DIETARY FAT CONSUMPTION AND BREAST CANCER: A REVIEW OF THE LITERATURE

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A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelors degree
With Honors in

Nutritional Sciences

THE UNIVERSITY OF ARIZONA

M A Y 2 0 1 9

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Abstract

Breast cancer is the most common type of cancer diagnosed among women. The literature suggests that increased total fat consumption may be associated with increased risk of breast cancer, although evaluation of specific types of fat may display contradicting results. The purpose of this review is to evaluate the association between total fat intake and its subtypes on risk, survival, and recurrence of breast cancer. Specific types of fat included in this review are saturated fat, polyunsaturated fat, and monounsaturated fat. Lastly, this review aims to identify the impact of fat and its subtypes on biomarkers that may be responsible for its effects, as well as suggest gaps in the current research and recommend areas of study that should be explored in the future. Overall this review found that increased consumption of saturated fat, animal fat and omega-6 polyunsaturated fat were positively associated with risk of breast cancer while omega-3 polyunsaturated fat was protective. Results did not show clear associations between monounsaturated fat and BC, although showed a clear inverse association for consumption of olive oil. Overall, consumption of fat and its subtypes may influence breast cancer risk, survival and recurrence although differential effects may be elicited by different fatty acids.

Introduction

Breast cancer (BC) is the most commonly diagnosed type of cancer among women worldwide and is the leading cause of cancer mortality in females. It has been estimated that the lifetime risk of BC in American females is 12.83% (1), and by 2021, the incidence of BC will increase to 85 per 100,000 women (2). Surprisingly, only ~10% of BC cases are inherited, most commonly a result of mutation in the *BRCA1* or *BRCA2* genes (3). Therefore, the majority of BC incidences are sporadic and the result of exposure to risk factors over a lifetime. For this reason, identification of dietary modifications that are associated with risk of sporadic BC is warranted.

Breast cancer survival post diagnosis has considerably increased due to early detection programs, increased awareness of symptoms, and treatment. This is reflected by current 5- and 10-year survival rates of 90% and 83%, respectively, for women diagnosed with invasive BC (3). Although survival rates have increased, dietary modifications may be beneficial to mitigate risk, survival, and recurrence of BC.

Risk factors for sporadic BC can be split up into two groups: modifiable vs. non-modifiable as seen in Table 1. Research regarding dietary factors that influence sporadic BC risk has been inconclusive, particularly in regard to consumption of dietary fat. It has been suggested this may be the result of assessing total fat intake, instead of specific types of fat (4). Fat sources vary, and consumption of different types of fat as seen in Figure 1 may be associated with differing effects on the risk of BC. Fat subtypes are largely categorized as saturated fat (SFA), unsaturated fat, and trans fat. Unsaturated fat consists of polyunsaturated fatty acids (PUFA), and monounsaturated fatty acids (MUFA). Consumption of PUFAs is commonly inversely related to BC risk, while SFA and trans fat are positively associated with BC risk. MUFAs have not been as widely investigated therefore trends are still equivocal.

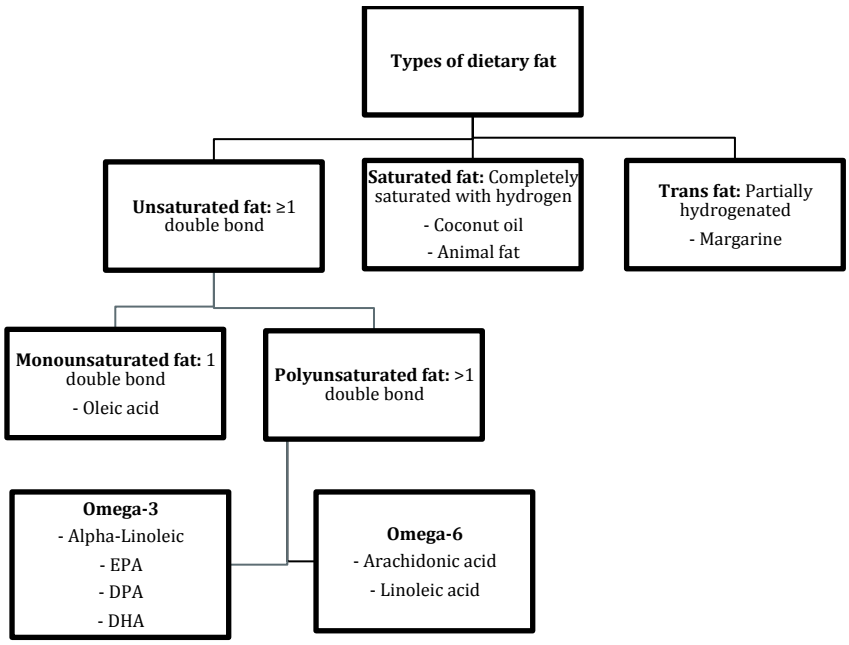

Figure 1- Flow chart of the specific types of dietary fat and their sources

This review aims to assess consumption of total fat and its subtypes on BC risk, survival, and recurrence through analysis of results from both epidemiological studies, and clinical trials. We also comment on fat and its subtypes regarding BC biomarkers that may be influencing these outcomes. Through this exercise we hope to determine gaps in the current research, and recommend areas of study that need to be addressed in the future.

Non-modifiable	**Modifiable**
Older age	Increased weight
Gender	Use of menopausal hormone therapy
Family history of breast or ovarian cancer	Increased alcohol consumption
Atypical hyperplasia	Physical inactivity
Increased breast density	Longer menstrual history
	Increased levels of sex hormones

Table 1 – Non-modifiable vs. modifiable risk factors for breast cancer

Fat consumption and risk of breast cancer

Total fat

Meta-Analyses

A systematic review and meta-analysis conducted in 2003 pooled risk estimates from 45 cohort (n=14) and case-control (n=31) studies to investigate associations between dietary fat and BC incidence (5). In total, 25,015 cases of BC and 580,000 controls were included in the pooled analysis and the majority of studies were conducted among US and European subjects. Results indicated a positive association between total fat intake and BC risk (RR: 1.13; 95% CI: 1.03–1.25) when comparing the highest and lowest levels of fat intake.

Another systematic review and meta-analysis assessed case-control and cohort studies to evaluate the relationship between dietary factors and BC risk among Chinese females (6). Altogether, 31 case-control studies and two cohort studies were included (9,299 cases; 11,413 controls) in the analysis. Six case-control studies that specifically focused on fat consumption were used in the meta-analysis to compare high vs. low levels of fat intake on BC risk. Results indicated high fat intake was significantly associated with increased risk of BC (OR: 1.36; 95% CI: 1.13-1.63; P: 0.088; N: 6). Interestingly, authors also reported high levels of soy consumption was significantly inversely associated with risk of BC with summary OR of 0.65 (95% CI: 0.43-0.99; $P < 0.001$; N: 13).

A larger systematic review and meta-analysis (n=57 studies) evaluated a relationship between dietary fat and BC risk and included subtype analyses on SFA, MUFA, and PUFA (7). Results from cohort studies indicated a marginal association between PUFA (1.091, 95% CI: 1.001; 1.184) and BC risk, although analysis of case-control studies indicated no association. However, in stratified analyses a significant association was observed between BC risk and intake of total fat (RR: 1.042, 95% CI: 1.013-1.073) and PUFA (RR: 1.22, 95% CI: 1.08-1.381) in postmenopausal, but not premenopausal women.

Other meta-analyses have recapitulated this potential influence of menopausal status on the effect of dietary fat in regard to BC risk (8). A systematic review and meta-analysis included 24 prospective

cohort studies (38,262 cases among 1,387,366 subjects) that evaluated total dietary fat and specific fatty acid intake. The mean follow-up of studies ranged from 2 to 25 years. Results indicated total fat intake was positively associated (RR: 1.10 95% CI: 1.02-1.19) with risk of BC when comparing the highest vs. lowest levels, however subgroup analysis revealed this effect was specific to postmenopausal women.

Clinical Trials

A randomized, controlled, primary prevention trial (9) conducted across 40 clinics in the US tested the effect of a low fat diet pattern on BC incidence in healthy post-menopausal women (n= 48,835, age 50-79). Women in the intervention group had the targets of 20% of energy from total fat, 5 servings of fruits and vegetables per day, and 6 servings of grains per day. The control group was not instructed to make any dietary modifications. Compared with women in the control group, participants in the intervention group had statistically significant lower consumption of fat and higher consumption of fruits and vegetables. At ~8 years follow-up, a statistically significant reduction in the incidence rates of invasive BC was not observed between intervention (0.42%) and control (0.45%) groups (HR: 0.91; 95% CI: 0.83-1.01). However, when tumors were classified by hormone receptor (estrogen and progesterone) status, there was evidenced for decreased occurrence of estrogen receptor-positive, progesterone receptor negative BC (HR: 0.64; 95% CI: 0.49-0.84).

Another randomized clinical trial, conducted in Canada, investigated the effect of an intervention with a low fat, high carbohydrate diet on BC risk in a high-risk population (10). Women (n= 4,960) identified during screening mammography to have increase mammographic density were divided into either the intervention or comparison group and followed on average for 10 years. The intervention group was counseled to decrease fat consumption to 15% of total calories and increase carbohydrate consumption to 65% of total calories. After follow-up, 118 cases of BC were identified in the intervention group compared with 102 in the control group (HR: 1.19; 95% CI: 0.91-1.55). Authors reported fat intake at neither baseline or after intervention were associated with risk of BC overall or in stratified analyses by menopausal status. Interestingly, higher fat intake was significantly inversely associated with ER-negative BC risk (IQOR: 0.18; 95% CI: 0.05-0.60). This outcome remained significant in separate analyses of

PUFA (IQOR: 0.26; 0.11–0.63) and MUFA (IQOR: 0.21; 0.07–0.64) intake, however SFA intake was not significant. No associations were found for ER-positive BC. Authors also reported a higher weight and lower carbohydrate consumption both at baseline and post-randomization that were associated with greater risk of estrogen-receptor positive breast cancer. Analysis of food records indicated the intervention group had ~9-10% lower intake of fat compared with the control group, however subjects in this group consumed ~20% of calories from fat and did not meet the goal of 15%. Summary of results with regard to BC risk and total fat consumption can be seen in Table 2.

Table 2 - Summary of studies investigating an association between total fat consumption and breast cancer risk

Design	Reference	Effect	HR/OR/RR (95% CI)
Meta-analysis			
	Boyd et al. (2003)	Increased risk	RR: 1.13 (1.03-1.25)
	Liu et al. (2014)	Increased risk	OR: 1.36 (1.13-1.63)
	Turner (2011)	Increased risk[a]	RR: 1.042 (1.013-1.073)
	Cao et al. (2016)	Increased risk[a]	RR: 1.10 (1.02-1.19)
Clinical trials			
	Martin et al. (2011)	No association	IQOR: 1.18 (0.81-1.71)[b] IQOR: 1.09 (0.58-2.06)[a]
	Prentice et al. (2006)	No association Reduced risk	HR: 0.91 (0.83-1.01) HR: 0.64 (0.49-0.84)[c]

[a] For postmenopausal women only
[b] For premenopausal women only
[c] For estrogen receptor-positive, progesterone receptor negative breast cancer only

Animal fat

Meta-Analyses

The systematic review and meta-analysis by Boyd et al (5), which demonstrated a positive association between total fat intake and BC incidence, also demonstrated an association between meat intake and BC incidence (RR, 1.17; 95% CI 1.06–1.29). On the other hand, a systematic review and meta-analysis of cohort studies indicated there was not a significant association between animal fat intake and BC risk when comparing the highest quartile of intake to the lowest (SRRE: 1.03; 95% CI: 0.76 -1.40) (11). Additionally, there was no association indicated for 5% increment increase in total % of energy from

animal fat on BC (SRRE: 1.02; 95% CI: 0.97-1.07). Results remained the same when stratifying by menopausal status. Overall, fat consumption based on source (animal vs. vegetable) remains controversial, and authors concluded that animal fat individually, or as a percent of total energy intake and risk of BC did not display an association. Other meta-analyses have confirmed these findings and comparison of studies can be seen in Table 3. For example, in the study by Cao at colleagues (8), which revealed an association between total fat consumption and postmenopausal BC, subgroup analysis indicated no specific association with consumption of animal fat (RR: 0.95 95% CI: 0.82-1.09). Despite the lack of association between animal fat consumption and BC risk found in pooled analyses, it is important to note 'animal fat' is a general term that encompasses several different sources (e.g., red meat, poultry, ruminant, etc.). Thus, in the following sections, we report on some of the significant findings with regard to animal fat sources reported in cohort and case-control studies.

Cohort Studies

Animal fat was associated with increased risk of BC contradicting previous results in a secondary analysis of the Nurses' Health Study (NHS) II that included 88,804 women aged 26-54 years old (mean: 36.4) (12). During the 20-year follow up, a total of 2,830 BC cases were diagnosed. Although total fat consumption was not associated with BC risk (*P*-trend: 0.10), there was a significant positive association found for consumption of animal fat when comparing the highest vs. lowest quintile of intake (RR: 1.18; 95% CI: 1.04-1.33; P-trend: 0.01). Subgroup analysis indicated this effect to be specific to premenopausal BC (P-trend: 0.02). Additionally, increased consumption of SFA, MUFAs, and cholesterol was associated with increased risk of BC; however this effect was not significant after the model was adjusted for intake of red meat. Analysis of data from the Norwegian Countries Study cohort (13) demonstrated consumption of ruminant fat was associated with increased risk of postmenopausal BC (HR: 1.17; 95% CI: 0.91-1.49; P-trend: 0.03), but not premenopausal. In this study a semi-quantitative food frequency questionnaire (FFQ) was used to assess diet on 77,568 men and women in which 12,004 cancer cases were diagnosed and 1,397 were specifically BC during a 24.8-year follow up.

Case-control

A positive relationship between red and processed meat consumption and risk of BC was reported in a study of Thai women (1,130 cases; 1,142 controls) (14). The mean age (43.7 ± 11.6 years) and BMI (mean BMI unreported) of the control group were significantly lower than the BC group (47.0 ± 10.4 years) in this study. Increased consumption of pork was associated with increased risk of BC only in postmenopausal women (OR: 1.54; 95% CI: 1.09-2.49). Increased consumption of chicken in postmenopausal women was positively associated with BC risk when comparing quartile 2 (OR: 1.53 95% CI: 1.06-2.21) and 3 (OR: 1.70; 95% CI: 1.20-2.41). A similar study administered in Uruguay, found that a western diet increased risk of BC (OR: 2.13; 95% CI: 1.09-4.15) in women (n = 111) that present with ductal carcinoma when compared to healthy women (n = 222) (15). Results were largely attributed to increased consumption of meat and fat in the diet. Specifically, the highest red meat consumers had a 4-fold increase in BC. A low-fat diet was found to be inversely associated with risk of BC (OR: 0.30; 95% CI: 0.16-0.60, P-trend: 0.001), as a result of consuming skinless poultry, skim milk, and low-fat yogurt.

A case-control study conducted in Eastern India found similar results that indicated increased consumption of fat (OR: 1.598; 95% CI: 1.310-1.852) and deep fried foods (OR: 1.420; 95% CI: 1.221-1.798) was positively associated with BC risk (16). In total 534 women (237 cases, 237 controls) were enrolled, mean age was 45.30 ± 10.23 years vs. 41.25 ± 10.9 years, and BMI was higher in the cases vs. controls, although most women included in the study were normal to overweight, in comparison to obese in both groups. An additional study among smokers in Argentina found that consuming more than 200g/day of fat from meat and 30g/day of fat and oils was associated with risk of BC (OR: 6.01; 95% CI: 1.99-8.19) (17). This study consisted of 393 individuals (100 cases, 293 controls) and results were stratified based on age and BMI of the participants. In comparison to the control group, women with BC had a greater mean consumption of meats, fat and oils, and calories ($P < 0.05$).

A study conducted in Poland recruited 858 women with BC (mean age = 55.30 ± 9.70 years, mean BMI = 26.20 ± 4.70) and 1,085 healthy controls (mean age = 54.80 ± 9.50, mean BMI = 25.30 ±

4.10) to evaluate the relationship between meat, animal and plant fat intake and BC risk (18). High animal fat consumption, defined as being equal to or greater than 5 servings per week, significantly increased BC risk from 1.7 times (OR: 1.66; 95%CI: 1.07-3.59) to 2.9 times (OR: 2.9; 95% CI: 1.37- 6.14) when comparing the third vs. lowest quartile. Sub-analyses showed processed meat were positively associated with increased risk for BC in physically inactive women (OR: 1.78; 95%CI: 1.04-3.59).

An Iranian case-control study involving 47 premenopausal women with BC and 105 healthy women investigated the association between consumption of animal fat, Kermanshahi oil, and other dietary fat sources in relation to BC risk (19). Diet was assessed by the KIDMED test, which questions dietary sources of fat (ex: solid animal fat, butter/margarine, fish oil/n-3 PUFAs, etc.). Mean age, and BMI went unreported, although authors state that there was no significant difference between the two groups. Dietary fat was categorized into 4 groups: Kermanshahi oil, animal oil, liquid oil (plant derived oil), and butter/margarine. Intake of Kemanshahi oil increased the likelihood of BC by 2.1-fold (OR: 2.123; 95% CI: 1.332- 3.38; P: 0.002), while animal oil increased it by 2.8-fold (OR: 2.754; 95% CI: 1.43- 5.273; $P < 0.001$). Consumption of soy and white meat products had a positive role in mitigating risk of BC (all $P < 0.001$). Kermanshahi animal oil is traditionally consumed and produced in Iran by the Tribes and Villagers.

Table 3 - Summary of studies investigating an association between animal fat consumption and breast cancer risk

Design	Reference	Source	Effect	HR/OR/RR (95% CI)
Meta-analysis				
	Boyd et al. (2003)	Meat	Increased risk	RR: 1.17 (1.06-1.29)
	Alexander et al. (2010)	Animal fat	No association	SRRE: 1.03 (0.76 -1.40)
	Cao et al. (2016)	Animal fat	No association	RR: 0.95 (0.82-1.09)
Cohort				
	Farvid et al. (2014)	Animal fat	Positive association	RR: 1.18 (1.04-1.33)
	Laake et al. (2013)	Ruminant fat	Increased risk[a]	HR: 1.17 (0.91-1.49)
Case-control				
	Sangrajrang et	Pork	Increased risk[a]	OR: 1.54 (1.09-2.49)

	al. (2013)			
	Ronco et al. (2010)	Western diet	Increased risk	OR: 2.13; (1.09-4.15)
	Datta et al. (2009)	Animal fat	Increased risk	OR: 1.598; (1.310-1.852)
	Roman et al. (2014)	Animal fat	Increased risk	OR: 6.01; (1.99-8.19)
	Kruk et al. (2013)	Animal fat Processed meat	Increased risk Increased risk[b]	OR: 2.9; (1.37- 6.14) OR: 1.78; (1.04-3.59)
	Salarabadi et al. (2015)	Animal oil Kemanshahi oil	Increased risk Increased risk	OR: 2.754 (1.43- 5.273) OR: 2.123 (1.332- 3.38)

[a] Postmenopausal women only
[b] Amongst physically inactive women

SFA

Meta-Analyses

Previous studies have reported animal meat consumption, with high SFA content (up to 49% total composition) is associated with increased risk of BC (20). The meta-analyses by Boyd and colleagues with the primary end point of determining a relationship between total fat intake and BC incidence have demonstrated an increased risk (RR: 1.19; 95% CI: 1.06–1.35) associated with high SFA consumption (5). Another meta-analysis of 24 cohort studies and 28 case-control studies set out to determine an association between intake of SFA and BC incidence (21). Both case-control (OR: 1.18; 95% CI: 1.03-1.34) and cohort (OR: 1.04; 95% CI: 0.97 – 1.11) studies indicated some degree of positive association between SFA intake and BC risk when comparing high vs. low consumption. Subgroup analyses in case-control studies demonstrated a significant association between increased SFA consumption and BC risk in Asians (OR: 1.17; 95% CI: 1.02-1.34), Caucasians (OR: 1.19; 95% CI:1.19 (1.00-1.41) and postmenopausal women (OR: 1.33; 95% CI: 1.02-1.73). Postmenopausal BC risk was only observed for women in case-control studies but was not apparent for cohort studies.

Cohort Studies

The European Prospective Investigation into Cancer and Nutrition (EPIC) study found similar results indicating increased consumption of SFA was associated with a 13% increase in risk (HR: 1.13; 95% CI: 1.00–1.27) for BC when comparing the highest vs. lowest quintile of intake (22). Altogether, in

this study ten European countries were included comprising 23 total sites with participants (n=519,978) ranging in age from 35-70 years of age. The analyses included evaluation of risk between several types of cancer (breast cancer, gastric, colorectal, lung, etc.) and dietary factors, a few for example were fat, vitamin C, fiber, and vitamin D. Analysis of postmenopausal women enrolled in the VITamins And Lifestyle (VITAL) Cohort found positive associations between SFA and trans fat consumption and risk of BC (23). In total 30,252 women were enrolled in the study and a FFQ was used to assess dietary fat intake. Total SFA intake was positively associated with an increased risk of BC (HR: 1.47; 95% CI: 1.00-2.15, P-trend: 0.09), however the trend for increasing intake was not significant. Moreover, increased consumption of specific types of SFA were associated with BC risk, including stearic acid (HR: 1.65; 95% CI: 1.12-2.43, P-trend: 0.03), palmitic acid (HR: 1.68; 95% CI: 1.13-2.50, *P*-trend: 0.02) and linolelaidic acid (HR: 1.53; 95% CI: 1.07-2.19, P-trend: 0.02) when comparing the highest vs. lowest quintile of intake. Summary of study results can be seen in Table 4.

Prospective studies have also suggested that increased intake of SFA (47.5g/day) is associated with increased risk of estrogen receptor positive (ER+), progesterone receptor positive (PR+), BC (HR: 1.28; 95% CI: 1.09-1.52) among a large cohort of women (n = 337,327) (24). In total, 10,062 BC cases were diagnosed upon an average 11.5-year follow up. Increased consumption of SFA was also significantly associated with greater risk of HER_2^- disease (HR: 1.29; 95% CI: 1.01; 1.64, highest vs. lowest) and a statistically significant trend was seen for SFA consumption (P = 0.04) although no association was found for HER_2^+ BC. In contrast, the Multiethnic Cohort study conducted in Hawaii and California, did not find an association for consumption of SFA (HR: 0.93; 95% CI: 0.83-1.04) when comparing the highest vs. lowest quintile of intake on risk of BC regardless of hormone receptor status in postmenopausal women (25).

Case-Control

Consumption of SFA has also been shown to be significantly associated with BC risk in case-control studies. For example, in a study by Sofi et al (26) 200 individual (100 cases, 100 controls) diets were assessed through use of a FFQ. A majority of the individuals were between 28-48 years of age for

both groups (69% and 70%), and BMI went unreported. Results demonstrated higher SFA intake was significantly associated with high BC risk (adjusted OR: 3.4; 95% CI: 1.4-8.1). The 4-Corners BC study also found that increased consumption of SFA was associated with risk of BC when comparing the percentage of daily calories between high (≥14.1%) vs. low (≤9.8%) quartiles of intake for both, white, non-Hispanic women (OR: 0.73; 95% CI: 0.58- 0.92; P-trend: <0.01) and Hispanic women (OR: 0.67; 95% CI: 0.48-0.93; P-trend: 0.02) (27).

The NHSII showed a positive relationship between BC risk and levels of trans fat when comparing the high vs. low quartile (OR: 2.33; 95% CI: 1.45-3.77, P-trend: <0.001, P: 0.007) and SFA (OR: 1.85; 95% CI: 1.18-2.88; P-trend: 0.006, P <0.001) measured in blood erythrocytes in overweight/obese women, and BC risk (28). Overall, 1,588 women (794 cases; 794 controls) were included and groups did not differ in age (44.7 ± 4.5 vs. 44.8 ± 4.4 years) nor BMI (25.1 ± 5.0 vs. 25.8 ± 6.0kg/m^2). Surprisingly, total SFA levels measured in erythrocytes were inversely associated with risk of BC amongst women with a BMI < 25 (OR: 0.68; 95% CI: 0.46-0.98, P-trend: 0.05, P: 0.01).

A case-control study of 621 postmenopausal invasive BC cases and 621 controls set out to evaluate diet-related metabolites in regards to BC risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (29). The mean age of participants at the time of blood collection was 64 ± 5.3 years, and mean BMI went unreported. Diet was assessed through self-administration of a 137-item FFQ, and prediagnostic serum concentrations were collected to measure metabolites. Serum concentrations of caprate (OR: 1.77; 95% CI: 1.28-2.43), a butter-associated SFA, and 10-undecenoate (OR: 1.43; 95% CI: 1.04-1.97), found in butter, ice cream and cheese, were associated with overall BC risk. Furthermore, increased risk of ER+ BC was associated with serum levels of butter-associated caprate (10:0) (OR: 1.81; 95% CI: 1.23-2.67); and fried food-associated 2-hydroxyoctanoate (OR: 1.46; 95% CI: 1.03, 2.07).

Table 4 - Summary of studies investigating an association between saturated fat consumption and breast cancer risk

Design	Reference	Source	Effect	HR/OR/RR (95% CI)
Meta-analysis				
	Boyd et al. (2003)	SFA	Increased risk	RR: 1.19 (1.06-1.35)
	Xia et al. (2015)	SFA	Increased risk[a]	OR: 1.33 (1.02-1.73)
Cohort				
	Gonzalez et al. (2010)	SFA	No association	HR: 1.47 (1.00-2.15)
		Steric acid	Increased risk	HR: 1.65 (1.12-2.43)
		Palmitic acid	Increased risk	HR: 1.68 (1.13-2.50)
		Linolelaidic acid	Increased risk	HR: 1.53 (1.07-2.19)
	Sieri et al. (2014)	SFA	Increased risk[b]	HR: 1.28 (1.09-1.52)
		SFA	Increased risk[c]	HR: 1.29 (1.01-1.64)
	Park et al. (2012)	SFA	No association	HR: 0.93 (0.83-1.04)
Case-control				
	Sofi et al. (2018)	SFA	Increased risk	OR: 3.4 (1.4-8.1)
	Murtaugh et al. (2008)	SFA	Inverse association[d]	OR: 0.73 (0.58-0.92)
		SFA	Inverse association[e]	OR: 0.67 (0.48-0.93)
	Hirko et al. (2018)	SFA	Increased risk	OR: 1.85 (1.18-2.88)
		Trans-fat	Increased risk	OR: 2.33 (1.45-3.77)
	Playdon et al. (2017)	Caparate	Increased risk	OR: 1.77 (1.28-2.43)
		10-undecenoate	Increased risk	OR: 1.43 (1.04-1.97)

[a] Postmenopausal women only
[b] For ER+/PR+ BC only
[c] For HER_2^- BC only
[d] For white non-Hispanic women
[e] For Hispanic women

Omega-3

Meta-Analyses

A meta-analysis and systematic review analyzed the dose dependent effect between the intake of fish and n-3 PUFAs on the risk of BC (30). Altogether, 26 publications were included (20,905 cases of BC and 883,585 participants) from 21 prospective cohort studies. The included studies focused on dietary fish intake, marine n-3 PUFA, and alpha linolenic acid (ALA). Overall, marine n-3 PUFA were associated with a 14% reduction for risk of BC when comparing the highest vs. lowest quartile (RR: 0.86;

95% CI: 0.78-0.94). Most significantly, analysis of a dose-dependent association indicated that BC risk was reduced by 5% per 0.1g/day of dietary marine n-3 PUFA intake (RR: 0.95; 95% CI: 0.90-1.00). There was no association observed for fish intake alone, or ALA. In summary, this study suggests the consumption of marine n-3 PUFA may be inversely associated with BC risk. Findings are further supported by another systematic review and meta-analysis that suggests n-3 PUFAs derived from fish have a protective effect against BC in Asian women (OR: 0.80; 95% CI: 0.73-0.87; $p<0.00001$) (31).

A meta-analysis on 11 independent prospective studies set out to identify the association between n-3: n-6 PUFA ratio on risk of BC, and to estimate a dose-response trend (32). An increased ratio of n-3: n-6 PUFAs were found to be inversely related to risk of BC (pooled RR: 0.90; 95% CI: 0.82-0.99). As for a dose-dependent trend, there was a 6% reduction in BC risk for every 1/10 increment in the ratio (pooled RR: 0.94; 95% CI: 0.90-0.99; P-trend: 0.012). In summary, there was a significant association between increased ratio of n-3: n-6 PUFAs and lower risk of BC in healthy women. Summary of studies can be seen in Table 5. Education on sources of n-3 and n-6 PUFAs may be warranted, as a higher-n-3:n-6 ratio may be protective against BC.

Cohort Studies

The Reykjavik study found that consumption of fish decreased risk of BC in women (n = 2,882) after a mean 27.3-year follow up (33). More than 4 servings of fish per week compared to 2 servings was significantly associated with decreased risk of BC when consumed during midlife (HR: 0.46; 95% CI: 0.22-0.97) and suggested an inverse association for consumption during adolescence (HR: 0.71; 95% CI: 0.44-1.13). Assessment of dietary intake of fat and risk of BC in the Shanghai Women's Health prospective cohort study (n = 72,571), found that women (mean age: 52.7) with the lowest intake of marine-derived n-3 PUFA consumption (≤0.045g/day) and highest intake of n-6 PUFA (>7.28 g/day) had elevated risk of BC (RR: 2.06; 95% CI: 1.27-3.34) (34).

The Japan Public Health Center based prospective study (JPHC) found that consumption of n-6 PUFAs (14.3g/day) was associated with increased risk of ER+PR+ BC (HR: 2.94; 95% CI: 1.26-6.89; P-trend: 0.02) while EPA consumption was associated with decreased BC risk (HR: 0.47; 95% CI: 0.25-

0.89) (35). In contrast, a cohort study conducted on 56,007 French women did not find an association for individual PUFA intake on the risk of BC upon a 8-year follow up (n = 1,650 cases of invasive BC), although an inverse relationship was observed for intake of ALA from fruits and vegetables (HR: 0.74; 95% CI: 0.63-0.88; P-trend < 0.0001), and from vegetable oils (HR: 0.83; 95% CI: 0.71-0.97; P-trend: 0.017) (36). Consumption of ALA from nut mixes and processed food was positively associated with risk of BC (P-trend 0.004). Postmenopausal women enrolled in the previously described VITAL cohort study found that BC risk was inversely associated with consumption of EPA (≥0.10 vs. <0.02g/day) (HR: 0.70; 95% CI: 0.54–0.90) and DHA (≥0.21 vs. <0.03g/day) (HR: 0.67; 95% CI: 0.52–0.87) (23).

Case-Control

The MASTOS study, the largest case-control study conducted in Cyprus found an inverse relationship for consumption of fish, a good source of PUFAs, and BC risk (OR: 0.88, 95% CI: 0.79-0.98) (37). In total 1,752 postmenopausal women were included (n = 935 cases; n = 817 controls), with the majority of participants being overweight or obese in both groups (67.3% and 64.1%, respectively). In another study, increased consumption of PUFAs was associated with a 30 – 50% reduced risk for all ER/PR BC combinations [ER-/PR- (OR: 0.6; 95% CI: 0.4-1.0); ER+/PR- (OR: 0.5; 95% CI: 0.3-0.9); ER+/PR+ (OR: 0.7; 95% CI: 0.5-0.9)], except ER-/PR+ BC (OR: 0.6; 95% CI: 0.3-1.4) (38). This hospital-based case-controlled study included 2,552 women (1,075 cases; 1,477 controls) living in Italy and investigated dietary intake on BC risk by ER and PR status. Women with BC had a median age of 53 years (range: 23 – 74 years), and controls had a median age of 56 years (range: 20 – 70 years). Results were stratified based on BMI, but mean went unreported; diet was assessed through administration of an FFQ.

A study conducted in China found that increased consumption of PUFAs was associated with decreased risk of BC (30). In total 876 individuals were enrolled (438 cases; 438 controls) and dietary intake was assessed through administration of a FFQ. Cases and controls were similar in age (47.04 ± 9.53 vs. 47.14 ± 9.58 years) and BMI (22.92 ± 3.33 vs. 22.46 ± 3.05kg/m^2). Specifically, consumption of PUFAs was associated with a 50% reduction in risk of BC when compared to the lowest quartile (OR:

0.50; 95% CI: 0.27-0.93; P- trend: 0.034). Overweight and obese women in a prospective analysis of the NHSII found that omega-3 FAs concentration in blood erythrocytes was inversely associated with risk of BC (OR: 0.57; 95% CI: 0.36-0.89; P-trend: 0.017) (28).

A case control study conducted among 2,074 Mexican women (1,000 cases; 1,074 controls) did not find an association between n-3 PUFA intake and risk of BC (39). A trend for decreased BC was observed for premenopausal women with an increased n-3: n-6 ratio, however the trend was not statistically significant (P: 0.06). Independently, increased consumption of n-6 PUFAs was associated with increased risk of BC (OR: 1.92; 95% CI: 1.13-3.26; P: 0.04), although this was specific to premenopausal women. Increased consumption of n-3 PUFAs was only associated with decreased risk in obese women (OR: 0.58; 95% CI: 0.39-0.87; P: 0.008), but not for overweight or normal weight individuals.

A study conducted in New York in 2,963 individuals (1,463 cases; 1,500 controls) found that high intake of omega-6 FAs and low intake of omega-3 FAs was associated with a 20% increase in BC incidence (OR: 1.20; 95% CI: 0.85-1.69) (40). The biggest contributor to n-3 PUFA intake was ALA, and linoleic acid (LA) was the largest contributor for total n-6 PUFA intake. A majority of women in the study were postmenopausal, Caucasian, and BMI was obtained although the mean was not reported.

A case-control study evaluating fatty fish intake and risk of BC found that increased consumption of n-3 PUFAs was associated with decreased risk of premenopausal BC (41). Altogether 718 women were enrolled in the study (358 cases; 360 controls) and diet was assessed through administration of a 103-item FFQ to determine relative consumption of fish, EPA, and DHA. The highest consumption of fatty fish was seen to be protective in all women (pre- and postmenopausal) when compared to the lowest level of intake (premenopausal: $p < 0.001$; postmenopausal: p: 0.005). In postmenopausal women, consumption of more than 0.101g of EPA and 0.213g of DHA per day were correlated with 62% (OR: 0.38; 95% CI: 0.15-0.96) and 68% decreased risk (OR: 0.32; 95% CI: 0.13-0.82) of BC, respectively, when compared to women who consumed less (0.014g EPA and 0.037g DHA). Premenopausal women

that consumed the highest amount of n-3 PUFAs displayed a significant reduction in BC risk (OR: 0.46; 95% CI: 0.22-0.96) when compared to the lowest amount of intake.

Table 5 - Summary of studies investigating an association between polyunsaturated fatty acid consumption and breast cancer risk

Design	Reference	Source	Effect	HR/OR/RR (95% CI)
Meta-analysis				
	Zheng et al. (2013)	Marine n-3 PUFA	Decreased risk	RR: 0.86 (0.78-0.94)
	Nindrea et al. (2019)	Fish	Decreased risk	OR: 0.80 (0.73-0.87)
	Yang et al. (2014)	↑ n-3:n-6 ratio	Decreased risk	RR: 0.90 (0.82-0.99)
Cohort				
	Haraldsdottir et al. (2017)	Fish	Decreased risk	HR: 0.46 (0.22-0.97)
	Murff et al. (2011)	↓ n-3:n-6 ratio	Increased risk	RR: 2.06 (1.27-3.34)
	Kiyabu et al. (2015)	n-6 PUFA	Increased risk	HR: 2.94 (1.26-6.89)
		EPA	Decreased risk	HR: 0.47 (0.25-0.89)
	Thiebaut et al. (2009)	n-3 PUFA	No association	HR: 0.99 (0.84-1.15)
		n-6 PUFA	No association	HR: 0.93 (0.80-1.09)
		ALA[a]	Decreased risk	HR: 0.74 (0.63-0.88)
		ALA[b]	Decreased risk	HR: 0.83 (0.71-0.97)
		ALA[c]	Increased risk	HR: 1.18 (1.01-1.38)
	Sczaniecka et al. (2012)	EPA	Inverse relationship	HR: 0.70 (0.54–0.90)
		DHA	Inverse relationship	HR: 0.67 (0.52–0.87)
Case-control				
	Demetriou et al. (2012)	Fish	Inverse relationship	OR: 0.88 (0.79-0.98)
	Rosato et al. (2013)	PUFA	Reduced risk	OR: 0.5 – 0.7 (range)
	Zheng et al. (2013)	PUFA	Reduced risk	OR: 0.50 (0.27-0.93)
	Hirko et al. (2018)	n-3 PUFA	Inverse relationship	OR: 0.57 (0.36-0.89)
	Chajes et al. (2012)	n-3 PUFA	Decreased risk[d]	OR: 0.58 (0.39-0.87)
		n-6 PUFA	Increased risk[e]	OR: 1.92 (1.13-3.26)
	Khankari et al. (2015)	↑ n-6 PUFA & ↓ n-3 PUFA	Increased risk	OR: 1.20 (0.85-1.69)
	Kim et al. (2009)	n-3 PUFA	Decreased risk[e]	OR: 0.46 (0.22-0.96)
		EPA	Decreased risk	OR: 0.38 (0.15-0.96)
		DHA	Decreased risk	OR: 0.32; (0.13-0.82)

[a] From fruits and vegetables
[b] From vegetables oils
[c] From nut mixes and processed food
[d] Obese women only
[e] Premenopausal women only

MUFA

Meta-Analyses

A systematic review and meta-analysis reported increased consumption of olive oil rich in MUFAs has protective effects against development of cancer in general and reported specific effects for BC and cancer of the digestive system (42). Altogether, 19 case-control studies were included (13,800 cases; 23,340 controls) in this analysis. Results showed that comparison between the highest vs. lowest quartile of olive oil consumption was associated with lower incidence of any type of cancer (OR: -0.41; 95% CI: -0.53, -0.29, p: 0.0002). Increased consumption of olive oil was inversely associated with BC development (OR: -0.45; 95% CI: -0.78, -0.12) when compared to the lowest quartile of intake. Collectively, results indicate increased olive oil consumption could serve as a possible preventative measure for any type of cancer highlighting BC.

Clinical Trials

The Mediterranean diet (MD) is a term used to describe the dietary pattern derived from cultures surrounding the Mediterranean Sea. Adherence to the Mediterranean Diet has been shown to be inversely associated with several health problems including cardiovascular disease, diabetes, neurodegenerative conditions and various cancers. An essential tenant of the recommended MD is the inclusion of olive oil at the majority of meals as the principle fat source.

The PREDIMED study showed that a MD supplemented with extra virgin olive oil (EVOO) had beneficial long-term effects in the prevention of BC in postmenopausal women (age = 67.7 ± 5.8 years) (43). The MD+EVOO diet was compared with a low fat diet and a MD supplemented with nuts. In total 4,282 women were randomized in a 1:1:1 fashion and were followed for a mean of 4.8 ± 1.7 years. A majority of the women were either overweight or obese (BMI = 30.4 ± 4.06) at baseline and all were considered to have high cardiovascular risk. Participants were provided food for free including 1 liter per week of EVOO, and 30 grams per day of mixed nuts (15g walnuts, 7.5g hazelnuts, and 7.5g almonds). Overall, there were 35 confirmed cases of BC upon follow up and the observed rate (per 1000 person-years) was 1.1 for MD with EVOO (HR: 0.32; 95% CI: 0.13-0.7), 1.8 for the MD group with nuts (HR:

0.59; 95% CI: 0.26-1.35), and 2.9 for the control group. Results suggest that a MD high in EVOO may confer protective effects against BC incidence in comparison to a low fat diet.

Case-Control

A case-control study including 10,000 subjects with cancer and 17,000 controls found that increased adherence to a MD were associated with decreased risk for all types of cancer (OR: 0.76 for a two-point increment in the MD score) (44). Cancer subtypes included oral, esophageal, colon, 2,569 BC cases, and others. Diet was assessed through administration of a FFQ. Consumption of olive oil was inversely correlated (OR: 0.89; 95 % CI: 0.81, 0.99) with BC risk that was in agreement with other studies in this review as summarized in Table 6.

A case-control study conducted in Turkey on 130 participants (65 cases; 65 controls) suggested cooking methods, olive oil consumption and adherence to the MD impacted the risk of BC (45). Data were collected through the use of questionnaires that inquired about the participant's general health, dietary habits, BMI (pre vs. post diagnosis), and physical activity. Assessment of the MD score was based on 11 food categories (fruits, vegetables, legumes, olive oil, etc.) that could receive a score of 0-5. Women that reported deep-frying red meat in comparison to stewing had a 6.77 more likely chance of being diagnosed with BC (OR: 6.77; 95% CI: 1.622-28.264; $P < 0.05$). Rare consumption (1 – 2 times per week) of olive oil compared to daily or regular consumption was associated with a 4.5-increased likelihood of developing BC (OR: 4.57; 95% CI: 1.396-14.548; P: 0.012). Adherence to the MD in participants that received a score higher than 29 (< 29 defined as inadequate) was significantly lower in the case group (15.4%) vs. the control group (44.6%) ($P < 0.05$).

The 4-Corners BC study, described earlier, found that increased consumption of MUFAs was associated with decreased risk of BC amongst postmenopausal women (P-trend < 0.01) (27). Contradicting results were reported from the previously described MASTOS study, which did not find any association between two different MD scores and risk of BC (37). However, there was an inverse relationship observed for olive oil consumption (OR: 0.76, 95% CI: 0.59-0.97) and BC risk.

Table 6 - Summary of studies investigating an association between monounsaturated fatty acid consumption and breast cancer risk

Design	Reference	Source	Effect	HR/OR/RR (95% CI)
Meta-analysis				
	Psaltopoulou et al. (2011)	Olive oil	Inverse association	OR: -0.45 (-0.78, -0.12)
	Toledo et al. (2015)	Mediterranean diet with EVOO	Decreased risk	HR: 0.32 (0.13-0.7)
Case-control				
	Bosetti et al. (2009)	Olive oil	Inverse association	OR: 0.89 (0.81, 0.99)
	Toklu et al. (2018)	↓ Olive oil	Increased risk	OR: 4.57 (1.396-14.548)
	Murtaugh et al. (2018)	Olive oil	Inverse association	OR: 0.76 (0.59-0.97)

EVOO: Extra virgin olive oil

Dietary fat consumption on BC recurrence and survival

Meta-Analyses

A meta-analysis conducted on 15 prospective cohort studies investigated the impact of total fat and saturated fat intake on BC mortality (46). The meta-analysis evaluated BC specific death in women by comparing the highest vs. lowest quartile of total fat and SFA intake (in g/day). The results showed no evidence of a relationship between total fat intake and BC specific death (n = 6 studies, HR: 1.14; 95% CI: 0.86-1.52; p: 0.34) or all-cause death (n = 4 studies; HR: 1.73; 95% CI: 0.82-3.66; P: 0.15) when comparing the highest vs. lowest quartile of intake. However, SFA intake was associated with increased risk of BC death (n = 4 studies; HR: 1.51; 95% CI: 1.09-2.09). A linear trend was not found as there was no significant increase for risk of BC specific death for every 20g incremental increase in SFA (n = 4; HR: 1.03; 95% CI: 0.77-1.38, P: 0.80).

Cohort Studies

Data from the NHS was used to evaluate the association between fat consumption and risk of BC related death (47). Results displayed a modest but not statistically significant increase in total mortality between the highest vs. lowest quintile of total fat intake (RR: 1.34, 95% CI: 0.97-1.85; P-trend: 0.40). The Life After Cancer Epidemiology study found that increased consumption (0.5 to ≥1.0 servings/day)

of high-fat dairy was associated with increased risk of BC mortality (HR: 1.49; 95% CI: 1.00-2.24; P-trend: 0.05), all cause mortality (HR: 1.55; 95% CI: 1.22-1.97; P-trend < 0.001), and non-BC related mortality (HR: 1.67; 95% CI: 1.13-2.47; P-trend: 0.007) when compared to the reference (0 to <0.5 servings/day) (48). In total, 1,893 women (75% postmenopausal) with BC participated, and upon a median 11.8-year follow up there were 349 cases of recurrence, and 372 deaths (50.8%, 189 cases related to BC). No association was observed for low-fat dairy consumption. Quality of fat consumption is particularly important when assessing total fat consumption on risk of recurrence and death in BC survivors. Comparison of studies regarding total fat and subtypes with regard to BC recurrence, survival, and mortality can be seen in Table 7.

Prospective investigation into fat subtypes in a cohort of 4,441 women revealed that increased SFA and trans fat consumption was also shown to be associated with increased risk of overall death (49). A mean follow-up of 5.5 years found that 525 participants died, in which 26.1% of deaths were due to BC. A median intake of 13% of total kcals (compared to 7%) coming from SFA was associated with a 41% increased risk for all-cause death (HR = 1.41; 95% CI: 1.06-1.87), while doubling the percentage of trans fat consumption was associated with 78% increased risk of death (HR: 1.78; 95% CI: 1.35-2.32; P-trend: 0.01). Similar results were seen for BC survival although did not reach significance.

In contrast, increased consumption of omega-3 PUFAs in a cohort of women in New York (n = 1,463) was associated with decreased all-cause mortality in BC survivors, upon a median follow-up of 14.7 years (50). Women included in the study were aged 20 – 98 years, primarily postmenopausal (67%), and Caucasian (94%). Specifically, increased consumption of docosapentaenoic acid (DPA) (HR: 0.71; 95% CI: 0.55-0.92) and EPA (HR: 0.71; 95% CI: 0.55-0.92) was associated with a 16-34% reduced risk for all-cause mortality when comparing the highest quintile of intake to never. Additionally, increased consumption of tuna (HR: 0.71; 95% CI: 0.55-0.92), and baked/broiled fish (HR: 0.75; 95% CI: 0.58-0.97) was associated with a 25-35% decreased risk of all-cause mortality. A study on another cohort of women with BC (n = 3,081) reported that increased consumption of EPA and DHA from food was associated with reduced risk of recurrence, and all-cause mortality upon a mean 7.3 year follow up (51).

Intake of >73mg/day of EPA and DHA reduced risk of recurrence by 25% when comparing tertile 2 and 3 to the lowest tertile of consumption (Tertile 2: HR: 0.74; 95% CI: 0.58-0.94; Tertile 3: HR: 0.72; 95% CI: 0.57-0.90). Additionally, a dose-dependent increase in EPA and DHA was associated with reduced risk of all-cause mortality (Tertile 2: HR: 0.75; 95% CI: 0.55-1.04; Tertile 3: HR: 0.59; 95% CI: 0.43-0.82).

Clinical Trials

The Women's Intervention Nutrition Study (WINS) evaluated how reduced fat intake impacts BC recurrence in postmenopausal women (52). This study was 5.2 years in total and enrolled 2,437 women that were randomly assigned to either the dietary intervention group (n = 975) or control group (n = 1,462). All women were within 48 to 75 years old. Body mass index went unreported although baseline weight was comparable between the groups (intervention group: 160.2 ± 35.1lbs; control group: 160.0 ± 35.0lbs). In the intervention group participants were required to reduce their dietary intake to <15% total daily kcal. Fat gram goal was calculated based on the participant's body weight divided by six; all gram fat goals remained between 20 – 30 grams per day. Daily fat recommendation adherence was assessed through 24-hour telephone recalls. At 5 years follow up, daily fat intake for the control group was 53.9 ± 26.7g/d and for the intervention group it was 34.9 ± 18.4g/d ($P < 0.0001$). Specifically, there was reduction in SFA (19 to 10g/d), MUFAs (22 to 12 g/d), and PUFAs (12 to 6 g/d) in the intervention group. Weight reduction was statistically significant ($P = 0.005$) between the intervention and control group (6.1 lb. mean weight difference). Altogether this study suggests that increased education on a low-fat dietary pattern may decrease intake of fat and reduce weight in women that could be associated with decreased BC recurrence.

Interestingly, DHA by itself has notably improved the outcome of chemotherapy in women with rapidly burgeoning visceral metastases (53). This observation may be a result of the capacity for DHA to enrich the cellular membranes of tumor cells thus increasing sensitivity to chemotherapy. This open-label single arm phase II study implemented 1.8g per day of DHA to an anthracycline-based chemotherapy (FEC) regimen in 25 BC patients. The median age was 58 years, while BMI, and ethnicity went

unreported. At a mean follow up of 31 months there was a significant difference in DHA total fatty acids (0% to 4.3%) determining two groups of high-DHA and low-DHA, respectively, the cut off between the two being 2.5%. Time to progression was significantly greater in the high-DHA group in comparison to the low-DHA group (8.7 months vs. 3.5 months; p: 0.02). Overall survival was also significantly greater in the high-DHA group compared to the low-DHA group (34 months vs. 18 months; p: 0.007). This study indicated that supplementation with increased amounts of DHA can attenuate progression of metastatic BC in patients undergoing chemotherapy and increase overall survival.

Table 7 - Summary of studies investigating an association between fat intake and its subtypes on breast cancer recurrence and survival

Design	Reference	Source	Effect	Outcome	HR/OR/RR (95% CI)
Meta-analysis					
	Brennan et al. (2017)	Total fat	No association	BC specific death	HR: 1.14 (0.86-1.52)
		Total fat	No association	All cause death	HR: 1.73 (0.82-3.66)
		SFA	Increased risk	BC specific death	HR: 1.51 (1.09-2.09)
Cohort studies					
	Holmes et al. (2009)	Total fat	Modest increase	BC specific death	RR: 1.34 (0.97-1.85)
	Kroenke et al. (2013)	HF dairy	Increased risk	BC specific death	HR: 1.49 (1.00-2.24)
		HF dairy	Increased risk	All cause death	HR: 1.55 (1.22-1.97)
		HF dairy	Increased risk	Non-BC related death	HR: 1.67 (1.13-2.47)
	Beasley et al. (2011)	SFA	Increased risk	All cause death	HR: 1.41 (1.06-1.87)
		Trans fat	Increased risk	All cause death	HR: 1.78 (1.35-2.32)
	Khankari et al. (2015)	DPA	Decreased risk	All cause death	HR: 0.71; (0.55-0.92)
		EPA	Decreased risk	All cause death	HR: 0.71; (0.55-0.92)
		Tuna	Decreased risk	All cause death	HR: 0.71; (0.55-0.92)
		Baked/broiled fish	Decreased risk	All cause death	HR: 0.75; (0.58-0.97)
	Patterson et al. (2011)	EPA & DHA	Decreased risk	Recurrence	HR: 0.72; (0.57-0.90)
Clinical trials					
	Hoy et al. (2009)	Reduced fat	No association	Recurrence	Unreported
	Bougnoux et al. (2009)	DHA	Reduce progression	Metastases	Unreported

HF: High fat

Discussion

Breast cancer is the second most common type of cancer diagnosed among women in America. Although survival rates have positively increased over the years due to improved treatment and awareness, decreased risk and increased survival may come about with dietary modifications, particularly with regard to fat consumption. Increased percentage of total calories coming from fat was associated with increased risk and reoccurrence in this review, however evaluation of specific types of fat displayed contradicting results. Evaluation of specific types of dietary fat displayed more clear associations that could be used for future recommendations regarding fat consumption to decrease risk of BC, recurrence and increase survival after BC diagnosis.

Four meta-analyses included in this review found that increased total fat consumption was positively associated with BC risk (5-8). Moreover, these meta-analyses found that increased total fat consumption was seen to be significantly associated with increased risk of BC among postmenopausal, but not premenopausal women. However, clinical trials failed to find an association between intake of total fat and risk of BC (9, 10) for both pre- and postmenopausal women. Surprisingly, increased intake of total fat was associated with decreased risk of ER+/PR- BC in one study (9). However, identification between specific types of fat and BC risk may lead to more explicit associations to support recommendations regarding sources of fat.

Increased consumption of animal fat (5, 12-14, 16-19) and SFA (5, 21, 22, 24, 26, 28, 29) in this review was strongly associated with increased risk of BC while consumption of fish (30, 31, 37) and PUFAs (30, 38) was inversely related with risk. Results regarding MUFA intake was inconsistent, but studies suggest that increased consumption of olive oil may be inversely related to risk of BC (27, 42-45). Risk, recurrence, and survival of BC could possibly be explained by the different types of fats and their effects on biomarkers of BC, such as breast tissue density, serum levels of sex hormones, and inflammatory markers.

Evidence presented in this review demonstrated a positive association between BC risk and the intake of both animal fat and SFA. This effect could possibly be explained by their influence on breast

density and sex hormone concentrations, both of which are a risk factor for BC. Studies have found that adolescent consumption of SFA (54) and animal fat (55) is associated with increased breast density in adulthood. Additionally, increased intake of SFA has been positively associated with increased concentrations of estradiol (56).

Intake of total PUFAs in this review was associated with decreased risk of BC (30, 38), however individual consumption of omega-3 and omega-6 fatty acids displayed contradicting associations. Omega-6 fatty acids were associated with BC risk (35, 39), while omega-3 fatty acids were shown to be protective (28, 30, 41). These results were upheld in this review when studies evaluated BC risk with n-3: n-6 PUFA ratio (32, 34, 40). Additionally, food sources such as fish were notably associated with decreased risk of BC in this review (31, 33, 37), as it is a good source of omega-3 fatty acids in the diet. Lastly, studies in this review that assessed EPA and DHA displayed a decreased risk with increased intake (23, 41).

Results in this review regarding total, and specific PUFA intake may be explained by their effect on risk factors associated with BC. For instance, studies have shown that mammographic density is notably decreased with increased consumption of fish (57), and intake of ALA, EPA, DHA, and DPA (58, 59) in the diet. Furthermore, a longitudinal study suggested that decreased consumption of PUFAs during adolescence was associated with increased breast density (54). Studies have also suggested that increased consumption of omega-3 FAs (EPA and DHA) were associated with decreased sex hormone concentrations (60), specific inflammatory biomarkers such as CRP (61), Ki-67 in breast tissue (62) and improved antioxidant status (63).

Studies also suggest that increased consumption of EPA and DHA during treatment for BC was associated with decreased peripheral neuropathy (PN) (64), and bone turnover (65) that may contribute to improved BC survival. PN is a common side effect of chemotherapy, and supplementation with n-3 PUFAs may be beneficial due to decreased reactive oxygen species and improved antioxidant status in the patient. In addition, bone turnover is a side effect of aromatase inhibitors usage, most often used to treat postmenopausal BC patients that are already at increased risk for decreased bone density due to age.

Supplementation with EPA and DHA may be beneficial for this patient population to decrease risk of fractures that is associated with decreased quality of life, and overall survival (66).

Consumption of olive oil was strongly associated with decreased BC risk although MUFAs with regard to BC risk is inconclusive. Studies suggest decreased consumption of MUFAs is associated with increased breast density (54). In contrast, increased consumption of MUFAs has also been associated with higher levels of sex hormones in nipple aspirate fluid (67). However, regular consumption of olive oil, a good source of MUFAs has been shown to decrease mammographic (68). The PREDIMED study included in this review highlights that increased adherence to a MD supplemented with EVOO in comparison to a low fat or MD diet supplemented with nuts was protective for postmenopausal BC risk (43). Overall, further research is needed to assess the relationship between MUFA consumption and BC risk, however intake of olive oil is emerging as a possible protective agent for BC.

The relationship between fat consumption and its subtypes is a supported dietary modification recommendation for BC overall. Limitations among the currently available literature of studies investigating fat intake and BC risk could be skewed. In this review, the majority of evidence was pulled from epidemiological studies. The majority of these studies rely on FFQ or 24-hour dietary recalls to collect data. Such methods rely on individual reports, which may not be entirely accurate due to memory recall issues, or misreporting amount, and frequency of intake by the individual. To solve this problem future studies should correlate data obtained from dietary reports, and serum levels of differing fat types to see if results coincide. Overall, this would curtail some of the results that are the outcome of misreporting, and may result in increased positive or negative associations.

Studies in this review regarding survival and reoccurrence were mixed based on type of fat. Total fat intake was not associated with BC specific death (46, 47) or all cause death (46). However, increased consumption of high fat dairy was significantly associated with increased risk of BC specific death, all cause death, and non-BC related death (48). Increased risk for all cause death in BC patients was positively associated with intake of SFA and trans fat in this review (49). In contrast, consumption of EPA and DHA was associated with decreased risk of all cause death (50) and recurrence (51).

This review summarizes key findings that are currently present in the literature regarding fat consumption and BC. Studies suggest that adherence to a low fat or MD dietary pattern supplemented with EVOO may decrease BC risk, particularly for postmenopausal women. The MD emphasizes consumption of both EVOO and fish as its main source of fat in the diet that was seen in this review to be protective against BC. Results also suggest that women should consume less food sources high in SFA and trans fat, for instance animal products, and processed food due to evidence suggesting increase BC risk, and all cause death. Additionally, supplementation with EPA and DHA may be beneficial to diminish BC risk, and for patients going through treatment. Overall, fat consumption in the literature is a recognized modifiable risk factor, although recommendations should be provided regarding specific types of fat as they display opposing effects.

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