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Systematic Review

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Lipid Intake and Breast Cancer Risk: Is There a Link? A New Focus and Meta-Analysis

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ABSTRACT

Objective: To determine if there is an association between total lipid intake, saturated fatty acid (SFA), Poly- and Mono-Unsaturated Fatty Acid (PUFA and MUFA) and cholesterol intake and breast cancer risk.

Materials and Methods: We conducted a systematic review of the literature and a meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included all cohort and case-control studies published up to December 2020 with subgroup analysis according to menopausal status.

Results: We included 44 articles for analysis. There was no association between total fat, SFA, MUFA, PUFA and cholesterol intake and breast cancer in the general population and in pre-menopausal women. In postmenopausal women, high SFA consumption was associated with increased breast cancer risk in case-control studies [relative risk (RR): 1.12; confidence interval (CI) 95%: 1.03–1.21; p = 0.006 but not in cohort studies (RR: 1.01; CI 95%: 0.85–1.19; p = 0.93).

Conclusion: There was a weak association between high SFA consumption and breast cancer risk in post-menopausal women, however there was high heterogeneity for this analysis. As lipids can have different actions in the same family, studies should rather focus on specific lipid consumption.

Keywords: Breast cancer risk; cholesterol; dietary fat intake; mono-unsaturated fatty acid; saturated fatty acid

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Key Points

- There was no association between total fat, saturated fatty-acids, mono and poly-unsaturated fatty acids and cholesterol intake and breast cancer incidence in the general population and in pre-menopausal women.
- There was a weak association between high saturated fatty acids consumption and breast cancer risk in post-menopausal women, but the results were heterogeneous.

Introduction

Among women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related mortality worldwide. It was estimated that in 2020 it represented over 2.2 million new cases (24.5% of all cancers) and caused over 680,000 deaths (15.5% of cancer-related deaths) (1). To date, different risk factors have been identified, some of which are potentially modifiable. Breast cancer is more commonly associated with age, environmental, hormonal and lifestyle factors than genetic factors ones (2). As it represents a major public health issue and both incidence and mortality will increase in the next decades (1), prevention focuses on acting on modifiable risk factors. Among lifestyle-related breast cancer risk factors, some are commonly accepted, including lack of physical activity (3) and overweight and obesity (4), while others are still controversial. Of interest, diet is known to play a role in the development of various cancers, such as colon cancer (5). Yet, in breast cancer the role of diet remains uncertain (2). Assessing the role of diet on breast cancer risk is complex, as diet varies between individuals, cultures and territories. Moreover, different evaluation methods exist, such as consumption of a particular food, a particular nutrient, or a particular pattern. For instance, the Mediterranean diet, dairy product consumption and fruit and vegetables intake seem to have a positive impact on reducing

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breast cancer incidence, while red meat consumption and alcohol intake seem to increase breast cancer risk (6). Similarly, organic food diet (7) and coffee consumption (8) seem to decrease breast cancer risk in postmenopausal women.

Commonly called "fats", lipids are, along with proteins and carbohydrates, one of the three major families of macronutrients. Natural dietary lipids, which are essential in the diet for normal nutrition, include cholesterols and fatty acids. A distinction is made between saturated (SFA), mono-unsaturated (MUFA) and poly-unsaturated (PUFA) fatty acids. However, industrial fatty acids, which are mainly unsaturated trans fatty acids (TFA), seem to increase the risk of breast cancer (9). The role of natural lipids in carcinogenesis, and in particular their carcinogenic impact on the breast, has been suggested (10). Several studies and meta-analyses investigated the impact of dietary lipid intake and breast cancer incidence but the results are contradictory and inconclusive (11-14).

Our goal was therefore to attempt to determine, through a meta-analysis based on an updated literature review including cohort and case-control studies, whether there is an association not only between total lipid intake and breast cancer, but also to determine the specific role of SFA, PUFA, MUFA, and dietary cholesterol on breast cancer risk. In addition, we performed a subgroup analysis on menopausal status.

Materials and Methods

Search Strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15). A search was conducted on the MEDLINE database for articles published up to December 2020 and written in English, French or Spanish. The query included the following keywords: "fat intake", "fatty acid", "cholesterol", "breast cancer risk", "breast carcinoma", "breast neoplasm". The full query was: ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields] OR ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "neoplasm"[All Fields]) OR "breast neoplasm"[All Fields]) OR ("breast"[All Fields] AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]))) AND ("fatty acids"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields]) OR "fatty acids"[All Fields] OR ("fatty"[All Fields] AND "acid"[All Fields]) OR "fatty acid"[All Fields] OR ("fat"[All Fields] AND ("intake"[All Fields] OR "intake s"[All Fields] OR "intakes"[All Fields])) OR ("cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol s"[All Fields] OR "cholesterol"[All Fields] OR "cholesterols"[All Fields])).

Eligibility Criteria

Prospective cohort or case-control studies were included if they met the following eligibility criteria:

- Population: pre- or post-menopausal women
- Exposure: high dietary intake of total fat, SFA, MUFA, PUFA, or cholesterol
- Comparator: low dietary intake of total fat, SFA, MUFA, PUFA, or cholesterol
- Outcome: risk increase of breast cancer

In addition, we included only articles where the population of each group was provided or could be precisely calculated. If more than one study involved the same population, only the most recent study or the one with the highest number of cases was included in the analysis.

Bibliographic Selection

The initial query gave 7,088 results. These articles were analyzed by two independent reviewers (M.L. and A.K.). Based on the title and abstract, 6,761 articles were excluded because they were not directly related to the subject under study, because of an unassessed association between breast cancer and dietary lipid intake, or because they were meta-analyses, correspondence, literature reviews, basic research articles, animal or *in vitro* studies. We retained 323 articles that were selected for full-text review. Among those, a further 279 articles were excluded because they did not investigate dietary intake of total fat, SFA, MUFA, PUFA or cholesterol and breast cancer risk, because no data was available in the published paper or because it was related to the same cohort of another included article. The final selection included 44 articles for the meta-analysis. Discrepancies between the two reviewers were resolved by consensus. The bibliographic selection, with exclusion reasons, is reported in the flow chart (Figure 1).

Data Collection

For each article, one reviewer (AK) extracted the following information: first author name, year of publication, type of study (cohort or case-control), population studied (pre- or post-menopausal or both), the type of lipid (total fat, SFA, MUFA, PUFA, cholesterol) and the number of patients in each group (high versus low exposure, case and controls). In addition, country, years of inclusion, group constitution method (*i.e.*, in two groups, in tertiles, quartiles, or quintiles), principal results and adjusting variables were retrieved. Verification of all these data was performed by the second reviewer (ML).

Statistical Analysis

For each article, we compared the group with the highest intake *versus* the group with the lowest. For instance, if patients were divided into five groups (quintiles), we compared the first with the fifth. The meta-analysis was performed using R (version: 3.6.1, 2019-07-05) (16) and with the metafor package (https://metafor-project.org/). Given the heterogeneity of the populations in the different studies, the random effect model was used in the meta-analysis. The articles were weighted on the standard error of each population, which in turn depended not only on the size of the cohort but also on its homogeneity. Summary relative risk (RR) was calculated with an estimated 95% confidence interval. Heterogeneity was quantified with a maximum-likelihood estimator for Tau^2 and we calculated the Higgins' I^2 statistic. For the test of heterogeneity, the Cochran Q p-value was obtained with Wald-type test.

Results

Forty-four articles were included in the meta-analysis, consisting of 28 case-control studies (17-44) and 16 cohort studies (45-60). Results of

each study are reported in Tables 1 and 2. In total, this meta-analysis involved 1,185,896 women, of whom 54,553 had breast cancer. Table 3 summarizes the pooled analysis results according to the studied population, lipids, and study type.

Total Fat Intake

Total fat intake was evaluated in 27 case-control studies (96%) (17-41, 43, 44) and in 15 cohort studies (94%) (45-57, 59, 60). Ten studies (18, 19, 21, 36, 38, 39, 41, 43, 54, 57) found an increased risk of breast cancer with elevated total fat intake. Considering menopausal status, one study in pre-menopausal (21) and two in post-menopausal (39, 54) women found an increased risk of breast cancer. Conversely, two studies found a decreased risk with high fat intake diet (26, 44), and one of them among pre-menopausal women (44). The remaining studies did not find significant association between total fat intake and breast cancer.

In the pooled analysis, there was no significant risk increase in high total fat intake on breast cancer risk, neither for cohort [RR: 0.98; confidence interval (CI) 95%: 0.65–1.48; p = 0.93] nor case-control (RR: 1.07; CI 95% 0.96–1.19; p = 0.225) studies.

Considering menopausal status, no difference was found in pre-menopausal (RR: 1.0; CI 95%: 0.90–1.11; p = 0.98) women. In post-menopausal women both cohort and case-control pooled analysis were not significant giving relative risk results of RR: 0.94; CI 95%: 0.84 - 1.04; p = 0.24 and RR: 1.07; CI 95%: 0.94–1.21; p = 0.31, respectively.

Saturated Fatty Acids Consumption

SFA intake was evaluated in 20 case-control studies (71%) (20-22, 24-28, 30-35, 37-41, 44) and in 15 cohort studies (94%) (45-57, 59, 60). Seven studies (21, 34, 37, 41, 54, 57, 60) found an increased risk of breast cancer with elevated SFA consumption. Only one study found significant association in post-menopausal women (21). Conversely, one cohort study found a decreased risk with high SFA consumption, independently from menopausal status (45). The remaining studies did not find significant association between total fat intake and breast cancer.

In pooled analysis, there was no significant risk increase with high SFA consumption in breast cancer risk, whether it was for cohort (RR: 0.94; CI 95%: 0.74–1.18; p = 0.58) or case-control (RR: 1.06; CI 95%: 0.97: 1.17; p = 0.20) studies.

Concerning post-menopausal women (Figure 2), the pooled analysis case-control studies showed a significant increase in breast cancer risk (RR: 1.12; CI 95%: 1.03–1.21; p = 0.006) while it was not significant in cohort studies (RR: 1.01; CI 95%: 0.85–1.19; p = 0.93). No statistical difference was found in pre-menopausal women (RR: 1.02; CI 95%: 0.86–1.2; p = 0.84).

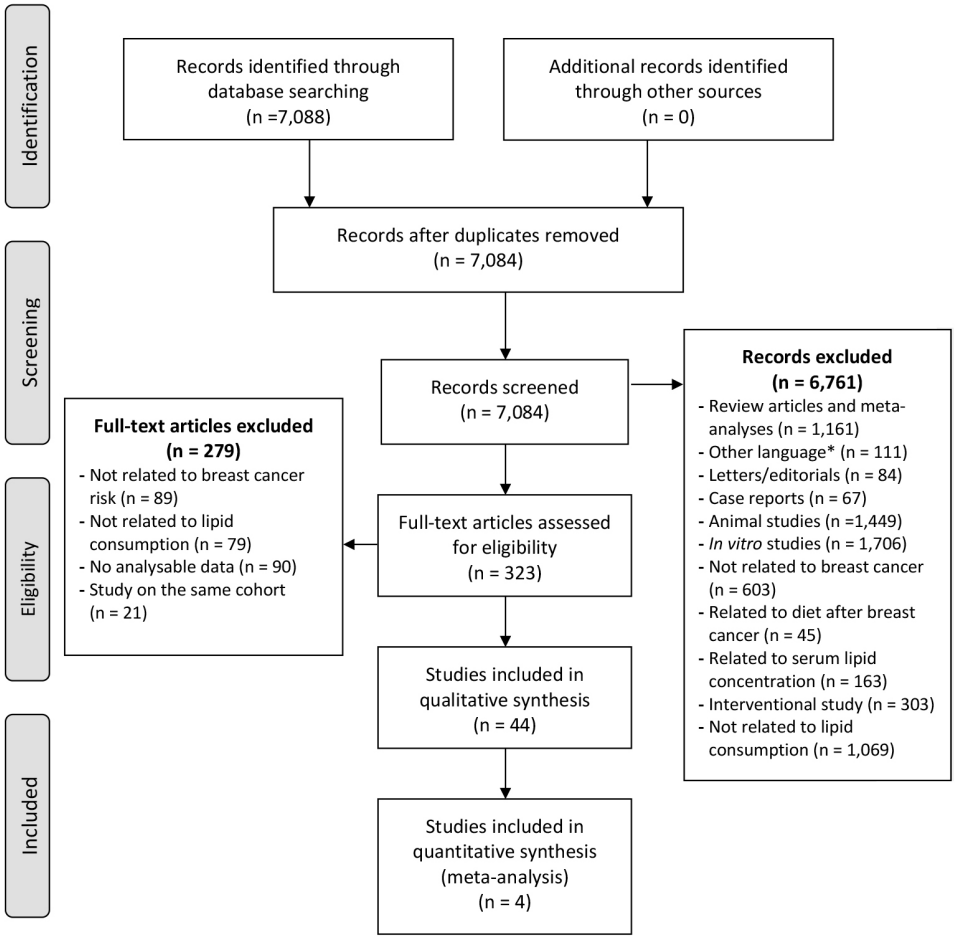

Figure 1. Flow chart diagram

n: number

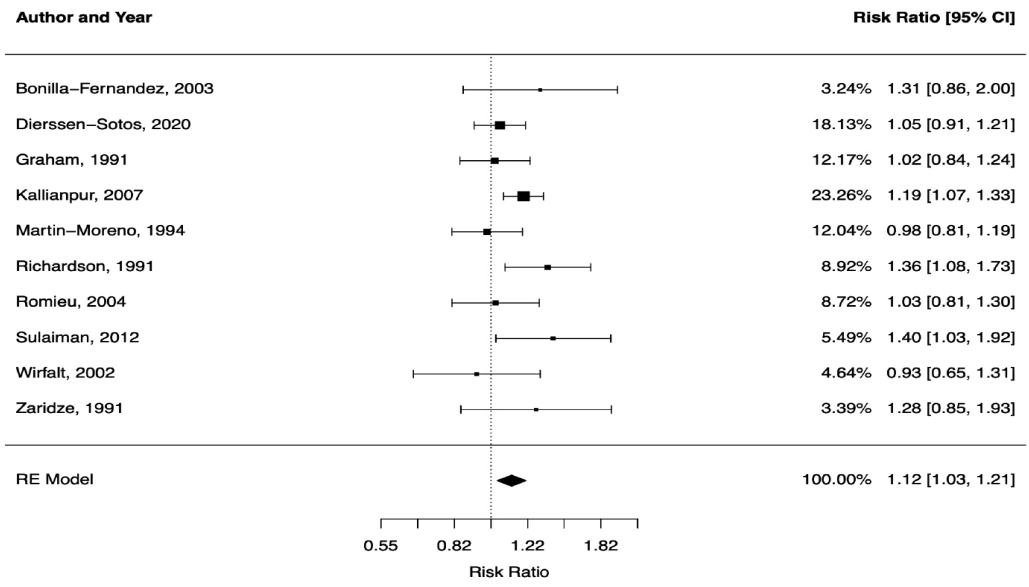

Figure 2. Forest plot of saturated fatty acids intake in case-control studies on post-menopausal women

CI: confidence interval

Unsaturated Fatty Acids Consumption

MUFA and PUFA consumption was evaluated in 15 case-control studies (54%) (21, 22, 24, 26, 28, 30, 31, 33-35, 37, 39, 40, 42, 44) and in 13 cohort studies (81%) (46-48, 50-57, 59, 60). Concerning PUFA, six articles found a decreased risk of breast cancer in women with elevated PUFA consumption (21, 22, 26, 31, 35, 40), among them one in pre-menopausal (40), and three in post-menopausal women (22, 31, 35). Conversely, five articles found an increased risk of breast cancer in women with elevated PUFA consumption (30, 34, 42, 47, 54), among them three in post-menopausal women (30, 47, 54). Concerning MUFA, six articles found an increased risk of breast cancer in women with elevated MUFA consumption (21, 30, 37, 54, 55, 57), among them four in post-menopausal women (30, 37, 54, 55). Conversely, one article found a decreased risk of breast cancer in pre-menopausal women with elevated MUFA consumption (44). The remaining studies did not find significant association between MUFA or PUFA consumption and breast cancer.

In pooled analysis there was no significant increased risk in high PUFA consumption on breast cancer risk, whether it was for cohort (RR: 1.02; CI 95%: 0.91–1.14; p = 0.78) or case-control (RR: 0.94; CI 95%: 0.82–1.08; p = 0.38) studies.

Considering menopausal status, no difference was found in pre-menopausal (RR: 1.07; CI 95%: 0.91–1.26; p = 0.42) women. In post-menopausal women both cohort and case-control pooled analysis were not significant (RR: 0.96; CI 95%. 0.83–1.11; p = 0.59 and RR: 0.88; CI 95%: 0.64–1.22; p = 0.44, respectively). Concerning MUFA, high consumption was not associated with increased breast cancer risk, whether it was for cohort (RR: 0.97; CI 95%: 0.87–1.08; p = 0.58) or case-control studies (RR: 1.03; CI 95%: 0.9–1.18; p = 0.66). No significant association was found in either pre-menopausal (RR: 0.99; CI 95%: 0.84–1.17; p = 0.93) or post-menopausal women, in either case-control studies (RR: 0.95; CI 95%: 0.83–1.08; p = 0.41) or cohort studies (RR: 1.16; CI 95%: 0.97–1.38; p = 0.11).

Cholesterol Consumption

Cholesterol consumption was evaluated in five case-control studies (18%) (21, 22, 26, 32, 34) and six cohort studies (43%) (45, 47, 48, 56, 58, 59). Three studies (34, 56, 58) found an increased risk of breast cancer with elevated cholesterol consumption, among them one found significant association in pre-menopausal women (56). None of the included studies found a decreased risk of breast cancer associated with high cholesterol consumption. The remaining studies did not find significant association between cholesterol consumption and breast cancer.

In pooled analysis there was no significant risk increase in high cholesterol consumption on breast cancer risk, whether it was for cohort (RR: 1.09; CI 95%: 0.71–1.61; p = 0.71) or case-control (RR: 1.22; CI 95%: 0.94–1.58; p = 0.13) studies.

Furthermore, no difference was found in post-menopausal women (RR: 0.98; CI 95%: 0.84–1.14; p = 0.772).

Discussion

The results of this meta-analysis does not demonstrate a statistically significant link between high consumption of total lipids, PUFA, MUFA and cholesterol and the occurrence of breast cancer. However, our results suggest that there is an association between SFA intake and breast cancer risk in postmenopausal women, although this was only found in case-controlled studies and not cohort studies. Nevertheless, it is necessary to underline the great heterogeneity in this meta-analysis. Lipid consumption may therefore play a role in breast health. Interestingly, another meta-analysis published in 2015 found a significant association between high SFA consumption and breast cancer risk among post-menopausal women, and the authors found this association only in case-control studies and not in cohort studies (61). These results are consistent with other previously published articles (62, 63). We investigated if high lipid consumption may act on breast tissue by the same mechanisms as obesity or if there were other underlying explanations.

Table 1. Case-control studies

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Alothaimeen, 2004	Saudi Arabia	499	498	Quartiles	Total population	Total fat	RR 1.6 (0.92–2.95)	Age, menopausal status
						SFA	**RR 2.4 (1.36–4.34)***	
						PUFA	**RR 2.1 (1.17–3.83)***	
						Cholesterol	**RR 1.9 (1.03–3.44)***	
Balasubramaniam, 2013	India	152	152	Binary	Total population	**Total fat**	**RR 2.4 (2.14–5.8)***	Age, age of menopause, parity, age of first pregnancy, breastfeeding
						SFA	**RR 2.16 (1.03–4.52)***	
Bonilla-Fernandez, 2003	Mexico	138	141	Binary	Total population	Total fat	RR 0.91 (0.28–2.95)	Family history of breast cancer, age, age at menopause, BMI, total energy intake, age of first delivery, parity, breastfeeding
						SFA	RR 0.91 (0.31–2.69)	
						MUFA	RR 0.66 (0.21–2.13)	
						PUFA	RR 0.62 (0.28–1.39)	
		68	69		Pre-menopausal	Total fat	RR 1.76 (0.41–7.53)	
						SFA	RR 0.67 (0.17–2.7)	
						MUFA	RR 1.1 (0.24–4.97)	
						PUFA	RR 2.2 (0.71–6.83)	
		69	72		Post-menopausal	Total fat	RR 0.77 (0.16–3.65)	
						SFA	RR 1.74 (0.47–6.45)	
						MUFA	RR 0.62 (0.15–2.53)	
						PUFA	**RR 0.1 (0.02–0.39)***	
Challier, 1998	France	345	345	Quintiles	Total population	Total fat	RR 1.7 (0.77–3.76)	Parity, BMI, total energy intake
						SFA	RR 1.6 (0.8–3.28)	
De Stefani, 1998	Uruguay	365	397	Quartiles	Total population	Total fat	RR 1.53 (0.89–2.62)	Age, menopausal age, total energy intake, BMI, parity, alcohol consumption, family history of BC
						SFA	RR 0.84 (0.34–2.07)	
						MUFA	RR 1.5 (0.69–3.23)	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Dierssen-Sotos, 2020	Spain	1,181	1,682	Tertiles	Total population	Total fat	OR 0.89 (0.67–1.19)	Age, province of recruitment, educational level, family history of breast cancer, BMI, age at first delivery, hormonal contraceptive use, and postmeno- pausal hormone therapy, physical activity, smoking status, alcohol consumption, total energy intake, menopausal status
						SFA	OR 0.87 (0.65–1.16)	
						MUFA	OR 0.88 (0.68–1.15)	
						PUFA	OR 1.21 (0.93–1.58)	
					Pre-menopausal	**Total fat**	**OR 0.51 (0.31–0.86)***	
						SFA	OR 0.87 (0.51–1.48)	
						MUFA	**OR 0.51 (0.32–0.82)***	
						PUFA	OR 1.33 (0.82–2.17)	
					Post-menopausal	Total fat	OR 1.12 (0.78–1.61)	
						SFA	OR 0.84 (0.59–1.20)	
						MUFA	OR 1.15 (0.83–1.60)	
						PUFA	OR 1.16 (0.84–1.61)	
Do, 2003	Korea	224	250	Quartiles	Total population	Total fat	RR 1.7 (0.9–2.45)	Family history of breast cancer, age at menopause, BMI, total energy intake, age of first delivery, parity, breastfeeding
						SFA	RR 1.2 (0.58–2.41)	
						Cholesterol	RR 1.3 (0.67–1.98)	
Ewertz, 1990	Denmark	1,474	1,332	Quartiles	Total population	**Total fat**	**OR 1.5 (1.17–1.8)***	Age, place of residence
Franceschi, 1996	Italy	2,569	2,588	Quintiles	Total population	**Total fat**	**OR 0.81 (0.72–0.90)***	Parity, education level
						SFA	OR 0.95 (0.86–1.04)	
						PUFA	**OR 0.70 (0.61–0.79)***	
						Cholesterol	OR 0.91 (0.82–1.00)	
Goodstine, 2003	USA	565	554	Quartiles	Total population	Total fat	RR 1.1 (0.64–1.84)	Family history of breast cancer, age at menopause, BMI, age of first delivery, parity, breastfeeding
						SFA	RR 1 (0.59–1.58)	
						MUFA	RR 1.2 (0.7–1.95)	
						PUFA	RR 1.1 (0.68–1.64)	
Graham, 1991	USA	439	494	Quartiles	Post-menopausal	Total fat	OR 0.9 (0.63–1.38)	Family history of BC, menarch age, education level, BMI, parity, age of first pregnancy
						SFA	OR 1 (0.71–1.53)	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Kallianpur, 2007	China	3,452	3,474	Quartiles	Total population	Total fat	OR 1.1 (0.92–1.31)	Family history of breast cancer, age, age at menopause, BMI, total lipid intake, parity, age of first delivery, alcohol consumption, smoking status, breastfeeding
						SFA	**OR 1.2 (1.01–1.42)***	
						MUFA	**OR 1.3 (1.12–1.56)***	
						PUFA	OR 0.9 (0.79–1.1)	
		2,086	1,968		Pre-menopausal	Total fat	OR 1 (0.82–1.32)	
						SFA	OR 1.1 (0.9–1.42)	
						MUFA	OR 1.2 (0.97–1.51)	
						PUFA	OR 1 (0.79–1.25)	
		1,366	1,506		Post-menopausal	Total fat	OR 1.2 (0.9–1.57)	
						SFA	OR 1.3 (0.99–1.66)	
						MUFA	**OR 1.5 (1.15–1.94)***	
						PUFA	OR 0.9 (0.68–1.15)	
Khankari, 2015	USA	1,463	1,500	Quartiles	Total population	**PUFA**	**RR 1.25 (1.2 –1.63)***	Age, family history of BC, oral contraceptive intake, BMI, parity, age of first pregnancy, education level, total energy intake, total cholesterol intake, age of menopause, economic level, religion, breastfeeding, radiation exposure
Lee, 2005	Taiwan	250	219	Binary	Total population	**Total fat**	**RR 1.9 (1.1–3.2)***	Age, education level
Levi, 1993	Switzerland	107	318	Tertiles	Total population	Total fat	RR 1.5 (0.86–2.71)	Age, education level

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Martin Moreno, 1994	Spain	762	988		Total population	Total fat	RR 0.98 (0.74–1.29)	Age, education, place of residence, BMI, total fat intake
						SFA	RR 1 (0.64–1.54)	
						MUFA	RR 0.85 (0.58–1.26)	
						PUFA	RR 1.34 (0.98–1.84)	
		247	356	Quartiles	Pre-menopausal	Total fat	RR 0.87 (0.53–1.42)	
						SFA	RR 0.77 (0.37–1.58)	
						MUFA	RR 0.71 (0.38–1.35)	
						PUFA	RR 1.58 (0.93–2.71)	
		515	632		Post-menopausal	Total fat	RR 1.1 (0.75–1.5)	
						SFA	RR 1.5 (0.91–2.62)	
						MUFA	RR 1 (0.6–1.57)	
						PUFA	RR 1.1 (0.73–1.59)	
Potischmann, 1998	USA	1,647	1,501	Quartiles	Pre-menopausal	Total fat	RR 0.9 (0.7–1.1)	Age, age at menopause, total energy intake, parity, education level, alcohol consumption
Pryor, 1989	USA	172	190	Quartiles	Pre-menopausal	Total fat	RR 0.7 (0.2–2.1)	Age, âde de menarche, BMI, Age de première grossesse, apport total en energie
		107	114	Quartiles	Post-menopausal	Total fat	RR 0.7 (0.2–2.7)	Age, menarch age, BMI, age of first pregnancy, total energy intake
Richardson, 1991	France	409	515	Tertiles	Total population	**Total fat**	**RR 1.6 (1.1–2.2)***	Age, menopause
						SFA	**RR 1.9 (1.3–2.6)***	
						MUFA	**RR 1.7 (1.2–2.5)***	
						PUFA	RR 102 (0.9–1.7)	
						Cholesterol	RR 1.3 (0.9–1.9)	
		93	133		Pre-menopausal	**Total fat**	**RR 1.8 (1-3.3)***	
						SFA	RR 1.7 (0.9–3.2)	
						MUFA	RR 2 (1.1–3.7)	
		161	202		Post-menopausal	Total fat	RR 1.4 (0.9–2.2)	
						SFA	**RR 2 (1.2–3.1)***	
						MUFA	**RR 1.5 (1–2.4)***	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Romieu, 2004	Mexico	475	1,391	Quartiles	Total population	Total fat	RR 0.9 (0.59–1.16)	Age, total energy intake, menopausal status, parity, family history of breast cancer
						SFA	RR 1.4 (0.83–2.25)	
						MUFA	RR 1.1 (0.67–1.91)	
						PUFA	**RR 0.5 (0.31–0.72)***	
		189	692		Pre-menopausal	Total fat	RR 1 (0.61–1.74)	
						SFA	RR 1.3 (0.59–3.01)	
						MUFA	RR 0.9 (0.39–2)	
						PUFA	RR 0.7 (0.36–1.3)	
		286	742		Post-menopausal	Total fat	RR 0.7 (0.45–1.12)	
						SFA	RR 1.2 (0.6–2.2)	
						MUFA	RR 1.6 (0.77–3.15)	
						PUFA	**RR 0.4 (0.2–0.66)***	
Sulaiman, 2012	Malasyia	382	382	Quartiles	Pre-menopausal	Total fat	RR 1.2 (0.61–2.38)	Age, family history of cancer, parity, age of first pregnancy, total fat intake, age of menopause, tobacco consumption, breastfeeding
						SFA	RR 1.6 (0.8–3.26)	
						MUFA	RR 1 (0.5–1.92)	
						PUFA	RR 0.9 (0.46–1.84)	
		166	166		Post-menopausal	**Total fat**	**RR 2.2 (1.56–3.19)***	
						SFA	RR 1.9 (0.71–3.76)	
						MUFA	RR 2.1 (0.57–2.89)	
						PUFA	RR 1.3 (0.56–3.11)	
Tayyem, 2019	Jordan	200	200	Quartiles	Total population	**Total fat**	**OR 3.87 (1.53–9.77)***	Age, marital status, education, work, income, physical activity, smoking, family history, health problem, number of pregnancies, lactation, contraceptives, hormonal replacement therapy
Toniolo, 1994	USA	180	829	Quintiles	Total population	Total fat	OR 1.5 (0.89–2.48)	Family history of breast cancer, age, age of first pregnancy, parity, BMI
						SFA	OR 1.5 (0.88–2.46)	
Van't Veer, 1990	Netherlands	133	289	Quintiles	Total population	**Total fat**	**RR 3.5 (1.64–7.64)***	Age, menarch age, age of first pregnancy, BMI, total energy intake, tobacco and alcohol consumption, parity, oral contraceptive intake, family history of BC

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Wang, 2008	USA	1,703	2,045	Quintiles	Total population	**Total fat**	**RR 1.4 (1.1-1.65)***	Family history of breast cancer, ethicity, age, age at menopause, age of first period, place of residence, total energy intake, parity, education level, alcohol consumption, total lipid consumption, breastfeeding
						SFA	RR 0.8 (0.63–1.07)	
Wirfalt, 2002	Sweden	237	673	Quintiles	Post-menopausal	Total fat	OR 1.5 (0.92–2.49)	Age, age at menopause, total energy intake, parity, education level, alcohol consumtion, parity, BMI, total energy intake
						SFA	OR 1 (0.57–1.61)	
						MUFA	**OR 2 (1.19–5.21)***	
						PUFA	**OR 3.2 (1.75–5.21)***	
Zaridze, 1991	Russia	139	139	Binary	Post-menopausal	Total fat	RR 0.5 (0.04–7)	Menarch age, education level, total energy intake
						SFA	RR 1.7 (0.24–11.7)	
						MUFA	RR 1.8 (0.19–16.7)	
						PUFA	**RR 0.14 (0.03–0.69)***	
Zhang, 2011	China	306	132	Quartiles	Pre-menopausal	Cholesterol	RR 0.5 (0.15–1.96)	Age, BMI, age of first pregnancy, family history of BC, total fat intake, income, physical activity, education level, alcohol and tobacco consumption, breastfeeding, parity, contraception, ethnicity, marital status, professional activity, parity
						Total fat	RR 0.8 (0.56–1.17)	
						SFA	RR 0.8 (0.57–1.2)	
						MUFA	RR 0.8 (0.58–1.22)	
						PUFA	RR 0.7 (0.5–1.06)	
						Total fat	RR 0.7 (0.38–1.17)	
						SFA	RR 0.5 (0.22–1.23)	
						MUFA	RR 0.6 (0.23–1.38)	
						PUFA	**RR 0.5 (0.21–0.97)***	
					Post-menopausal	Total fat	RR 1.2 (0.52–2.94)	
						SFA	RR 1.7 (0.41–7.03)	
						MUFA	RR 2.2 (0.52–9.33)	
						PUFA	RR 0.6 (0.19–2.02)	

*Significant values are shown in bold.

RR: relative risk; OR: odds ratio; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid; BMI: body mass index

Table 2. Cohort studies

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Byrne, 2002	**NHS**	United States (1976–1992)	1,071	44,697	Quintiles	Post-menopausal	Total fat	RR 0.94 (0.77–1.15)	Age, family history of breast cancer, BMI, parity, age at first pregnancy, alcohol consumption, age at first period, age at menopause, hormonal replacement therapy, total energy intake
							SFA	RR 0.88 (0.70–1.12)	
							MUFA	RR 1.13 (0.81–1.57)	
							PUFA	RR 0.93 (0.74–1.16)	
Farvid, 2014	**NHS II**	United States (1991–2011)	2,830	88,804	Quintiles	Total population	Total fat	RR 1.07 (0.95–1.21)	Age, family history of breast cancer, oral contraceptive, BMI, physical activity, parity, age at first delivery, education level, total energy intake, age at menopause, hormonal replacement therapy, menopausal status, alcohol consumption, smoking, fiber consumption
							SFA	RR 1.11 (0.99–1.25)	
							MUFA	RR 1.13 (1–1.27)	
							PUFA	RR 0.95(0.84–1.07)	
							Cholesterol	RR 1.05(0.87–1.26)	
						Pre–menopausal	Total fat	RR 1.07 (0.91–12.6)	
							SFA	RR 1.1 (0.93–1.29)	
							MUFA	RR 1.08 (0.91–1.27)	
							PUFA	RR 0.98 (0.83–1.15)	
							Cholesterol	**RR 1.32 (1.03–1.7)***	
						Post–menopausal	Total fat	RR 1.02 (0.83–1.26)	
							SFA	RR 1.03 (0.83–1.27)	
							MUFA	RR 1.12 (0.91–1.37)	
							PUFA	RR 0.96 (0.78–1.2)	
							Cholesterol	RR 1.03 (0.75–1.42)	
Gago-Domingez, 2003	**SCS**	Singapore (1993–1998)	314	35,298	Quartile	Total population	Total fat	RR 0.94 (0.68–1.31)	Age, family history of breast cancer, age at menopause, alcohol consumption, ethnicity
							SFA	RR 1.35 (0·69–2·61)	
							MUFA	RR 1.02 (0.73–1.43)	
							PUFA	RR 1.27 (0.92–1.74)	
Howe, 1991	**CNBSS**	Canada (1980–1987)	519	56,837	Quartile	Total population	Total fat	OR 1.35 (1–1.82)	Age, family history of breast cancer, BMI, parity, age at first delivery, education level, total energy intake, fiber consumption, age at menopause, hormonal replacement therapy
							SFA	OR 1.08 (0.43–1.59)	
							MUFA	OR 1.23 (0.81–1.89)	
							PUFA	OR 1.3 (0.93–1.82)	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Jones, 1987	**NHANES**	United States (1070–1975)	99	5,495	Quartile	Total population	**Total fat**	**HR 0.34 (0.16–0.73)***	Age, family history of breast cancer, BMI, menopausal status, age at menopause, age of first period
							SFA	**HR 0.44 (0.23–0.86)***	
							Cholesterol	HR 0.7 (0.36–1.37)	
Kim, 2017	**SKCCR**	Korea (2002–2014)	72	5,046	Binary	Total population	**Cholesterol**	**HR 1.69 (1.01–2.82)***	Age, family history of breast cancer, oral contraceptive, BMI, physical activity, parity, education level, age of first period, age at menopause, menopausal status, alcohol consumption, smoking
						Pre–menopausal	Cholesterol	HR 1.42 (0.75–2.67)	
						Post-menopausal	Cholesterol	HR 1.97 (0.81–4.80)	
Kushi, 1992	**IWHS**	United States (1985–1989)	459	34,388	Quartile	Post-menopausal	Total fat	RR 1.16 (0.87–1.55)	Age of first period, age at menopause, age of first delivery, BMI, alcohol consumption, total energy intake
							SFA	RR 1.07 (0.68–1.68)	
							MUFA	RR 1.9 (0.7–1.7)	
							PUFA	**RR 1.49(1.01–2.02)***	
							Cholesterol	RR 1.24 (0.87–1.76)	
Löf, 2007	**SWLHC**	Sweden (1991–2004)	974	44,569	Quintiles	Total population	Total fat	HR 1.02 (0.72–1.45)	Age, family history of cancer, oral contraceptive, BMI, parity, age of first pregnancy, education level, alcohol consumption, age of first period, total fat intake
							SFA	HR 1.12 (0.69–1.81)	
							MUFA	HR 0.88 (0.53–1.46)	
							PUFA	HR 0.72 (0.52–1)	
Park, 2012	**TSS**	United States (1993–2007)	3,885	85,089	Quintiles	Post-menopausal	Total fat	HR 0.94(.085–1.0.5)	Age, family history of cancer, BMI, parity, age of first delivery, ethnicity, age at menopause, alcohol consumtion, smoking
							SFA	HR 0.93 (0.83–1.02)	
							MUFA	HR 1.01 (0.91–1.13)	
							PUFA	HR 0.97 (0.88–1.08)	
							Cholesterol	HR 1.01(0.9–1.12)	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Sczaniecka, 2012	**VITAL**	United States (2000–2007)	772	29,480	Quintiles	Post-menopausal	Total fat	HR 1.43 (0.95–2.14)	Age, ethnicity, BMI, family history of breast cancer, age of first pregnancy, physical activity, age of first period, hysterectomy, oral contraceptive, total energy intake, fruit consumption, alcohol consumption, age at menopause
							SFA	HR 1.47 (1.00–2.15)	
							MUFA	**HR 1.61 (1.08–2.38)***	
							PUFA	**HR 1.07 (0.76. 1.52)**	
Sellem, 2018	**NNS**	France (2009–2017)	545	44,039	Quintiles	Total population	Total fat	HR 1.43 (0.92–2.22)	Age, family history of breast cancer, education level, alcohol consumption, smoking, BMI, total energy intake, vegetables consumption, physical activity
							SFA	**HR 1.98 (1.24–3.17)***	
							MUFA	HR 1.29 (0.76–2.21)	
							PUFA	HR 0.89 (0.62–1.28)	
Sieri, 2014	**EPIC**	Europe (1992–2004)	10,062	337,327	Quintiles	Total population	**Total fat**	**HR 1.06 (1.01–1.12)***	Menopausal status, hormone replacement therapy, alcohol consumption, smoking, education level, BMI, parity
							SFA	**HR 1.05 (1.02–1.08)***	
							MUFA	**HR 1.06 (1.02–1.11)***	
							PUFA	HR 0.98 (0.95–1.01)	
Thiébaut, 2007	**AARP DHS**	United States (1995–2000)	5,301	188,736	Quintiles	Post-menopausal	**Total fat**	**HR 1.22 (1.03–1.45)***	Age, family history of breast cancer, BMI, physical activity, parity, age of first pregnancy, age at menopause, hormone replacement therapy, alcohol consumption, smoking
							SFA	**HR 1.18 (1.06–1.31)***	
							MUFA	**HR 1.12 (1.00–1.24)***	
							PUFA	**HR 1.12(1.01–1.25)***	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Van den Brandt, 1993	**NLCS**	Netherlands (1986–1989)	471	62,573	Binary	Post-menopausal	Total fat	RR 1.08 (0.73–1.59)	Age, family history of breast cancer, BMI, oral contraceptive, age of first period, parity, age of first pregnancy, alcohol consumption, smoking, age at menopause, total energy intake
							SFA	RR 1.39 (0.94–2.06)	
							MUFA	RR 0.75 (0.50–1.12)	
							PUFA	RR 0.95 (0.64–1.40)	
							Cholesterol	RR 1.09 (0.74–1.61)	
Velie, 2000	**BCDDP**	United States (1979–1995)	996	40,022	Quintiles	Post-menopausal	Total fat	RR 1.07 (0.86–1.32)	Age, family history of breast cancer, BMI, oral contraceptive, parity, age of first pregnancy, total energy intake, age of first period, age at menopause, education level, alcohol consumption, smoking
							SFA	RR 1.12(0.87–1.45)	
Wakai, 2005	**JACC Study**	Japan (1988–1997)	129	26,991	Quintiles	Total population	Total fat	RR 0.80 (0.46–1.38)	Age, family history of breast cancer, oral contraceptive, BMI, age of first period, parity, age at first pregnancy, education level, place of residence, age at menopause
							SFA	RR 0.68 (0.40–1.15)	
							MUFA	RR 1.1 (0.63–1.9)	
							PUFA	RR 0.62 (0.36–1.09)	
						Post-menopausal	Total fat	RR 0.99 (0.5–1.95)	
							SFA	RR 0.64 (0.34–1.22)	
							MUFA	RR 0.96 (0.45–2.05)	
							PUFA	RR 1.98 (0.94–4.18)	

*Significant values are shown in bold.

RR: relative risk; HR: hazard risk; OR: odds ratio; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid; BMI: Body Mass Index; AARP DHS: American Association of Retired Persons, Diet and Health study; BCDDP: Breast Cancer Detection, Demonstration Project; CNBSS: Canadian National Breast Screening Study; EPIC: European Prospective Investigation into Cancer and Nutrition, IWHS: Iowa Women's Health Study, JACC Study: Japan Collaborative Cohort Study, NHANES: National Health and Nutrition Examination Survey; NHS Nurses' Health Study; NLCS: Netherlands Cohort Study; NNS: Nutri-Net Santé; SCS: Cancer Screenee Cohort Study; SKCCR: South Korea Central Cancer Registry; SWLHC: Scandinavian Women's Lifestyle and Health Cohort; TSS: The Sister Study; VITAL: VITamins and Lifestyle; n: number

Table 3. Meta-analysis results

Population	Lipid	Study type	Studies (n)	RR	(95% CI)	p-value	I2 (%)
Total population	Total fat	Cohort	8	0.98	(0.65–1.48)	0.9311	97
		Case-Control	20	1.07	(0.96–1.19)	0.225	89
	SFA	Cohort	8	0.94	(0.74–1.18)	0.579	92
		Case-Control	15	1.06	(0.97–1.17)	0.198	82
	MUFA	Cohort	8	0.97	(0.87–1.08)	0.578	56
		Case-Control	10	1.03	(0.9–1.18)	0.659	90
	PUFA	Cohort	8	1.02	(0.91–1.14)	0.780	64
		Case-Control	12	0.94	(0.82–1.08)	0.384	91
	Cholesterol	Cohort	3	1.09	(0.71–1.66)	0.706	69
		Case-Control	6	1.22	(0.94–1.58)	0.129	92
Pre-menopausal	Total fat	Case-Control	9	1	(0.9–1.11)	0.981	55
	SFA	Case-Control	7	1.02	(0.86–1.2)	0.838	70
	MUFA	Case-Control	7	0.99	(0.84–1.17)	0.931	71
	PUFA	Case-Control	6	1.07	(0.91–1.26)	0.421	67
Post-menopausal	Total fat	Cohort	8	0.94	(0.84–1.04)	0.242	62
		Case-Control	11	1.07	(0.94–1.21)	0.309	66
	SFA	Cohort	8	1.01	(0.85–1.19)	0.932	84
		Case-Control	10	**1.12**	**(1.03–1.21)**	**0.006**	**26**
	MUFA	Cohort	7	0.95	(0.83–1.08)	0.413	69
		Case-Control	9	1.16	(0.97–1.38)	0.108	82
	PUFA	Cohort	7	0.96	(0.83–1.11)	0.592	77
		Case-Control	8	0.88	(0.64–1.22)	0.444	94
	Cholesterol	Cohort	4	0.98	(0.84–1.14)	0.772	42

Significant values are shown in bold.

RR: relative risk; CI 95%: confidence internal at 95%; I2: Higgin's I2 statistic of heterogeneity; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid, n: number

Role of Obesity in Breast Carcinogenesis

Obesity, a documented breast cancer risk factor after menopause (4), is directly related to physical activity and diet (64). Mechanisms underlying the increased risk of breast cancer related to overweight and obesity are becoming better known and seem to rely largely on metabolic changes related to the endocrine action of excessive adipose tissue. These are mainly due to changes in steroid hormone metabolism as well as the action of inflammatory mediators (64). Mechanisms involving steroid hormones are the predominant hypothesis to explain the associations between obesity and breast cancer. The two main sites of estrogen synthesis are the ovaries before menopause, and adipose tissue through aromatization of adrenal androgen and ovarian androgens after menopause (65). Once released, estrogens act on breast epithelial cells and as a promoter of cell proliferation and this leads to an increased risk of mutation and malignant transformation of breast cells (65). This partly explains the increased risk of breast cancer after menopause in overweight or obese women. However, adipocytes, which are present in large numbers in breast tissue, secrete a range of adipokines/cytokines. Two of the cytokines are leptin and adiponectin. Leptin is a pro-inflammatory cytokine that causes post-prandial satiety and activation of cell proliferation. Adiponectin has an anti-inflammatory and antineoplastic action (66). These two cytokines balance each other in normal body weight, but in obese people there is a loss of this balance. and the production of pro-inflammatory cytokines is promoted. Clinical and experimental studies (67, 68), have found a deleterious link between adipocytes present at the tumor invasion front and the progression of breast cancer (69, 70). Breast adipocytes are involved in tumor initiation, proliferation, progression and metastasis (66). Adipocytes now appear to be important cellular contributors to tumor progression. Taken together, these biological mechanisms may explain how obesity increases breast cancer risk.

Lipid Consumption Is Not Directly Linked to Obesity

However, diet and obesity may not have an effect on the breast through the same mechanisms. Indeed, lipid consumption is not directly related to obesity and overweight. There is evidence that high total energy intake (71) and high carbohydrate intake (72) are directly related to weight gain. The link between obesity and higher

fat consumption without an increase in total energy consumption is still debated. Surprisingly, epidemiological studies do not demonstrate the role of high lipid intake in the occurrence of obesity, beyond their contribution to making the energy balance positive. In the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study of over 89,000 subjects with mean lipid intakes of 31.5%–36.5% of total energy intake, dietary lipids were not associated with weight change (73). In addition, weight gain appears to be independent of the percentage of total fat consumed (74) and there is no evidence that overweight subjects ingest more lipids than others (75). Therefore, there must be other biological explanations for our findings.

Specificity and Action of Different Lipid Subtypes

The role of the different classes of fatty acids in breast carcinogenesis has been the subject of numerous studies, mainly based on animal models. In these models, high lipid intake (40% of ingested energy) stimulated mammary carcinogenesis with a dose-effect, independent from the nature of the lipids that made up the diet (76).

We found that high SFA consumption may increase breast cancer risk among post-menopausal women. However, biological mechanisms linking SFA and breast cancerogenesis are still unknown. *In vitro* studies on a breast cancer cell line (MDA-MB-231) found that SFA stimulated proliferation while unsaturated fatty acids inhibited proliferation and induced apoptosis (77). Still, a possible explanation would be that SFA intake increased insulin resistance and may therefore lead to an increased breast cancer risk (78). However, results of our meta-analysis do not show a significant impact of PUFA, MUFA and cholesterol consumption on breast cancer risk. Unlike SFA, MUFA derived from olive oil reduced insulin resistance and therefore had a benefit on breast cancer risk (79). However, this was not found for non-vegetable MUFA. Results from the E3N-EPIC study found that high plasma levels of natural MUFA were not associated with an increased breast cancer risk while there was an increased risk for *trans*-mono-saturated fatty acids (9).

PUFA may reduce the binding between estrogen and serum proteins, including sex-hormone binding globulin (SHBG) and albumin, thereby increasing the circulating level of biologically potent estrogens that can activate breast cell growth (76). Long-chain PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inhibit the production of arachidonic acid-derived eicosanoids in tumors (80). Lipid peroxidation can induce apoptosis (81, 82). The n-3 PUFA can therefore bind and activate the peroxisome proliferator-activated gamma receptor, leading to activation of the proteoglycan syndecan-1 in human breast cancer cells, thereby inducing apoptosis and inhibition of cell growth (80). Linoleic acid can generate 13-hydroxylinoleic acid, which enhances the growth-stimulating signal of peptide growth factors, such as epidermal growth factor (EGF) and insulin, which may stimulate the growth of cancer cells (83). A meta-analysis found that high plasma levels of n-3 PUFA were associated with a decreased risk of breast cancer (84). Conversely, high levels of MUFA and SFA (palmitic and oleic acids) were associated with increased breast cancer risk (84).

High blood cholesterol levels appear to increase the risk of breast cancer (85). Interventional studies in mice have highlighted the role of cholesterol in mammary tumor cells (86). Some derivatives such as 6-oxo-cholestan-3β,5α-diol (OCDO) and 27-hydroxycholesterol (27HC) are involved in the promotion, proliferation and migration of cancer cells (87, 88). To date, it is not confirmed that high dietary cholesterol intake is a risk factor for breast cancer, as shown in our meta-analysis and other articles (89, 90). This may be explained in part by the low proportion of cholesterol (about 30%) in the diet, while the rest comes from the degradation of lipids and carbohydrates by the liver (91).

Limitations of Our Study

It is important to consider certain elements that may have led to sources of bias in our results in view of the great heterogeneity of the selected studies. In fact, the studies included in our meta-analysis were carried out on populations from five continents with significant cultural and dietary diversity. The types of oils used in the diet also vary from one country to another, with a particular consumption of olive oil around the Mediterranean rim, as for example in Italy (26) or Spain (24), which is one of the main sources of MUFA. Conversely, in the United States and Canada, MUFA are largely provided by products of animal origin (46, 55). In Asian countries such as China, Korea, Japan and Singapore, women have a diet that is predominantly vegetarian or with low meat content (40, 51, 52). Moreover, each lipid family (SFA, MUFA, PUFA) contains a broad range of lipids. As previously described, effects may differ even among the same family. Consequently, it is possible that our results do not reflect the effect of a particular lipid, which may be specifically implicated in breast carcinogenesis.

In addition, methods of data collection, which differed across studies, must be considered when explaining the differences in outcomes between cohort and case-control studies. Case-control studies are subject to a recall bias, as dietary habits were collected with a questionnaire after the onset of the disease. Conversely, the results of cohort surveys are considered more conclusive because they are based on the collection of dietary habits in healthy subjects at the beginning of the studies and have a prospective setting. Moreover, cohort studies have a higher number of patients and a longer duration of follow-up (up to 20 years) and therefore higher statistical power.

Finally, our results were adjusted according to menopausal status but not with other variables, as data was not available for the meta-analysis. In the different studies, relative risks and odds ratio were adjusted with different variables such as body mass index, age, and parity. These variables are reported in Tables 1 and 2.

Conclusion

Despite the heterogeneity of the included articles, follow-up durations, populations and number of patients, most studies are consistent with respect to total lipids, MUFA, PUFA and cholesterol. Nevertheless, an association was found between high intake of SFA and the occurrence of breast cancer in post-menopausal women for case-controlled studies but not for cohort studies, requiring additional investigation. These studies should focus more on the type of SFA rather than the whole lipid family, as each lipid intake may have specific consequences.

At this stage, therefore, it is not possible to establish nutritional recommendations regarding the consumption of lipids to decrease breast cancer risk. However, even if lipid intake does not play a significant role in the etiology of breast cancer, its proven adverse effect on pathologies, such as cardiovascular disease, justifies the consolidation of nutritional education efforts.

Moreover, adipocytes have a role in promoting and regulating breast cancer. Current studies are of interest (87, 92) and contribute to an understanding of biochemical mechanisms. The discovery of new molecules with anti-tumor properties, such as dendrogenin A (DDA), a natural cholesterol derivative (87), opens doors to the development of new therapeutics.

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