA-21 is strongly correlated with poor prognosis in breast cancer, demonstrating a negative impact on overall survival and disease/recurrence-free survival (104,106,108). As part of its mechanism of action, DHA treatment promotes inhibition of receptor-interacting protein 1 kinase and AMP-activated protein kinase-α, resulting in nuclear accumulation of Foxo3a, which, in turn, binds to the miRNA-21 promoter causing its transcriptional repression (107). Other studies have demonstrated that expression levels of certain miRNA, including let-7a, miRNA-23b, miRNA-27a/b, miRNA-21, let-7 and miRNA-320b, in breast cancer cell exosomes have been increased by DHA treatment (47-109). An *in vitro* study on mammary cancer cell models indicated that DHA treatment inhibited the expression of colony stimulating factor 1 and miRNA-21, supporting the evidence found by an *in vivo* study (110). In MCF-7 and MDA-MB-231 breast cancer cell lines, the promoter of miRNA-21 contains a NFκB binding element, which, in association with the DHA treatment, leads to decreased miRNA-21 expression levels by inhibiting NFκB activity (105,110). Although the mechanisms by which ω-3 PUFAs contribute to the altered expression of these miRNA remain unclear, some authors suggest that its direct targets are involved, together with other associated proteins, including PTEN, Bcl-2, programmed cell death 4 and NFκB (110-112).

A PUFA-enriched diet correlates with changes in circulating miRNA (upregulated miRNA include miRNA-18a, -19b, -106a, -130b, -192, -486-5p and -769-5p; downregulated miRNA include miRNA-125a-5p, -221, -328 and -330-3p) that may serve an important role in the PUFA dietary systemic effect (113). In a rat model of inflammation, dietary ω-3 and ω-6 PUFAs may alter the miRNA expression profile (42). Functional analyses of these changes in miRNA expression profiles have indicated that dietary PUFAs are implicated in the maintenance of immune homeostasis via the expression of miRNA (43). In same study by Zheng *et al* (42), it was demonstrated that ω-3 PUFAs suppress inflammation *in vivo* by inhibiting the expression levels of miR-18-5p, -19b-3p and -146b-5p.

In addition to inflammation homeostasis, ω-3 PUFAs have also been implicated in the downregulation of miRNA-26a/b expression, promoting the upregulation of 15-hydroxyprostaglandin dehydrogenase, which catalyzes the oxidation of the pro-inflammatory lipid mediator, prostaglandin E2, leading to a decrease in cell proliferation (34). DHA may positively modulate expression levels of miRNA related to lipid metabolism, including miRNA-30c and -192, in cancer and obesity (114-117). Studies in breast cancer have demonstrated that miRNA-30c negatively regulates NFκB signaling and cell cycle progression (118), while miRNA-192 inhibits cell proliferation (119). Knockdown of DICER in enterocyte Caco-2 cells exposed to DHA lipid micelles revealed multiple genes regulating lipid metabolism that are modulated by miRNA-30c and miR-192 (117). miR-33a and miR-122 expression levels in the liver are upregulated in rats with cafeteria-diet induced dyslipidemia; however, these levels are counteracted by the presence of ω-3 PUFAs *in vivo* (120).

The beneficial effects of ω-3 PUFAs extend to its related metabolites, such as Resolvin D1 (RvD1), which is a well-known anti-inflammatory agent that induces upregulation of miRNA-208a and miR-219 in *in vivo* transgenic mice overexpressing N-formyl peptide receptor 2 (121). A study by Krishnamoorthy *et al* (121) indicated that this RvD1-induced upregulation of miRNA-208a promotes increased secretion levels of the anti-inflammatory cytokine, interleukin-10, in human macrophages.

9. Conclusion

Dietary factors, such as fatty acids, have been recognized as influential factors in the activation of carcinogenic events or disease progression, and have been associated with a direct

connection to breast cancer prevention. PUFAs differentially inhibit mammary tumor development by inflicting modifications to the morphology of cell membranes, and influencing signaling pathways, gene expression and apoptosis. Observing the molecular mechanisms involved in the activity of dietary PUFAs on breast cancer development and progression suggests that dietary supplements, in combination with anticancer drugs, should be provided under medical supervision. The majority of studies recommend that patients consume a diet rich in ω-3 PUFAs, while reducing the intake of ω-6 PUFAs, particularly in the case of chemoprevention purposes. Therefore, modification of dietary habits, particularly regarding the choice and amounts of fats consumed, may be used as a strategy for breast cancer prevention. For better results in this field, additional clinical trials are required to evaluate the specific effects of PUFAs on breast cancer outcomes.

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