Breast Cancer RESEARCH

REVIEW

Role of dietary fatty acids in mammary gland development and breast cancer

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Abstract

Breast cancer is the most common cancer among women worldwide. Estimates suggest up to 35% of cases may be preventable through diet and lifestyle modification. Growing research on the role of fats in human health suggests that early exposure in life to specific fatty acids, when tissues are particularly sensitive to their environment, can have long-term health impacts. The present review examines the role of dietary fat in mammary gland development and breast cancer throughout the lifecycle. Overall, n-3 polyunsaturated fatty acids have promising cancer-preventive effects when introduced early in life, and warrant further research to elucidate the mechanisms of action.

Introduction

Cancer is one of the leading causes of mortality worldwide, having significant impact on individuals and healthcare systems. Breast cancer (BC) is one of the top five cancers contributing to overall cancer mortality worldwide, and the incidence is predicted to continue to rise [1-3].

Although the causes of BC are widely unknown, anthropometric, diet and other traits observed at specific stages of life have been associated with BC risk. Birth weights of 4 kg or more, height, level of obesity, early puberty onset and later age at first pregnancy or nulliparity have been positively correlated with BC risk [4-6]. These observations support the notion that timing and critical periods of development modify BC risk, which is also mirrored in experimental studies [7-9]. Epidemiological studies have provided early clues and highlight the impact that our environment, which includes dietary factors, has on BC risk.

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Asian women, who typically have a low rate of BC and a high level of fish oil consumption compared with western women, experience an increase in BC incidence as well as obesity after emigration to the West. In Asian women who have immigrated to the United States, BC rates increase to a level equal to westerners within a generation, and obesity increases twofold between first and second US-born generations [10-12]. This observation suggests that the environment, which includes changes to dietary habits, may contribute to an increase in BC risk and risk factors. Since this change was evident in the generation born post emigration, diet exposure as early as *in utero* should be considered a factor that modifies BC risk. Findings such as these provide evidence suggesting that early life exposure to environmental factors such as diet may modify disease risk later in life.

Dietary factors, including specific classes of fatty acids, may be important modifiers of BC risk. Dietary fat is composed of a complex matrix of fatty acids, with unique chemical and biophysical properties that underlie their impact on health and disease. Saturated fatty acids (SFA) (see Figure 1a), monounsaturated fatty acids (MUFA) (see Figure 1b) and trans fatty acids (TFA) (see Figure 1c) have all been found to be potentially associated with an increase in cancer risk in rodent models [13] and in humans [14,15]. Specific polyunsaturated fatty acids (PUFA), however, may have anticancer effects. There are two major classes of PUFA: omega-6 polyunsaturated fatty acids (n-6 PUFA) and omega-3 polyunsaturated fatty acids (n-3 PUFA). Linoleic acid (LA, 18:2n6) (see Figure 1d) and arachidonic acid (AA, 20:4n6) are the two most common n-6 PUFA in typical western diets [16,17] and have been suggested to have cancer-promoting effects. In contrast, n-3 PUFA may have anticancer effects. α-Linolenic acid (ALA, 18:3n3) (see Figure 1e) is the predominant form of n-3 PUFA in western diets [18]. The metabolism of ALA, involving sequential desaturation and elongation steps, gives rise to two important long-chain n-3 PUFA: eicosapentaenoic acid (EPA, 20:5n3) (see Figure 1f) and docosahexaenoic acid (DHA, 22:6n3) (see Figure 1g). In addition, EPA and DHA can be obtained directly from seafood and fish oils [19]. For a

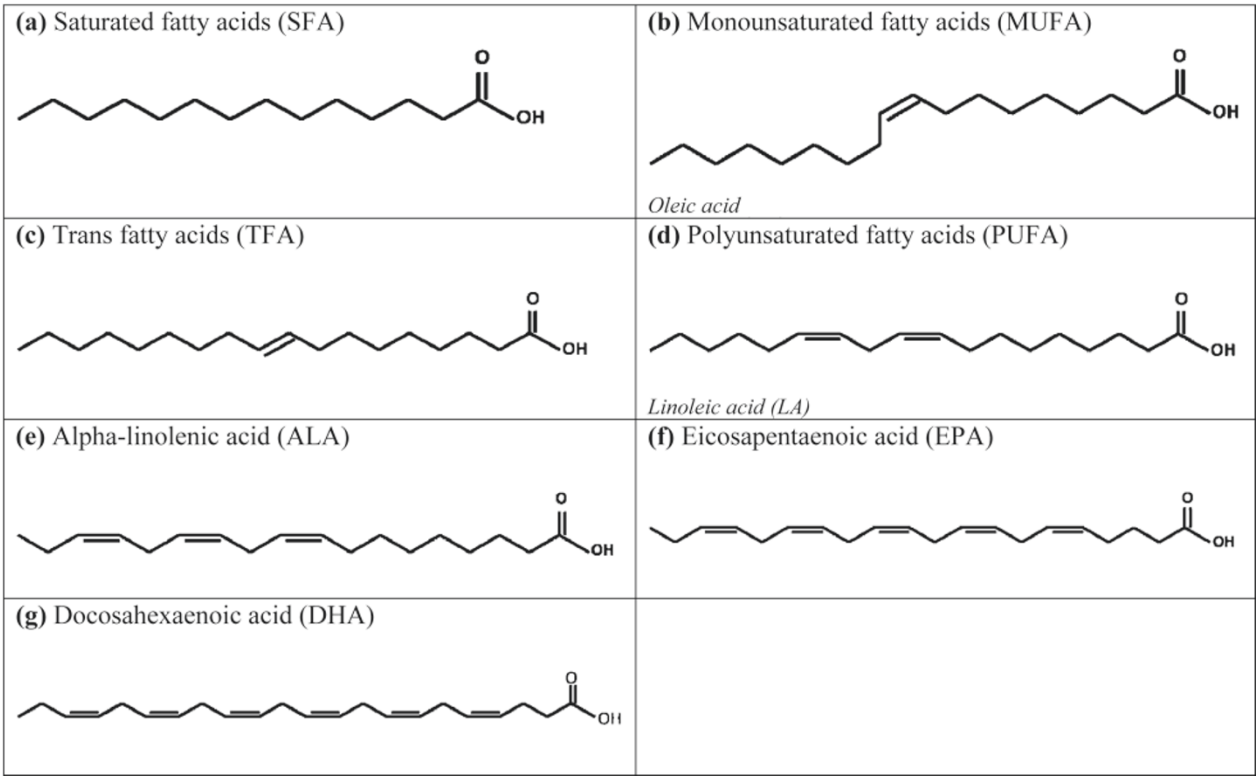

Figure 1. Representation of molecular connectivity of different dietary fatty acid classes. (a) Saturated fatty acids. **(b)** Monounsaturated fatty acids, specifically oleic acid. **(c)** Trans fatty acids. **(d)** Polyunsaturated fatty acids, specifically linoleic acid. **(e)** α-Linolenic acid. **(f)** Eicosapentaenoic acid. **(g)** Docosahexaenoic acid.

more in-depth look at fatty acid metabolism, see the article by Shanklin and Cahoon [20].

A growing body of research focusing on the role of diet in early life has emerged; in particular, on the consumption of specific fatty acids and cancer risk. The purpose of the present review is therefore to evaluate the linkages between dietary fatty acids and cancer risk at different life stages of the lifecycle and the contribution of specific families of fatty acids and their individual members. Attention will also be given to how specific fatty acids modify the development of the mammary gland (MG), which may underlie how fatty acids modify the BC risk.

Role of fatty acids in mammary gland development and impact on breast cancer risk

Development of the MG is unique and continues throughout life. The ductal branching system within the MG originates at the nipple with a primary duct that extends and branches posteriorly throughout the fat pad in childhood at a slow, gradual pace until the onset of puberty, at which point the process rapidly accelerates [21]. Although the rate of branching is reduced post puberty, it continues throughout the reproductive years of the female. At the ends of each ductal branch are zones of high cell proliferation called terminal ductal lobular units, which differentiate into lobuloalveolar units during pregnancy and later stages of development [21].

The development of the MG is comparable between humans and rodents, thus rodents are often used in MG-related research [21]. The equivalent structures for human terminal ductal lobular units and lobuloalveolar units in rodents are terminal end buds (TEB) and alveolar buds, respectively [10]. The highly proliferative structures have been identified as the initiation sites in tumorigenesis [21].

In humans, cessation of branching begins around 35 years of age or at pregnancy, when differentiation occurs and the gland prepares for lactation. Each stage may represent a sensitive developmental window during which exposure to environmental factors modifies BC risk.

Our understanding of mammary carcinogenesis continues to advance through basic research using rodent models [13,21-24]. Recent evidence suggests that timing of exposure to dietary fats is an important factor in modulating cancer risk at multiple stages, including *in utero*, prepuberty/puberty, as well as during pregnancy and lactation, which are probably periods most sensitive to dietary exposure [7-9]. The following sections detail

how dietary fatty acids may affect MG development at specific stages throughout the lifecycle.

In utero stage

In utero development may be influenced via maternal interaction and exposure to the surrounding environment. A direct link between the developing fetus and the environment is the transfer of placental nutrients from the maternal diet. Maternal nutrition is therefore of great importance in the development of the fetus, which includes the MG.

When pregnant rats were fed high-fat diets using oils high in n-6 PUFA, serum estradiol levels increased in the mothers and resulted in the female offspring having significantly higher incidence of mammary tumors (Table 1) [25,26]. The increase in tumor incidence was attributed to changes in the MG of the female offspring. The effects of the high n-6 PUFA diet were similar to animals injected with estradiol during pregnancy, which suggests that n-6 PUFA induces adipose cells to produce and release estrogen in the body, leading to the promotion of tumor growth [25,26]. Additionally, female offspring exposed to maternal high-fat diets had earlier menarche than controls, which is a marker of increased BC risk, and is associated with significantly higher numbers of TEB (Table 1) [25,26]. Moreover, the MG of female rodents exposed to estradiol or a high n-6 PUFA diet developed TEB that persisted longer, and with reduced differentiation to alveolar buds (Table 1) [25].

In a human study following pregnant mothers' diets and circulating fatty acids and hormone levels, PUFA had a significant positive association with levels of estrogenic compounds (Table 2) [27]. When long-chain n-3 PUFA levels were examined, however, a significant inverse relationship with estrogenic levels was found (Table 2) [27].

Combined, these factors linked to n-6 PUFA consumption potentially increase the risk of carcinogenesis by prolonging the presence of greater numbers of highly proliferative cells that are sites for tumorigenesis. When high-fat n-6 PUFA diets were co-supplemented with n-3 PUFA via fish oil during pregnancy in rats, a decrease in BC risk in the offspring was observed (Table 1) [28], suggesting that maternal intake of PUFA requires an optimal balance between n-6 PUFA and n-3 PUFA to mitigate the BC risk.

The opposing effects of these families of PUFA relate to their competition for similar enzymes involved in their metabolism, including desaturases, elongases and enzymes involved in eicosanoid synthesis such as cyclooxygenases and lypoxygenases. The metabolism of n-6 PUFA produces proinflammatory eicosanoids such as prostaglandin E_2, but the presence of n-3 PUFA inhibits their synthesis [29]. The ratio of n-6/n-3 PUFA is thus of considerable importance. There is some controversy as to whether or not this fatty acid ratio is truly important [30], but historical trends suggest that a lower n-6/n-3 ratio is potentially associated with a decreased incidence of cancer [31,32].

Birth to pubescence

Physical status at birth as well as early nutritional intake are potentially telling of future cancer risk. Studies have shown that high birth weights of 4 kg or more are positively associated with BC risk, nearly doubling the risk when compared with normal weights of 2.5 to 2.9 kg (Table 1) [5,33,34]. n-6 PUFA consumption has been shown to be positively associated with birth weight in humans [27].

Breastfeeding has been shown to reduce an infant's risk of developing BC before menopause by up to 35% (Table 1) [33]. The long-chain PUFA DHA, present in breast milk, is known to be important for supporting neuronal and visual development, constituting, on average, 2.88% of an infant's total energy (Table 1) [35]. As will be discussed, the presence or supply of DHA at this early stage of life may also impact on the long-term development of the MG and consequently modify future cancer risk. The supply of DHA is further modified by maternal intake of TFA, which may interfere with DHA synthesis, thus reducing the DHA concentration in breast milk (Table 1) [36]. As DHA plays an important role in fetal development, interactions such as these stress the importance of being aware of interactive effects between different fatty acids – particularly in the maternal diet, as negative effects on fetal development can result.

The literature on estrogenic effects during prepubescence is more complex than that for other developmental stages. Estrogen in rodent fetal development translates to an increase in BC risk [25,26], but studies in both humans [37] and rodents [8,38] indicate that estrogen may be protective in the prepubescent period. Rat studies have shown that continuous postnatal exposure to estradiol during the first 30 days after birth decreases the susceptibility of the MG to carcinogen-induced tumorigenesis (Table 1) [39,40]. Similar effects have been observed on the MG when estradiol exposure is replaced with high n-6 PUFA diets (Table 1) [8]. Additionally, fat intake and a high body mass index surrounding puberty, which is correlated with increased production of estrogens, have been linked to MG development [8]. It has been reported that a higher body mass index during childhood and adolescence reduces the risk of both premenopausal and postmenopausal BC (Table 1) [8,37,41,42]. Some studies, however, suggest no association exists between high body mass index during childhood or adolescence and BC risk [43]. Adding to the complexity of effects at this stage, higher childhood body mass index is linked to early

Table 1. Diet-related factors effecting mammary gland development in critical periods of development

Time period	Effect	Reference
In utero	n-6: decreased number of alveolar buds in female offspring	[25]
	n-6: increased incidence of mammary tumors	[25,26]
	n-6: earlier menarche of female offspring	[25,26]
	n-6: increased number and duration of TEB in female offspring	[25,26]
	n-3: decreased BC risk in female offspring	[28]
Lactation	Breastfeeding decreased infant's BC risk	[33]
	DHA in breast milk important for fetal development	[35]
	Maternal trans fatty acid consumption decreased DHA levels in milk	[36]
Birth to pubescence	Birth weight >4 kg increased risk of BC	[5,33,34]
	Earlier menarche increased risk of BC	[4,45]
	Higher body mass index decreased risk of BC	[8,37,41,42]
	Estradiol exposure decreased risk of mammary tumors	[39,40]
	n-6: decreased mammary tumorigenesis	[8]
	n-6: increased mammary tumor incidence	[9]
	n-3: decreased number of TEB	[46]
Pregnancy	Later first pregnancy increased mother's risk of BC	[4,50]
	High-fat diet increased mother's risk of BC	[26]
	Weight gain >15 kg increased mother's risk of BC	[45]

BC, breast cancer; DHA, docosahexaenoic acid; TEB, terminal end buds.

menarche [44], which is associated with increased BC risk (Table 1) [4,45].

The type of fat consumed is also another modifying factor in this complex relationship. A rodent study that provided high n-6 PUFA diets to rats during various stages of life found that all rats exposed to the high n-6 PUFA diets *in utero* or postnatally prior to pubescence experienced a significant increase in mammary tumor incidence, when compared with rats that were only exposed to high n-6 PUFA post puberty (Table 1) [9]. When considering long-chain n-3 PUFA, there is an inverse association with estrogenic levels (Table 2) [27], which may be beneficial to the MG during early developmental stages. Consuming a low-fat n-3 PUFA diet during prepubescence resulted in a protective effect against mammary carcinogenesis in rats (Table 1) [46]. In contrast, in the same study, a high-fat n-3 PUFA diet led to lower TEB numbers relative to n-6 PUFA controls, but immunohistochemistry revealed that cells comprising the TEB had higher levels of cell proliferation and increased incidence of mammary tumorigenesis (Table 2) [46]. Such observations may be attributable to the overall high fat content of the diet, as high-fat diets have been linked to mammary tumors that have increased protein kinase C activity [47-49].

Pregnancy and late-stage mammary gland development

Pregnancy and lactation is a time of considerable remodeling of the MG in the mother. During pregnancy, the breast tissue undergoes rapid proliferation followed by differentiation in preparation for lactation [50]. The timing of first pregnancy has been observed to affect BC risk, which may be due to the accumulation of mutations. First pregnancy later in life results in more time having elapsed for mutations to develop, which become potential tumor sites in the developing MG [45]. In fact, if the first full-term pregnancy occurs before the age of 18, BC risk is decreased to 40% that of nulliparous women (Table 1) [4,50]. In contrast, having a first birth after 35 years of age increases risk by 20% over nulliparous women [50]. A maternal diet high in fat increases BC risk for the mother by raising estrogenic levels (Table 1) [26]. In addition, high pregnancy weight gain, where women gained more than the recommended 11 to 15 kg throughout pregnancy, increased risk by 62% (Table 1) [45].

Effect of fatty acids on breast cancer

Depending on the type, fatty acids may differentially promote BC or, alternatively, may play a role in inhibiting BC. Cell culture studies have found that SFA, MUFA and n-6 PUFA promote BC cell growth [13], whereas ALA, EPA and DHA inhibit BC cell growth [51-53] (Table 2).

An exception within the MUFA class is oleic acid (18:1n9) (see Figure 1b), which has been shown to exert anti-tumorigenic effects by suppressing overexpression of human epidermal growth factor receptor-2 (HER2) (Table 2) [54]. Additionally, oleic acid intake levels are

Table 2. Effects of dietary fatty acids on breast cancer risk

Fat type	Effect	Reference
SFA	Increased risk of BC	[13,95]
	Compromise cell response to DNA damage	[94]
TFA	Positively associated with mammary tumors	[14]
	Effect similar to cis fats on BC	[96]
	Conjugated linoleic acid supplements inhibit cancer cell growth	[97,98]
MUFA	Increased risk of BC	[13]
	Oleic acid suppresses HER2 in BC cells	[54]
n-6 PUFA	Promote mammary tumor growth	[13]
	Increased cell proliferation in mammary gland	[16]
	Protumorigenic in mammary gland	[16,46]
	Increased circulating estrogenic compound levels	[27]
	Promote tumorigenesis via inflammation	[29,56]
	Positively associated with HER2 oncogene	[52,57]
n-3 PUFA	Decreased circulating estrogenic compound levels	[27]
	Decreased mammary tumor incidence/growth rate (low-fat dose)	[46]
	Increased tumor cell proliferation and growth rate (high-fat dose)	[46]
	Decreased BC cell growth	[51-53]
	Inhibit HER2 expression	[57]
	Inhibit mammary tumor growth	[58,59]
	Increased apoptosis	[62]
	Decreased tumor growth rate	[63]
	Decreased tumor cell proliferation; increased apoptosis	[67-70]
	Increased syndecan-1 synthesis	[74]
	Decreased premenopausal/postmenopausal BC risk	[80,85-89]
	Fish oil consumption decreased BC risk	[86]
ALA	Strongly suppresses HER2 and mammary carcinoma	[52]
	Promotes regression of estrogen receptor+ MCF-7 cancer	[60]
	Significantly slows tumor growth rate	[61]
	Inversely associated with BC risk (natural sources)	[99]
	Positively associated with BC risk (processed sources)	[99]
EPA	Slows mammary tumor growth rate	[53]
	Inhibits lung metastases; decreased eicosanoids	[64]
	Suppresses cell proliferation in MCF-7 cells	[76]
DHA	Enhances treatment effect of taxanes	[51]
	Reduces cell viability in some cancer cell lines	[51]
	Downregulation of HER2	[52]
	Higher tumor regression than other n-3 PUFA	[77]

ALA, α-linolenic acid; BC, breast cancer; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HER2, human epidermal growth factor receptor-2; MUFA, monounsaturated fatty acids; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; SFA, saturated fatty acids; TFA, trans fatty acids.

high in the Mediterranean diet, which boasts low cancer levels [55].

The n-6 PUFA, including LA and AA, are observed to promote a tumor-enhancing environment in the MG (Table 2) [16,46]. AA is a long-chain n-6 PUFA, linked to cell proliferation within the MG, and is associated with enhancing early stages of angiogenesis (Table 2) [16]. AA is the direct precursor of eicosanoids, which mediate proinflammatory processes contributing to tumorigenesis in women [29] and in female rodents [56] (Table 2).

Studies have also shown that n-6 PUFA are positively associated with the HER2 oncogene, present in 40% of BC cases (Table 2) [52,57].

In contrast, n-3 PUFA have been shown to reduce the risk of mammary carcinogenesis (Table 2) [58,59]. Cell culture work found that ALA strongly suppressed over-expression of HER2-positive mammary carcinomas (Table 2) [52]. The use of flaxseed treatments (57% ALA) on MCF-7 cells in ovariectomized mice produced a significant reduction in tumor growth when compared with a diet containing no flaxseed (Table 2) [60]. In conjunction with these effects, it was found that flaxseed consumption actually enhanced the inhibitory effects of tamoxifen, a drug used in BC treatment [60]. A study on mice treated with MDA-MB-231 BC cells comparing diets of corn oil (1% ALA) with diets of canola oil (10% ALA) found the tumor growth rate to be significantly reduced in canola-fed mice (Table 2) [61].

The n-3 PUFA are thought to be linked to increased susceptibility to peroxidative damage, leading to cell death (Table 2) [62]. In one study, when compared with an n-6 PUFA diet, the n-3 PUFA diet decreased the tumor growth rate by 66% in mice carrying human BC xenografts (Table 2) [63]. These benefits are seen particularly with the long-chain n-3 PUFA EPA and DHA, which occur in high concentrations in fish oils [29,59,64]. Despite these supportive studies, a few limited studies on rodents [13] and humans [65,66] have shown that fish oil and n-3 PUFA are not always consistently shown to inhibit BC.

Little is known in terms of the mechanistic pathways by which n-3 PUFA inhibit cancer growth, but several mechanisms have been proposed. EPA and DHA have both been found to inhibit the production of AA-derived eicosanoids in tumors [64]. Lipid peroxidation, which induces apoptosis, is another potential mechanism by which n-3 PUFA suppress cell proliferation in tumors (Table 2) [62,67-70]. Numerous experimental studies have looked at apoptotic effects induced by n-3 PUFA mediated by peroxisome proliferator-activated receptor gamma (PPARγ) [57,62,67,68,71-74]. n-3 PUFA bind and activate PPARγ, leading to activation of the proteoglycan syndecan-1 in human BC cells, which promotes apoptosis leading to cell growth inhibition [73,74]. n-3 PUFA containing low-density lipoproteins deliver both EPA and DHA to cells and cause a significant twofold increase in syndecan-1 synthesis (Table 2) [74]. These mechanistic studies help to explain potential mechanisms by which n-3 PUFA inhibits cancer cell growth, which supports a role for n-3 PUFA as an effective means of treating BC. Further investigation is necessary, however, as a study conducted recently showed that both the amount and type of fatty acid have an impact on cellular activity, with low-fat n-3 PUFA diets decreasing cell proliferation via PPARγ expression and high-fat n-3 PUFA diets increasing cell proliferation via cyclin D_1 expression [75].

Fish oil is a mixture of EPA and DHA, and specific individual effects of each fatty acid remain to be fully clarified. In support of EPA as the principal effector, a study examining cancer progression in mice with induced mammary tumorigenesis found that 4% EPA in the diet had greater efficacy than 4% DHA in inhibiting lung metastases (Table 2) [64]. EPA was also found to suppress an inhibitory G protein-coupled free fatty acid receptor-mediated signal transduction pathway involved in cell proliferation in MCF-7 cell xenografts on mice (Table 2) [76]. Moreover, EPA was observed to slow the tumor growth rate and to reduce metastasis when an EPA diet was compared with a LA diet in mice inoculated with KPL-1 human BC cells (Table 2) [53]. Evidence of DHA being the primary effector in inhibiting tumorigenesis was observed in patients with localized BC. In this study, adipose tissue with high concentrations of DHA showed the greatest extent of tumor regression (Table 2) [77]. DHA itself has also been linked to downregulation of the HER2 oncogene (Table 2) [52] and to the reduction of cancer cell viability (Table 2) [51]. Additionally, DHA has been shown to synergistically enhance the cytotoxic activity of taxanes, in some cases by up to 13-fold (Table 2) [51]. Recent research has shown that DHA is the precursor to potent lipid mediators, identified as resolvins, that regulate inflammation [78,79]. Further attention is warranted in order to distinguish and understand the effects of individual n-3 PUFA.

Human studies and n-3 PUFA

While a considerable amount of cell culture and animal-based research suggests that n-3 PUFA may modify BC risk and provide protection against mammary tumorigenesis [8,46,59,80,81], human cohort, case–control studies have failed to provide similar strong support, often finding null relationships between EPA and DHA consumption and BC risk [19,82-84]. Nevertheless, a limited number of studies support a beneficial relationship between n-3 PUFA and BC risk, many of which are conducted in Asian populations that typically consume higher levels of n-3 PUFA (Table 2) [80,85-89]. One could argue that if such a beneficial effect truly existed then it should be quite obvious. The wide disparity in findings may reflect methodological limitations, specifically the use of dietary measures reliant on self-reports that are often biased [8,13,26,49,90-92]. Moreover, North American populations may not be the most appropriate study population for epidemiological research to investigate the link between n-3 PUFA and BC, as the dynamic range between low consumers and high consumers is not very great and is therefore too low to elicit any health benefits, as compared with studies conducted in Asian countries

that show a strong link [12,86]. A recent study conducted on Korean women found BC risk in both premenopausal women and postmenopausal women to be reduced with EPA and DHA consumption (Table 2) [80]. Furthermore, longitudinal studies have only focused on dietary effects in adulthood; potential effects during pregnancy/fetal developmental period and puberty have therefore yet to be rigorously examined.

Another factor that may contribute to the disparity between North American and Asian studies is the source of dietary n-3 PUFA. While Asian countries have higher intake of marine foods containing EPA and DHA, the North American diet contains mainly ALA. Conversion of ALA to EPA and DHA is limited in humans, yielding only ~5.0% and ~0.5%, respectively [19]. Unfortunately, despite numerous dietary options, daily intake of ALA in North American women is low, in some instances averaging less than one-half of their recommended intake of 1.1 g/day [19,93]. Additional research is needed to determine the specific biological effects of ALA, EPA and DHA in order to ascertain their relative effectiveness in modifying BC risk.

The effects of other fatty acids on BC, including SFA, MUFA and TFA, in human studies are also limited. Studies conducted on BC cell lines and rodents have shown SFA to promote carcinogenesis by inhibiting cellular responses to DNA damage (Table 2) [13,94], and SFA consumption in humans is observed to be associated with increased BC risk (Table 2) [95]. What is not clear, however, is whether these are truly direct effects of SFA or a marker of a poor diet and obesity, which is associated with cancer risk. A rat study comparing trans and cis fatty acids showed no significant difference between groups (Table 2) [96]. In contrast, French data from a large-scale European health and nutrition prospective cohort study (Etude Epidémiologique de femmes de la Mutuelle Générale de l'Education Nationale (E3N) 1989–2002) found that BC risk was positively associated with TFA, but was not associated with *cis*-MUFA (Table 2) [14]. Despite negative connotations with TFA to human health, conjugated LAs are an exception. Conjugated LAs, naturally occurring TFA found in ruminant fat products such as dairy and beef products, have been shown to exert anti-carcinogenic effects in BC cell lines and animal models (Table 2) [97,98]. Further studies conducted on E3N data found ALA to be inversely associated with BC risk, but only when the source was from vegetable oils or fruits and vegetables (Table 2) [99]. Conversely, an increase in BC incidence was noted in relation to ALA when it was obtained through processed foods (Table 2) [99].

Directions for future research

The present review has outlined the widely varying effects dietary fatty acids have on MG development and BC. There remains much inconsistency in the literature regarding the effects of specific classes of fatty acids and their role in BC. The lack of support may not truly be due to a lack of effect, but rather to a lack of our understanding of temporal effects and of specific dietary fatty acids during critical periods of development. Most promising is the ability of n-3 PUFA to alter MG development in the early stages of life, thus protecting against mammary tumorigenesis later in life. The role of dietary fat in BC is indeed a complex relationship. Given that there is mechanistic evidence and emerging data supporting a role for nutrition during pregnancy and early stages of life that modify BC risk, further investigations are warranted. A better appreciation for diet during early life and critical periods of development may help enhance our ability to conduct more rigorous human studies to ascertain the effect of dietary components in the development of BC.

This review identifies evidence suggesting that n-3 PUFA may have a beneficial role for both the prevention and treatment of BC. Future research in this field should focus on the effect of early n-3 PUFA exposure on long-term BC risk, targeting early critical windows in development as discussed throughout the present review. Furthermore, a closer look at the role of individual fatty acids in MG development and BC risk, specifically ALA-enriched, EPA-enriched and DHA-enriched diets, is justified to elucidate differential effects. Such studies are warranted since prevention of BC, as opposed to treatment modalities, will not only have the most impact for individuals but is also economically sustainable.

Overall, the present review highlights additional complexities underlying the relationship between diet and BC and new directions for future research to improve our understanding of the role of dietary fatty acids in BC prevention and treatment.

Abbreviations

AA, arachidonic acid; ALA, α-linolenic acid; BC, breast cancer; DHA, docosahexaenoic acid; E3N, Etude Epidémiologique de femmes de la Mutuelle Générale de l'Education Nationale; EPA, eicosapentaenoic acid; HER2, human epidermal growth factor receptor-2; LA, linoleic acid; MG, mammary gland; MUFA, monounsaturated fatty acids; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; PPARγ, peroxisome proliferator-activated receptor gamma; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TEB, terminal end buds; TFA, trans fatty acids.

Competing interests

The authors declare that they have no competing interests.

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