Published in final edited form as:

Annu Rev Nutr. 2013 ; 33: . doi:10.1146/annurev-nutr-112912-095300.

Dietary Fat in Breast Cancer Survival

Nour Makarem¹, Urmila Chandran^{2,3}, Elisa V. Bandera^{2,3}, and Niyati Parekh^{1,4}

Niyati Parekh: niyati.parekh@nyu.edu

¹Department of Nutrition, Food Studies and Public Health, New York University, New York, New York 10003

²The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, New Jersey 08903

³School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey 08854

⁴Department of Population Health, New York University Langone School of Medicine, New York, New York 10016;

Abstract

Laboratory evidence suggests a plausible role for dietary fat in breast cancer pathophysiology. We conducted a systematic literature review to assess the epidemiological evidence on the impact of total dietary fat and fat subtypes, measured pre- and/or postcancer diagnosis, in relation to breast cancer-specific and all-cause mortality among breast cancer survivors. Studies were included if they were in English, had a sample size ≥ 200 , and presented the hazard ratio/rate ratio for recurrence, diseasespecific mortality, or all-cause mortality ($n = 18$). Although the results are mixed, most studies suggested that higher saturated fat intake prediagnosis was associated with increased risk of breast cancer-specific and all-cause mortality. Postdiagnostic *trans* fat intake was associated with a 45% and 78% increased risk of all-cause mortality. Higher monounsaturated fat intake before and after diagnosis was generally associated with increased risk of all-cause and breast cancer-specific mortality, albeit the majority of the studies were statistically nonsignificant. Two studies evaluating omega-3 fat intake suggested an inverse association with all-cause mortality. Although there were too few studies on fat subtypes to draw definitive conclusions, high consumption of saturated fat may exert a detrimental effect on breast cancer-specific and all-cause mortality, whereas omega-3 fat may be beneficial. The inconsistent and limited evidence warrants research to assess the impact of consumption of fat subtypes on breast cancer recurrence and mortality.

Keywords

dietary fat; fat subtypes; cancer survival; cancer recurrence; breast cancer

INTRODUCTION

Breast cancer is the most commonly diagnosed nonskin cancer among women (1, 56). With approximately 226,870 estimated incident cases of breast cancer in 2012, the number of cancer survivors is expected to be steadily on the rise over the next few years (1). According to the American Cancer Society, the five-year relative survival rate for female breast cancer patients has improved from 63% in the early 1960s to 90% currently (1, 4). However, despite the higher survival rates, breast cancer survivors remain at considerable risk of recurrence, as well as new primary breast cancers, and mortality compared to women without a personal history of breast cancer (4). Therefore, the investigation into modifiable

risk factors of breast cancer mortality and all-cause mortality, specifically diet, has received increasing attention (48).

Several studies have evaluated the role of dietary fat on breast cancer risk, but the epidemiologic evidence has been inconclusive (39, 63). There has also been considerable interest in investigating the impact of fat consumption on breast cancer recurrence and mortality; however, few studies have addressed these issues. Western diets that are high in fats have been hypothesized to play a role in breast cancer pathophysiology (24, 33, 48). Early ecologic studies demonstrated that dietary fat consumption per capita is highly correlated with breast cancer mortality (6, 13). A study among Japanese immigrants showed increased breast cancer mortality rates in the US compared to those observed in Japan, suggesting that environmental factors including components of the Western diet may play a role in decreased survival (13). More recently, several human studies have investigated the associations between dietary fat and breast cancer recurrence, mortality, and all-cause mortality (9, 12, 15, 40, 45, 46). Therefore, integration of the available data is needed to clarify the associations between dietary fats and these breast cancer outcomes. Despite the longstanding recommendations to limit total fat intake to 20% to 35% of total caloric intake and to restrict saturated fat consumption (61), there has been little change in the average fat intakes of Americans over the past 15 years (7), with total fat and saturated fat intakes contributing, on average, 34% to 37% and 11% to 13% of total calories, respectively. The evidence needs to be reviewed in light of the potential dietary fat intake recommendations for cancer survivors.

Previous reviews evaluate overall dietary fat but do not sufficiently address the timing of exposure to fats or the potential variation in the impact of fat subtypes on the course of the illness postdiagnosis (24, 32, 41, 48, 59). The purpose of the current review is to summarize the results from epidemiological studies investigating dietary fat in relation to breast cancer mortality as well as all-cause mortality following a breast cancer diagnosis. The limited available evidence regarding the association between dietary fat intake and breast cancer recurrence is also discussed. The insights from this review also provide important information to guide clinical practice for preventing breast cancer recurrence and improving survival.

POTENTIAL MECHANISMS LINKING DIETARY FAT TO CANCER

Dietary fats have been hypothesized to play a key role in the etiology of breast cancer malignancy (19). Previous evidence demonstrates that the quantity and/or the subtype of fat may influence the cancer process (18). The postulated mechanisms by which dietary fats may exert these modulatory effects on cancer initiation and progression, though not fully understood, may include their impact on oxidative stress, alteration of the hormonal metabolism, modulation of cell-signaling transduction pathways, and regulation of gene expression (19). These potential mechanisms are interrelated and are briefly described below and in Figure 1.

Hormonal and Adipokine Imbalances

High-fat diets are calorie dense and are associated with higher body adiposity (7). Higher body adiposity is associated with excessive production of reactive oxygen species, hyperinsulinemia, elevated adipokine secretion, and elevated tumor necrosis factor alpha, which together lead to a state of chronic inflammation, thereby creating an environment conducive to tumor growth (44, 58, 62). A higher circulating concentration of insulin-like growth factor 1 (IGF-1) in overweight and obese women may promote proliferation and survival of cancer cells through the activation of the PI3K/Akt pathway (47, 58). In addition, leptin produced by adipocytes has been hypothesized to promote an aggressive breast cancer

phenotype by virtue of its mitogenic properties, which can be independent of hormonal pathways (54). Body adiposity augments the production of estrogen because adipocytes in breast cancer tissue are capable of producing estrogens (30). Furthermore, obesity-related hormonal imbalances in IGF-1 and insulin result in increased bioavailable estrogens that are theorized to increase cell proliferation through activation of target genes, thereby promoting carcinogenesis (30).

Eicosanoid Synthesis

Eicosanoids are short-lived, hormone-like lipids derived from omega-3 and omega-6 fatty acids and act as signaling molecules in various cellular and hormonal pathways (36). Dietary fatty acids can impact synthesis of eicosanoids, which may in turn influence carcinogenesis through their modulation of the inflammatory and immune response, their impact on cell angiogenic and mitotic properties, and their alteration of hormonal status (52, 53, 57). In general, omega-3-derived eicosanoids appear to have anti-inflammatory effects, whereas omega-6-derived eicosanoids have proinflammatory effects (19). Arachidonic acid, the most abundant omega-6 long-chain polyunsaturated fatty acid (LCPUFA) produced within the body, has been shown to stimulate tumor growth and metastasis (51, 52). In contrast, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the omega-3 LCPUFAs, inhibit tumor growth and proliferation and induce apoptosis in human breast cancer cells (16, 55) by suppressing the Akt pathway and inhibiting the production of arachidonic acid–derived eicosanoids (55).

Angiogenesis, a key process for tumor growth and metastasis, is influenced by eicosanoid synthesis from fatty acids (53). Early evidence from laboratory studies suggests that omega-6-derived eicosanoids promote angiogenesis (53). However, diets high in omega-3 appear to have antiangiogenic properties by suppressing omega-6 PUFA stimulation of mammary carcinoma growth, metastasis, and tumor vascularization (51, 53).

Fatty acid–derived eicosanoids may also influence cancer progression through their influence on estrogen synthesis (19). Prostaglandin E₂, an arachidonic acid–derived mediator, increases estrogen synthesis by enhancing aromatase activity and expression. This is contrary to the impact of EPA and oleic acid, which decrease the production of prostaglandin E₂, thereby reducing estrogen production and consequently estrogen-induced downstream effects (19, 36).

Oxidative Stress and DNA Damage

High consumption of dietary fat is linked to oxidative stress due to the production of reactive oxygen species. Malondialdehyde, a major end product of the peroxidative degradation of PUFA, induces higher levels of DNA adducts in normal breast tissue of breast cancer patients compared to controls (8, 31). Reactive oxygen species induce mutations in the p53 tumor suppressor gene, responsible for cell cycle regulation, apoptosis, facilitating DNA repair, and antagonizing angiogenesis in both human and mouse studies (11, 21, 31). Therefore, reactive oxygen species–induced loss of functional p53 would allow unchecked cell divisions and increased susceptibility to DNA damage (26, 31). These persistent elevations in oxidative stress from a high-fat diet may lead to genomic instability, thereby promoting carcinogenesis (31).

Regulation of Gene Expression

Fatty acids influence the cancer process through the regulation of transcription and RNA processing and by modulating the expression of genes involved in cell growth, survival, apoptosis, and differentiation (29, 38). Fatty acids or their metabolites may control transcription factor activity by binding to various nuclear receptors or may affect nuclear

abundance (29). Nuclear factor kappa- β , a transcription factor that binds to promoters of various inflammatory factors (e.g., cytokines) and a promoter of tumorigenesis, has reduced expression and activity under the action of omega-3 LCPUFA, thereby reducing tumorigenesis (29).

Fatty acids also influence the expression of genes involved in cell signaling pathways, oncogenes, and tumor suppressor genes and change the expression and/or the activity of enzymes involved in the production of eicosanoids (18, 19). For example, linoleic acid has been shown to decrease protein levels of tumor suppressor p53, whereas DHA up-regulated expression of p53 (19, 60). Furthermore, dietary lipids have been shown to affect the expression of the suppressor genes breast cancer susceptibility gene 1 (BRCA1) and BRCA2, two genes implicated repeatedly in breast cancer recurrence (10). Omega-3 LCPUFA increased BRCA1 and BRCA2 mRNA expression (10).

METHODS

For this systematic literature review, we searched PubMed for English language articles that had been published through May 30, 2012, relevant to total dietary fat, *trans* fat, saturated fat, monounsaturated fat, and polyunsaturated fat and breast cancer. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (37) as applicable for the topic of this review to search systematically for cross-sectional, case-control, cohort, and experimental studies examining the association between dietary fat and breast cancer recurrence and mortality as well as all-cause mortality. The Population, Intervention, Comparator, and Outcomes (PICO) method was used to narrow the focus of the research question (37). The exposure of interest was total dietary fat and/or one or more of the dietary fat subtypes, and the outcome was breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality. We included articles that displayed our search terms in their title and/or abstract as indicated by “[tiab]”. The search terms used are: (dietary fat[tiab] OR omega 6[tiab] OR omega 3[tiab] OR fat intake[tiab] OR fat[tiab] OR saturated fat[tiab] OR *trans*-fat[tiab] OR monounsaturated fat[tiab] OR polyunsaturated fat[tiab]) AND (survival[tiab] OR prognosis[tiab] OR progression[tiab] OR recurrence[tiab] OR mortality[tiab]) AND (breast cancer[tiab]).

Additionally, we manually searched bibliographies to supplement the online search process and to ensure that all studies that met our inclusion criteria were captured. The search process is summarized in Figure 2

Inclusion Criteria

The purpose of this review is to integrate the literature on dietary fats in relation to breast cancer and overall survival. Hence, we included original research manuscripts that (a) reported estimates for recurrence, disease-specific mortality, or all-cause mortality among breast cancer patients, (b) had a total sample size of at least 200 subjects, (c) presented hazard ratios or rate ratios, (d) conducted follow-up in cancer cases, and (e) presented multivariate analysis (not univariate analysis).

After eliminating studies that did not meet our inclusion criteria, a total of 18 manuscripts were considered in this review. In presenting the results, we separated findings based on whether dietary intake was assessed before or after diagnosis. Within these two categories, we evaluated the influence of total fat, saturated fat (or animal fat), *trans* fat, monounsaturated fat, and polyunsaturated fat separately to determine whether total fat and the various subtypes of fat influence breast cancer recurrence and mortality differently.

RESULTS

Total Dietary Fat

A total of seven studies reported results on prediagnostic total fat intake in relation to breast cancer and all-cause mortality as shown in Table 1 (12, 17, 23, 27, 28, 35, 40, 64). Two manuscripts were from the same Canadian study (27, 28). Five studies (12, 17, 27, 28, 35, 64) evaluated the association between prediagnostic total dietary fat and breast cancer mortality. Of these, only one study that was conducted among the Iowa Women's Health Study participants (>56 years) observed a significant (>2-fold) increased breast cancer-specific mortality risk among women in the highest tertile compared to the lowest tertile of fat intake in grams and as a percentage of total energy, and a statistically significant linear trend was observed across the tertiles of intake (p -trend = 0.016 and p -trend = 0.044, respectively) (64). Two additional studies (12, 27, 28) were suggestive of increased risk of breast cancer-specific mortality among women with higher fat intake, although risk estimates were not statistically significant. The associations persisted even after adjustment for estrogen receptor (ER) status, progesterone receptor (PR) status, nodal status, and tumor status in one study (27). In contrast, two cohort studies, one conducted in a Japanese (35) and the other in an Italian population (17), reported risk of death estimates below one, but confidence intervals included the null.

Three studies (17, 23, 40) evaluated the association between prediagnostic total dietary fat and all-cause mortality, but a statistically significant association was observed in only one study (40), where increased dietary fat was associated with more than threefold increased risk of all-cause mortality in postmenopausal women in the third tertile compared to the first tertile of intake, with a statistically significant linear trend. Another study that stratified analyses by tumor behavior (localized, regional, and distal) showed that total fat intake was related to worse prognosis only for subjects with distant disease at diagnosis, for whom the risk of all-cause mortality increased 44% for each additional 1,000 grams of fat consumed monthly (23). However, similar detrimental associations were not observed in an Italian cohort (17).

Postdiagnostic total fat intake in relation to breast cancer and all-cause mortality was investigated in nine studies as shown in Table 2 (9, 15, 20, 22, 25, 42, 43, 46, 50). When examining the association between total fat intake and breast cancer mortality, out of five cohort studies (9, 25, 42, 43, 50), all of which expressed total fat intake as categories, only two studies (25, 43) reported statistically significant increased risk of death with higher fat intake. In the Nurses' Health Study, higher total fat intake was associated with 44% increased risk of breast cancer-specific mortality (95% CI: 1.01–2.04) for highest versus lowest quintile, albeit with a nonsignificant linear trend (25). Similarly, a study conducted in Hawaii observed a significant threefold increased risk of breast cancer mortality corresponding to high versus low fat intake in Caucasian women but not in Japanese women, where an inverse association was observed (43). Moreover, in an Australian cohort, a nonsignificant HR >1 suggestive of elevated risk of breast cancer mortality with higher fat intake was detected (50). In contrast, two other studies did not detect an association (9, 42).

Of the four cohort studies that evaluated the relationship between postdiagnostic total fat intake and all-cause mortality (9, 20, 22, 25), only one study suggested a statistically significant 51% increased risk of death with higher fat intake (25). In contrast, a Canadian study observed significant increased risk of overall mortality for the lowest (compared to the highest) intake of total fat as a percentage of calories (22). In this study, there was no evidence for increased risk of all-cause mortality with higher intakes of total fat, and moderate rather than low intake of total fats (40% to 45%) was associated with the lowest

risk of overall survival. The remaining two studies found little support for an association (9, 20).

In addition to the seven cohort studies evaluating postdiagnostic fat intake, two randomized clinical trials were identified with median or mean follow-up ranging from approximately five to seven years (15, 46). The first one was the Women's Intervention Nutrition Study, for which the interim results indicated that women in the dietary intervention group receiving a low-fat diet had a 24% lower risk of recurrence than those in the control group (15). There was no statistically significant difference in overall survival when comparing women receiving the dietary intervention with women in the control group (HR = 0.89, 95% CI: 0.65–1.21). However, both relapse-free and recurrence-free survival were significantly higher in the intervention group consuming lower fat compared to the control group, suggesting that the dietary intervention may have a favorable impact on both of these outcomes. In addition, the intervention appeared to have a greater impact on relapse-free survival in women with ER-negative cancer compared to those with ER-positive cancer. Similarly, in the Women's Healthy Eating and Living trial, there were no statistically significant differences for dietary fat in relation to breast cancer events (HR = 1.13, 95% CI: 0.81–1.58) or all-cause mortality (HR = 0.98, 95% CI: 0.64–1.49) between the intervention group, which received intensive dietary counseling to consume low-fat diets rich in fruits, vegetables, and fiber, and the control group, which received 5-a-day dietary guidelines (46).

Fat Subtypes

Saturated fat—Two studies (12, 27, 28) that evaluated the association between saturated fat intake assessed before diagnosis and breast cancer mortality (Table 3) found significantly increased mortality risk corresponding to increased percentage of energy intake from saturated fat when treated as a continuous variable (27, 28) or when comparing highest to lowest quartile of saturated fat intake (12, 28). In addition, a statistically significant linear trend across the quartiles of intake was observed in a Canadian cohort for saturated fat expressed as percent of total fat and as percent of total energy (28). Another cohort study conducted in Japan found a suggestion of increased risk for breast cancer mortality (HR: 1.3) associated with consuming animal fat in the highest quartile compared to the lowest, but the association was not statistically significant (35).

Few studies stratified analyses of the dietary fat and breast cancer progression link in subgroups on the basis of important characteristics known to influence breast cancer. The Canadian cohort study in which the analyses were stratified by menopausal status showed that higher intakes of saturated fat as a percentage of total energy significantly increased the risk of breast cancer death by 63% in postmenopausal women but did not achieve statistical significance in the premenopausal group (28). These associations persisted among women who were node negative; had smaller tumors; were ER positive, ER negative, or PR negative; and even among women who performed the breast self-examination, an indicator for healthy behaviors (28). A significant association was also observed in a subsequent analysis of the Canadian cohort (27), in which every 5% increase in saturated fat intake, as percentage of total energy, was associated with approximately 65% increased risk of breast cancer mortality in models including ER status as a covariate (HR = 1.65, 95% CI: 1.07–2.56), and the association was borderline significant in models excluding ER status (HR = 1.55, 95% CI: 1.00–2.37).

When evaluating all-cause mortality as a primary outcome, two studies that examined saturated fat in relation to all-cause mortality among postmenopausal women yielded significant results (40, 64). In the Iowa Women's Health Study population, saturated fat intake in grams, but not as percentage of total energy, resulted in a significant 2.4-fold increased risk of all-cause mortality when comparing women in the third versus the first

tertile of intake, and a significant linear trend was observed ($P = 0.022$) (64). These results were corroborated by another US study, where women in the highest versus lowest tertile of saturated fat intake, as percentage of total energy, had more than fourfold increased risk of mortality ($HR = 4.45$, 95% CI : 2.26–8.78), with a significant linear trend (p -trend < 0.0001) (40).

Two studies evaluating postdiagnostic saturated fat intake and breast cancer mortality (Table 4) suggested an increased risk of 55% and 65% (9, 50), albeit confidence intervals included the null. Of the three studies that evaluated the association between postdiagnostic saturated fat intake and all-cause mortality (9, 22, 25), one study showed a nonsignificant 23% increased risk when comparing women with the highest consumption of saturated fat to those with the lowest (25), whereas the larger US cohort indicated a statistically significant 41% elevation in risk of death (9). In contrast, a Canadian cohort reported a nonsignificant increased risk for women with the lowest intake of saturated fat compared to women with the highest intake (22).

Trans fats—To our knowledge, no studies have evaluated the association between prediagnostic *trans* fat intake and breast cancer–specific or all-cause mortality. However, the impact of postdiagnostic *trans* fat intake on breast cancer mortality was evaluated in one study that was suggestive of an increased risk, with a RR of 1.42 (although not significant) among women in the highest versus the lowest quintile of *trans* fat consumption (9) (Table 4). In contrast, both US studies that evaluated the association between postdiagnostic *trans* fat intake and all-cause mortality (Table 4) (9, 25) reported significant 45% and 78% increased risks of death with increased intake of *trans* fat. The association was stronger among women with negative lymph nodes in one study (25).

Monounsaturated fats—Four manuscripts from three separate studies reported on prediagnostic monounsaturated fatty acid (MUFA) intake (27, 28, 40, 64), of which the two reports from the Canadian National Breast Screening Study investigated the association with breast cancer–specific mortality (27, 28) and two investigated the association with all-cause mortality as a primary study outcome (Table 3) (40, 64). In two separate analyses of the Canadian National Breast Screening Study cohort evaluating the association between MUFA and breast cancer mortality, oleic acid, the most common MUFA, in units of 10 grams/day was nonsignificantly associated with increased risk of breast cancer mortality in all models (27, 28). In the two studies (40, 64) that used all-cause mortality as the primary outcome, increased intakes of MUFA (64) and oleic acid (40) were associated with a significant 2.3- and 3.56-fold increased risk, respectively, of all-cause mortality among postmenopausal women. A significant linear association across the tertiles of MUFA (in grams) (64) and oleic acid (as percentage of energy intake) (40) intakes was also detected in both studies (p -trend = 0.025 and p -trend = 0.0007, respectively).

Four studies examined the association between postdiagnostic MUFA intakes and breast cancer–specific and all-cause mortality after cancer diagnosis (Table 4) (9, 22, 25, 50). Two of these studies evaluated the association between MUFA and breast cancer mortality and provided inconsistent results (9, 50). Although in the Australian cohort a nonsignificant positive HR suggestive of an increase in risk with higher MUFA intake was observed (50), no association was observed in the US cohort (9). However, for both studies evaluating the association between MUFA intake and all-cause mortality, nonsignificant RR greater than 1 was observed (9, 25). In addition, although the Nurses' Health Study (25) indicated a nonsignificant increase in the risk of all-cause mortality with higher oleic acid intake, a statistically significant increase in risk of death ($p = 0.03$) was observed in the Canadian study that used the quadratic form of the variable representing oleic acid intake when comparing the lowest quintile of intake to the highest (22).

Polyunsaturated fats—Five studies have examined the relationship between prediagnostic PUFA intake and breast cancer–specific and all-cause mortality among patients diagnosed with breast cancer (Table 3) (25, 28, 35, 40, 64). One study evaluating the link between PUFA and breast cancer mortality showed that PUFA intake was nonsignificantly associated with 50% increased risk of breast cancer mortality (64). Similarly, in another study PUFAs of fish origin were nonsignificantly associated with a 1.4-fold increased risk of breast cancer mortality when comparing the highest quartile of intake to the lowest (35). For linoleic acid, there was no association with breast cancer mortality (28). On the other hand, among studies investigating all-cause mortality as an outcome (25, 40), the Nurses' Health Study indicated a significant 37% reduction in risk of all-cause mortality with higher omega-3 fat intakes (95% CI: 0.42–0.95) (25). However, another US cohort study noted that higher linoleic acid intake, expressed as a percentage of total energy, was significantly associated with >2-fold increased risk of all-cause mortality (95% CI: 1.21–4.69) in postmenopausal women and observed a significant linear trend across the tertiles (p-trend = 0.01) (40).

Six studies evaluated the association between PUFA intakes after a breast cancer diagnosis and breast cancer–specific and all-cause mortality (Table 4) (9, 22, 25, 43, 45, 50). Three of these studies focused on breast cancer mortality as a primary outcome (9, 43, 50), with two of them (43, 50) presenting nonsignificant increased RR/HR of 1.72 and 1.57, respectively, corresponding to higher intake of PUFA, whereas the third study reported no association (9).

Four studies evaluated postdiagnostic PUFA intake and all-cause mortality, and, as Table 4 shows, results were inconsistent (9, 22, 25, 45). Although one study showed no association between PUFA intake and all-cause mortality (9), other studies showed that different associations with all-cause mortality are observed when the different types of PUFA are evaluated separately. For linoleic acid, for instance, the Nurses' Health Study showed no association (25), whereas a Canadian cohort reported a nonsignificant HR of 1.3 comparing the lowest to the highest intake (22). For omega-3 fats, the Nurses' Health Study showed that higher total omega-3 fat intake and EPA intake, in particular, were nonsignificantly associated with decreased risk of all-cause mortality (25). In addition, a statistically significant decrease in risk of all-cause mortality across the quintiles of intake detected for EPA (p-trend = 0.007) and omega-3 fats was associated strongly with reduced mortality among women with negative lymph nodes (25).

Similar results were also noted in an intervention study. An analysis of the Women's Healthy Eating and Living trial that examined the associations between postdiagnostic omega-3 fat intake and overall survival reported that higher intakes of total dietary omega-3 LCPUFA (EPA plus DHA) were associated with a 25% reduced risk of breast cancer events, including recurrence from the original cancer or developing a new invasive breast cancer (45). In addition, higher intakes of EPA and DHA were significantly associated with reduced risk of all-cause mortality, and a statistically significant linear trend across the tertiles of intake from food and food plus supplements was observed (p = 0.006 and p = 0.04, respectively).

DISCUSSION

This systematic review integrates the epidemiologic evidence on total and subtypes of dietary fat, assessed before and after a cancer diagnosis, in relation to breast cancer recurrence (only two studies) and mortality as well as all-cause mortality among breast cancer survivors. Although some studies have suggested a detrimental effect of total dietary fat intake on breast cancer survival, most results were not statistically significant, and, overall, the current evidence is inconsistent. Only three analyses from two large intervention

studies evaluated breast cancer recurrence in relation to total fats. Hence, this review indicates a large knowledge gap that remains to be addressed to better understand these relationships.

Evidence evaluating the impact of the fat subtypes on breast cancer recurrence and breast cancer-specific or overall mortality is notably scarce, with very few studies addressing these associations for each subtype of fat. The available epidemiological evidence on fat subtypes suggests a potentially differential impact on breast cancer depending on type of fat consumed, thus confirming the need for separate investigations of fat subtypes in additional studies. Existing evidence on saturated fat and *trans* fat indicates that intakes of these fats are associated with reduced breast cancer-specific and overall survival. Inconsistent findings were reported for MUFA and PUFA (omega-6 plus omega-3 fats) intake. However, in studies that evaluated omega-3 LCPUFA separately, higher EPA and DHA intakes were associated with decreased risk of both breast cancer-specific and overall mortality. Future studies using a combination of dietary and fatty acid biomarker data are required to confirm results pertaining to specific PUFAs, including omega-3 LCPUFA, DHA, and EPA, to determine the optimal intake of these fatty acids to maximize survival.

Several methodological issues were noted from the papers reviewed and are discussed herein. One issue relates to the measurement of dietary fat intake using different dietary assessment methods. Although the majority of the studies used food frequency questionnaires, a few studies also used diet history questionnaires, diet records, and 24-hour recalls that may lead to various degrees of measurement error of fat intake and make results difficult to compare across studies. In addition, dietary intake was often assessed at one point in time only. Findings from the studies reviewed indicate that the relationship between timing of fat exposure and cancer may be complex and important to decipher in future studies.

Although the majority of studies used highquality medical records and cancer registries to obtain medical information and mortality data, the accuracy of reported breast cancer deaths using death certificates and cancer registries may be compromised. Particularly, breast cancer deaths may be misclassified with deaths from other neoplasms and other related causes.

A potential source of the observed inconsistencies in study results may be due to inappropriate adjustment for known breast cancer risk factors. For instance, studies that evaluated the postdiagnostic dietary fat intake did not adjust for prediagnostic intake, with the exception of one study, which may contribute to bias. On the other hand, studies that evaluated prediagnostic fat intake did not account for alterations in postdiagnostic fat intake and healthier lifestyles. Moreover, not all studies accounted for treatment modalities, disease stage, histology, tumor size, and grade of malignant disease. This is important because dietary fats may influence the cancer process differently depending on the clinical and pathological aspects of a tumor.

Finally, an important methodological issue that may account for the variation among study results pertains to sample selection. Selection bias inevitably occurs when analyses among survivors recruited a year or more postdiagnosis exclude patients who died early, thus resulting in potential underestimation of the relationship (20). Selection bias may have also occurred in a sample consisting of volunteers, resulting in the “healthy volunteer effect.” Differences in the results can also be ascribed to sample characteristics with respect to disease stage, age, treatment regimen, prognosis following original diagnosis, and ethnicity. In most studies, the population was Caucasian, which limits the generalizability of the results to other ethnicities.

More observational and intervention studies that evaluate the impact of the various fat subtypes on breast cancer and overall survival are needed, along with studies in minority populations. The literature on racial differences in nutritional factors and breast cancer risk and survival is severely limited, with practically no studies on dietary fat and breast cancer survival that report findings stratified by race; the lack of such studies is possibly due to insufficient sample sizes. It is well known that women of African ancestry experience worse survival rates from the disease at every stage (2) and can present with different tumor biology compared to Caucasian women. In parallel, dietary fat intakes can also vary by race. Hence, the relationships of dietary fat and cancer recurrence and mortality should be specifically investigated in minority groups, especially since there is some suggestion that fat intake has a detrimental impact on women with ER-negative tumors (15), which are commonly seen in women of African ancestry. In the interim, results from the ongoing Life After Cancer Epidemiology (14) study and the Pathways Study (34) in breast cancer survivors may help clarify the role of dietary fat and its various subtypes in cancer survival and provide further insight to guide future research and ultimately dietary fat recommendations among breast cancer survivors.

Currently, the American Cancer Society considers the dietary fat recommendations for the general population for heart disease prevention appropriate for the population of cancer survivors due to shared risk factors between cancer and heart disease (3, 49). Its 2012 report recommends that cancer survivors consume 20% to 35% of their energy from fat and limit their intake of saturated fat (49). In addition, although there is insufficient evidence to confirm the protective effects of omega-3 fats for survivors, consumption of foods that are rich in omega-3 fats is encouraged due to the known effects of omega-3 fats in lowering the risk of cardiovascular diseases and all-cause mortality (49). At a population level, cancer survivors should be encouraged to meet the recommendations of the American Cancer Society and the American Institute for Cancer Research (5, 49). However, at an individual level, intensive, personalized, and motivational counseling by a trained dietitian should be encouraged after a breast cancer diagnosis to address the specific needs of patients whose nutritional status may range from being undernourished to obese.

Acknowledgments

DISCLOSURE STATEMENT

The authors acknowledge financial support from the American Cancer Society [ACS#RSG-12-005-01-CNE (to N.P.)] and the National Cancer Institute [K22CA138563 (to E.V.B.) and P30CA072720]. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Am. Cancer. Soc. Cancer. Facts & Figures 2012. Atlanta, GA: Am. Cancer. Soc; 2012. <http://www.Cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-031941.pdf>
2. Am. Cancer. Soc. Cancer. Facts & Figures for African Americans 2011–2012. Atlanta, GA: Am. Cancer. Soc; 2012. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-027765.pdf>
3. Am. Cancer. Soc. Nutrition and Physical Activity During and After Cancer. Treatment: Answers to Common Questions. Atlanta, GA: Am. Cancer. Soc; 2012. <http://www.Cancer.org/Treatment/SurvivorshipDuringandAfterTreatment/NutritionforPeoplewithCancer/nutrition-and-physicalactivity-during-and-after-cancer-treatment-answers-to-common-questions>
4. Am. Cancer. Soc. Survival Rates for Breast Cancer. Atlanta, GA: Am. Cancer. Soc; 2011. <http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-survival-rates>

5. Am. Inst. Cancer. Res. AICR Recommendations for Cancer. Prevention. Washington, DC: Am. Inst. Cancer. Res; 2012. <http://www.aicr.org/assets/docs/pdf/brochures/10-ways-to-reducecancer.pdf>
6. Armstrong B, Doll R. Environmental factors and Cancer incidence and mortality in different countries, with special reference to dietary practices. *Int. J. Cancer.* 1975; 15(4):617–631. [PubMed: 1140864]
7. Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971–2006. *Am. J. Clin. Nutr.* 2011; 93(4):836–843. [PubMed: 21310830]
8. Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and Cancer.s of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis.* 1999; 20(12):2209–2218. [PubMed: 10590211]
9. Beasley JM, Newcomb PA, Trentham-Dietz A, Hampton JM, Bersch AJ, et al. Post-diagnosis dietary factors and survival after invasive breast Cancer. *Breast Cancer. Res. Treat.* 2011; 128(1): 229–236. [PubMed: 21197569]
10. Bernard-Gallon DJ, Vissac-Sabatier C, Antoine-Vincent D, Rio PG, Maurizis J, et al. Differential effects of n-3 and n-6 polyunsaturated fatty acids on BRCA1 and BRCA2 gene expression in breast cell lines. *Br. J. Nutr.* 2002; 87(4):281–289. [PubMed: 12064337]
11. Blackburn AC, Jerry DJ. Knockout and transgenic mice of Trp53: What have we learned about p53 in breast Cancer? *Breast Cancer Res.* 2002; 4(3):101–112. [PubMed: 12052252]
12. Borugian MJ, Sheps SB, Kim-Sing C, Van Patten C, Potter JD, et al. Insulin, macronutrient intake, and physical activity: Are potential indicators of insulin resistance associated with mortality from breast Cancer? *Cancer. Epidemiol. Biomarkers Prev.* 2004; 13(7):1163–1172. [PubMed: 15247127]
13. Buell P. Changing incidence of breast Cancer in Japanese-American women. *J. Natl. Cancer. Inst.* 1973; 51:1479–1483. [PubMed: 4762931]
14. Caan B, Sternfeld B, Gunderson E, Coates A, Quesenberry C, Slattery ML. Life After Cancer Epidemiology (LACE) study: a cohort of early stage breast Cancer survivors (United States). *Cancer Causes Control.* 2005; 16(5):545–556. [PubMed: 15986109]
15. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, et al. Dietary fat reduction and breast Cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J. Natl. Cancer. Inst.* 2006; 98(24):1767–1776. [PubMed: 17179478]
16. Connolly JM, Gilhooly EM, Rose DP. Effects of reduced dietary linoleic acid intake, alone or combined with an algal source of docosahexaenoic acid, on MDA-MB-231 breast Cancer cell growth and apoptosis in nude mice. *Nutr. Cancer.* 1999; 35(1):44–49. [PubMed: 10624705]
17. Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, et al. Effect of obesity and other lifestyle factors on mortality in women with breast Cancer. *Int. J. Cancer.* 2008; 123(9):2188–2194. [PubMed: 18711698]
18. Escrich E, Moral R, Grau L, Costa I, Solanas M. Molecular mechanisms of the effects of olive oil and other dietary lipids on Cancer. *J. Mol. Nutr. Food Res.* 2007; 51(10):1279–1292.
19. Escrich E, Solanas M, Moral R, Escrich R. Modulatory effects and molecular mechanisms of olive oil and other dietary lipids in breast Cancer. *Curr. Pharm. Des.* 2011; 17(8):813–830. [PubMed: 21443482]
20. Ewertz M, Gillanders S, Meyer L, Zedeler K. Survival of breast Cancer patients in relation to factors which affect the risk of developing breast Cancer. *Int. J. Cancer.* 1991; 49(4):526–530. [PubMed: 1917153]
21. Gasco M, Shami S, Crook T. The p53 pathway in breast Cancer. *Breast Cancer Res.* 2002; 4(2): 70–76. [PubMed: 11879567]
22. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Trudeau ME, Hood N. Diet and breast Cancer: evidence that extremes in diet are associated with poor survival. *J. Clin. Oncol.* 2003; 21(13): 2500–2507. [PubMed: 12829669]
23. Gregorio DI, Emrich LJ, Graham S, Marshall JR, Nemoto T. Dietary fat consumption and survival among women with breast Cancer. *J. Natl. Cancer. Inst.* 1985; 75(1):37–41. [PubMed: 3859694]
24. Hauner D, Janni W, Rack B, Hauner H. The effect of overweight and nutrition on prognosis in breast Cancer. *Dtsch. Ärztebl. Int.* 2011; 108(47):795–801. [PubMed: 22190993]

25. Holmes MD, Stampfer MJ, Colditz GA, Rosner B, Hunter DJ, Willett WC. Dietary factors and the survival of women with breast carcinoma. *Cancer*. 1999; 86(5):826–835. [PubMed: 10463982]
26. Hussain SP, Aguilar F, Amstad P, Cerutti P. Oxy-radical induced mutagenesis of hotspot codons 248 and 249 of the human p53 gene. *Oncogene*. 1994; 9(8):2277–2281. [PubMed: 8036011]
27. Jain M, Miller AB. Tumor characteristics and survival of breast Cancer patients in relation to premorbid diet and body size. *Breast Cancer. Res. Treat.* 1997; 42(1):43–55. [PubMed: 9116317]
28. Jain M, Miller AB, To T. Premorbid diet and the prognosis of women with breast Cancer. *J. Natl. Cancer. Inst.* 1994; 86(18):1390–1397. [PubMed: 8072032]
29. Jump DB. Fatty acid regulation of gene transcription. *Crit. Rev. Clin. Lab. Sci.* 2004; 41(1):41–78. [PubMed: 15077723]
30. Kaaks R, Lukanova A. Energy balance and Cancer: the role of insulin and insulin-like growth factor-I. *Proc. Nutr. Soc.* 2001; 60(1):91–106. [PubMed: 11310428]
31. Kang DH. Oxidative stress, DNA damage, and breast Cancer. *AACN Adv. Crit. Care*. 2002; 13(4): 540–549.
32. Kellen E, Vansant G, Christiaens MR, Neven P, Van Limbergen E. Lifestyle changes and breast Cancer prognosis: a review. *Breast Cancer Res. Treat.* 2009; 114(1):13–22. [PubMed: 18389367]
33. Kroenke CH, Fung TT, Hu FB, Holmes MD. Dietary patterns and survival after breast Cancer diagnosis. *J. Clin. Oncol.* 2005; 23(36):9295–9303. [PubMed: 16361628]
34. Kwan ML, Ambrosone CB, Lee MM, Barlow J, Krathwohl SE, et al. The Pathways Study: a prospective study of breast Cancer survivorship within Kaiser Permanente Northern California. *Cancer. Causes Control*. 2008; 19(10):1065–1076. [PubMed: 18478338]
35. Kyogoku S, Hirohata T, Nomura Y, Shigematsu T, Takeshita S, Hirohata I. Diet and prognosis of breast Cancer. *Nutr. Cancer*. 1992; 17(3):271–277. [PubMed: 1437645]
36. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of Cancer: a review of potential mechanisms. *Am. J. Clin. Nutr.* 2004; 79(6):935–945. [PubMed: 15159222]
37. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Br. Med. J.* 2009;339–2700.
38. Mandal CC, Ghosh-Choudhury T, Yoneda T, Choudhury GG, Ghosh-Choudhury N. Fish oil prevents breast Cancer cell metastasis to bone. *Biochem. Biophys. Res. Commun.* 2010; 402(4): 602–607. [PubMed: 20971068]
39. McCullough ML, Giovannucci EL. Diet and Cancer prevention. *Oncogene*. 2004; 23(38):6349–6364. [PubMed: 15322510]
40. McEligot AJ, Largent J, Ziogas A, Peel D, Anton-Culver H. Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast Cancer. *Nutr. Cancer*. 2006; 55(2):132–140. [PubMed: 17044767]
41. McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic Cancers. *J. Clin. Oncol.* 2010; 28(26):4074–4080. [PubMed: 20644095]
42. Newman SC, Miller A, Howe GR. A study of the effect of weight and dietary fat on breast Cancer survival time. *Am. J. Epidemiol.* 1986; 123(5):767–774. [PubMed: 3962960]
43. Nomura A, Le Marchand L, Kolonel LN, Hankin JH. The effect of dietary fat on breast Cancer survival among Caucasian and Japanese women in Hawaii. *Breast Cancer. Res. Treat.* 1991; 18:135–141.
44. Parekh N, Chandran U, Bandera EV. Obesity in Cancer survival. *Annu. Rev. Nutr.* 2012; 32:311–342. [PubMed: 22540252]
45. Patterson RE, Flatt SW, Newman VA, Natarajan L, Rock CL, et al. Marine fatty acid intake is associated with breast Cancer prognosis. *J. Nutr.* 2011; 141(2):201–206. [PubMed: 21178081]
46. Pierce JP, Natarajan L, Caan BJ, Parker BA, Greenberg ER, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast Cancer. *J. Am. Med. Assoc.* 2007; 298(3):289–298.
47. Renehan AG, Roberts DL, Dive C. Obesity and Cancer: pathophysiological and biological mechanisms. *Arch. Physiol. Biochem.* 2008; 114(1):71–83. [PubMed: 18465361]

48. Rock CL. Diet and breast Cancer: Can dietary factors influence survival? *J. Mammary Gland Biol. Neoplasia*. 2003; 8(1):119–132. [PubMed: 14587867]
49. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, et al. Nutrition and physical activity guidelines for Cancer survivors. *CA-Cancer. J. Clin.* 2012; 62(4):242–274.
50. Rohan TE, Hiller JE, McMichael AJ. Dietary factors and survival from breast Cancer. *Nutr. Cancer*. 1993; 20:167–177. [PubMed: 8233982]
51. Rose DP. Dietary fatty acids and Cancer. *Am. J. Clin. Nutr.* 1997; 66(4):998–1003S.
52. Rose DP. Effects of dietary fatty acids on breast and prostate Cancers: evidence from in vitro experiments and animal studies. *Am. J. Clin. Nutr.* 1997; 66(6):1513–1522S.
53. Rose DP, Connolly JM. Regulation of tumor angiogenesis by dietary fatty acids and eicosanoids. *Nutr. Cancer*. 2000; 37(2):119–127. [PubMed: 11142082]
54. Rose DP, Gilhooly EM, Nixon DW. Adverse effects of obesity on breast Cancer prognosis, and the biological actions of leptin (review). *Int. J. Oncol.* 2002; 21(6):1285–1292. [PubMed: 12429979]
55. Schley PD, Jijon HB, Robinson LE, Field CJ. Mechanisms of omega-3 fatty acid-induced growth inhibition in MDA-MB-231 human breast Cancer cells. *Breast Cancer Res. Treat.* 2005; 92(2): 187–195. [PubMed: 15986129]
56. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011. *CA-Cancer. J. Clin.* 2011; 61(4): 212–236. [PubMed: 21685461]
57. Spencer L, Mann C, Metcalfe M, Webb M, Pollard C, et al. The effect of omega-3 FAs on tumour angiogenesis and their therapeutic potential. *Eur. J. Cancer*. 2009; 45(12):2077–2086. [PubMed: 19493674]
58. Sung MK, Yeon JY, Park SY, Park JHY, Choi MS. Obesity-induced metabolic stresses in breast and colon Cancer. *Ann. N. Y. Acad. Sci.* 2011; 1229(1):61–68. [PubMed: 21793840]
59. Thomson CA, Thompson PA. Dietary patterns, risk and prognosis of breast Cancer. *Future Oncol.* 2009; 5(8):1257–1269. [PubMed: 19852740]
60. Tillotson J, Darzynkiewicz Z, Cohen L, Ronai Z. Effects of linoleic-acid on mammary-tumor cell-proliferation are associated with changes in p53 protein expression. *Int. J. Oncol.* 1993; 3(1):81–87. [PubMed: 21573330]
61. U.S. Dep. Health Human Serv. Dietary Guidelines for Americans. Washington, DC: U.S. Dep. Health Human Serv.; 2010. <http://health.gov/dietaryguidelines/2010.asp>
62. Weichhaus M, Broom I, Bermano G. The molecular contribution of TNF- α in the link between obesity and breast Cancer. *Oncol. Rep.* 2011; 25(2):477–483. [PubMed: 21165572]
63. World Cancer. Res. Fund Int./Am. Inst. Cancer. Res. Continuous Update Project Report Summary. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. London: World Cancer. Res. Fund Int; 2010. http://www.dietandcancerreport.org/cancer_resource_center/cup_summaries.php
64. Zhang S, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast Cancer survival for post-menopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. *Cancer*. 1995; 76(2):275–283. [PubMed: 8625103]

Figure 1.

Description of the potential mechanisms that may underlie the hypothesized association between dietary fats and breast cancer progression. The key mechanisms include eicosanoid synthesis, hormonal imbalances, oxidative stress and DNA damage, and alteration of gene expression.

Figure 2.

The PubMed search process for the original research manuscripts included in the present systematic review per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines. HR, hazard ratio; RR, rate ratio.

Table 1
Studies evaluating prediagnosis total dietary fat in relation to breast cancer and all-cause mortality^a

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
Gregorio et al. 1985 (23)	United States	Prospective cohort study	953 white females with local to distant; cancers 854 completed dietary intake interviews Age: >46 years	FFQ	Relative to any level of fat intake, increase in risk of death per 1,000 g fat consumed	Not available	1.14 (all cases combined) (P = 0.11)	Disease stage, age at diagnosis, treatment delay, relative obesity
Kyoguku et al. 1992 (35)	Japan	Prospective cohort study (follow-up of cases from a case-control study)	212 Japanese women Mean age: 55 years Stage I–III cancer 47 deaths	Diet history	Total fat (g/wk) Quartile 4 versus 1	0.4 (0.1–1.3)	Not available	Disease stage, BMI, age at menarche, age at first birth, age at operation, radiation therapy, chemotherapy, endocrine therapy, operative procedure, and each of the nutrients
Jain et al. 1994 (28)	Canada	Prospective cohort study (follow-up of cases from an RCT)	678 histologically confirmed cases of invasive carcinoma Age: 45–64 years 83 total deaths 76 breast cancer deaths	Diet history questionnaire	Total fat (g) per 20 units/d Total fat energy/energy% per 5 units/d Total fat (% energy) Quartile 4 versus 1	1.21 (0.91–1.61) 1.18 (0.98–1.44) 1.89 (0.96–3.70)	Not available	Energy, age at biopsy, body weight, smoking
Zhang et al. 1995 (64)	United States	Prospective cohort study	698 postmenopausal women with unilateral (in situ to distal) breast cancer Age: 56–67 years 56 total deaths 40 cancer deaths	FFQ	Total fat (g) Tertile 3 versus 1 Total fat (% energy) Tertile 3 versus 1	2.5 (1.2–5.3) 2.2 (1.0–4.7)	Not available	Age, extent of disease (in situ, local, regional, distant), ER status, tumor size, smoking, education
Jain & Miller 1997 (27)	Canada	Prospective cohort study (follow-up of	676 cases of invasive breast carcinoma with	Diet questionnaire	Total fat (unit: 20 g)	Not available	Not available	Energy, age at diagnosis, body weight, smoking,

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
		cases from an RCT)	dietary information within the Canadian National Breast Screening Study Mean age: 49.9 years 76 breast cancer deaths		Adjusted for ER Not adjusted for ER	1.26 (0.90–1.78) 1.19 (0.85–1.67)		ER status
Borugian et al. 2004 (12)	Canada	Prospective cohort study	603 breast cancer patients Age: 19–75 years 112 breast cancer deaths	FFQ	Total fat (g/day) Quartile 4 versus 1	1.8 (0.9–4.8)	Not available	Age, energy, disease stage at diagnosis
McEligot et al. 2006 (40)	United States	Prospective cohort study	516 postmenopausal women Mean age: 65 years 96 total deaths 41 breast cancer deaths	FFQ	Total fat (% energy) Tertile 3 versus 1	Not available	3.12 (1.79–5.44)	Disease stage, age at diagnosis, BMI, parity, HR, alcohol use, multivitamin use, energy
Dal Maso et al. 2008 (17)	Italy	Prospective cohort study (follow-up of a case-control study)	1,453 women with incident invasive breast cancer Age: 23–74 years 503 total deaths 398 breast cancer deaths	FFQ	Total fat (tertiles) Tertile 3 versus 1	0.9 (0.75–1.22)	0.93 (0.75–1.16)	Energy, age at diagnosis, region of residence, year of diagnosis, stage of disease, receptor status (ER/PR status)

^a Abbreviations: BMI, body mass index; ER, estrogen receptor; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; PR, progesterone receptor; RCT, randomized controlled trial; RR, relative risk.

Table 2
Studies evaluating postdiagnosis total dietary fat in relation to breast cancer and all-cause mortality^a

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
Newman et al. 1986 (42)	Canada	Prospective cohort study (follow-up of cases from a case-control study)	300 females with nonmetastatic disease Age: 35–74 years 87 deaths 73 breast cancer deaths	Diet history, 24-hour recall Diet record	RR of dying from breast cancer associated with greater than average daily total fat intake (77.7 g) near diagnosis	0.99 (p = 0.963)	Not available	Weight near time of diagnosis
Nomura et al. 1991 (43)	United States (Hawaii)	Prospective cohort study (follow-up of cases from a case-control study)	182 Japanese 161 Caucasian Age: 45–74 years	Diet history interview	High versus low fat intake (g/wk)	In Japanese women: 0.66 (0.25–1.76) In Caucasian women: 3.17 (1.17–8.55)	Not available	Disease stage, menopausal status, obesity index, estrogen use
Ewertz et al. 1991 (20)	Denmark	Prospective cohort study	2,445 patients with stage I–III invasive breast cancer Age: < 70 years 805 deaths	FFQ	Fat consumption (quartiles) Quartile 4 versus 1	Not available	0.96 (0.75–1.22)	Tumor size, skin invasion, number of positive lymph nodes, grade, and stratified for residence
Rohan et al. 1993 (50)	Australia	Prospective cohort study (follow-up of cases from a case-control study)	412 cases Age: 20–74 years 112 breast cancer deaths	FFQ	Total fat (g) Quintile 5 versus 1	1.40 (0.66–2.96)	Not available	Energy, age at menarche, BMI
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,982 women with invasive breast cancer 686 premenopausal 1,267 postmenopausal	FFQ	Total fat (g) Quintile 5 versus 1	1.44 (1.01–2.04)	1.51 (1.02–2.24)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HR T, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size,

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
								energy
Goodwin et al. 2003 (22)	Canada	Prospective cohort study	477 women with surgically resected breast cancer Age <75 years 52 deaths 50 breast cancer deaths	FFQ	Quadratic form of: Total fat (g/d) Quintile 1 versus 5 Total fat (% energy) Quintile 1 versus 5	Not available	2.9 (p = 0.10) 1.7 (p = 0.03)	Age, energy, BMI, tumor and node stage, HRT, adjuvant chemotherapy
Chlebowski et al. 2006 (15)	United States	RCT	2,437 women with resected early-stage breast cancer receiving conventional cancer management Intervention: n = 975 Control: n = 1,462 Age: 48–79 years	Intervention: low-fat diet postdiagnosis (20% of energy from fat) Both groups had 30% of energy from fat at baseline	Overall survival in intervention versus control Recurrence-free survival in intervention versus control Disease-free survival in intervention versus control Relapse-free survival in intervention versus control	Not available 0.71 (0.53–0.94) 0.81 (0.65–0.99) 0.76 (0.60–0.98)	0.89 (0.65–1.21)	Systemic adjuvant therapy, nodal status, tumor size, mastectomy
Pierce et al. 2007 (46)	United States	RCT	3,088 women previously treated for early breast cancer Age: 18–70 years Intervention: n = 1,537 155 deaths 127 breast cancer deaths Control: n = 1,551 160 deaths 135 breast cancer deaths	Intervention: Very high vegetable, fruit, and fiber and low-fat diet Control: 5-a-day dietary guidelines	Intervention effects: Fat (% energy) Quartile 4 versus 1	Not available	0.98 (0.64–1.49)	Anti-estrogen use, oophorectomy status, and stratification factors (tumor stage, clinic site, and age)
Beasley et al. 2011 (9)	United States	Prospective cohort study	4,441 women with history of	FFQ	Total fat (% energy)			Age, state of residence,

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
			invasive breast cancer and no history of recurrence Age: 29–70 years 525 breast cancer Deaths		Quintile 5 versus 1	0.92 (0.53–1.60)	1.05 (0.79–1.39)	menopausal status, smoking, disease stage, alcohol, history of HRT, energy, treatment, BMI, physical activity

^a Abbreviations: BMI, body mass index; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; RCT, randomized controlled trial; RR, rate ratio.

Table 3
Studies evaluating prediagnosis dietary fat subtypes in relation to breast cancer and all-cause mortality^a

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
Saturated fat (SF)/animal fat								
Kyoguku et al. 1992 (35)	Japan	Prospective cohort study (follow-up of cases from a case-control study)	212 Japanese women Mean age: 55 years Stage I–III cancer 47 deaths	Diet history	Animal fat Quartile 4 versus 1	1.3 (0.4–4.1)	Not available	Disease stage, BMI, age at menarche, age at first birth, age at operation, radiation therapy, chemotherapy, endocrine therapy, operative procedure, each of the nutrients
Jain et al. 1994 (28)	Canada	Prospective cohort study (follow-up of cases from an RCT)	678 histologically confirmed cases of invasive carcinoma Age: 45–64 years 83 total deaths 76 breast cancer deaths	Diet history questionnaire	SF (g): 10 units/d	1.23 (0.97–1.55)	Not available	Energy, age at biopsy, body weight, smoking
					SF/total fat%: 10 units/d	2.00 (1.12–3.56)		
					SF energy/energy%: 5 units/d	1.50 (1.08–2.08)		
					SF(g) Quartile 4 versus 1	1.91 (0.73–5.02)		
					SF (% energy) Quartile 4 versus 1	2.32 (1.22–4.40)		
Zhang et al. 1995 (64)	United States	Prospective cohort study	698 postmenopausal women with unilateral (in situ to distal) breast cancer Age: 56–67 years 56 total deaths	FFQ	SF/total fat (%) Quartile 4 versus 1	1.93 (1.00–3.74)	Not available	Age, extent of disease (in situ, local, regional, distant), ER status, tumor size, smoking,
					SF(g) Tertile 3 versus 1 SF (% energy)	2.4(1.1–4.9) 1.7 (0.8–3.5)		

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
			40 cancer deaths		Tertile 3 versus 1			education
Jain & Miller 1997 (27)	Canada	Prospective cohort study (follow-up of cases from an RCT)	676 cases of invasive breast carcinoma with dietary information within the Canadian National Breast Screening Study cohort Mean age: 49.9 years 76 breast cancer deaths	Diet questionnaire	SF (unit: 10 g) Not adjusted for ER Adjusted for ER SF energy/energy (unit: 5%) Not adjusted for ER Adjusted for ER	1.16 (0.88–1.53) 1.21 (0.92–1.60) 1.55 (1.00–2.37) 1.65 (1.07–2.56)	Not available	Energy, age at diagnosis, body weight, smoking, ER status
Borugian et al. 2004 (12)	Canada	Prospective cohort study	603 breast cancer patients Age: 19–75 years 112 breast cancer deaths	FFQ	SF (g/day) Quartile 4 versus 1	2.5 (1.2–5.3)	Not available	Age, energy, and stage at diagnosis
McEligot et al. 2006 (40)	United States	Prospective cohort study	516 postmenopausal women Mean age: 65 years 96 total deaths 41 breast cancer deaths	FFQ	SF (% energy) Tertile 3 versus 1	Not available	4.45 (2.26–8.78)	Stage of disease, age at diagnosis, BMI, parity, HRT use, alcohol use, multivitamin use, energy
Monounsaturated fat (MUFA)								
Jain et al. 1994 (28)	Canada	Prospective cohort study (follow-up of cases from an RCT)	678 histologically confirmed cases of invasive carcinoma Age: 45–64 years 83 total deaths 76 breast cancer deaths	Diet history questionnaire	Oleic acid (g) per 10 units/day	1.25 (0.90–1.74)	Not available	Energy, age at biopsy, body weight, smoking
Zhang et al. 1995 (64)	United States	Prospective cohort study	698 postmenopausal women with unilateral (in situ to distal)	FFQ	MUFA (g) Tertile 3 versus 1 MUFA (% energy)	Not available	2.3 (1.1–4.7)	Age, extent of disease (in situ, local, regional, distant), ER status, tumor

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
			breast cancer Age: 56–67 years 56 total deaths 40 cancer deaths		Tertile 3 versus 1		1.8 (0.9–3.8)	size, smoking, education
Jain & Miller 1997 (27)	Canada	Prospective cohort study (follow-up of cases from an RCT)	676 cases of invasive breast carcinoma Mean age: 49.9 years 76 breast cancer deaths	Diet questionnaire	Oleic acid (unit: 10 g) No ER in models With ER in models	1.27 (0.87–1.85) 1.33 (0.91–1.95)	Not available	Energy, age at diagnosis, body weight, smoking, ER status
McEligot et al. 2006 (40)	United States	Prospective cohort study	516 postmenopausal women Mean age: 65 years 96 total deaths 41 breast cancer deaths	FFQ	Oleic acid (%) Tertile 3 versus 1	Not available	3.56 (1.67–7.59)	Disease stage, age at diagnosis, BMI, parity, HRT, alcohol use, multivitamin use, energy
Polyunsaturated fat (PUFA)								
Kyoguku et al. 1992 (35)	Japan	Prospective cohort study (follow-up of cases from a case-control study)	212 Japanese women Mean age: 55 years Stage I–III cancer 47 deaths	Diet history	Fish origin Quartile 4 versus 1	1.4 (0.5–4.3)	Not available	Disease stage, BMI, age at menarche, age at first birth, age at operation, radiation therapy, chemotherapy, endocrine therapy, operative procedure, and each of the nutrients
Jain et al. 1994 (28)	Canada	Prospective cohort study (follow-up of cases from an RCT)	678 histologically confirmed cases of invasive carcinoma Age: 45–64 years 83 total deaths 76 breast cancer deaths	Diet history questionnaire	LA (g): per 5 units/day	0.92 (0.67–1.24)	Not available	Energy, age at biopsy, body weight, smoking

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR (95% CI) for all-cause mortality	Covariates
Zhang et al. 1995 (64)	United States	Prospective cohort study	698 postmenopausal women with unilateral (in situ to distal) breast cancer Age: 56–67 years 56 total deaths 40 cancer deaths	FFQ	PUFA (g) Tertile 3 versus 1 PUFA (% energy) Tertile 3 versus 1	1.5 (0.7–3.0) 1.3 (0.6–2.6)	Not available	Age, extent of disease (in situ, local, regional, distant), ER status, tumor size, smoking status, education level
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,504 women with invasive breast cancer	FFQ	Omega-3 FA (g) Quintile 5 versus 1	Not available	0.63 (0.42–0.95)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HRT, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy
McEligot et al. 2006 (40)	United States	Prospective cohort study	516 postmenopausal women Mean age: 65 years 96 total deaths 41 breast cancer deaths	FFQ	LA (% energy) Tertile 3 versus 1	Not available	2.39 (1.21–4.69)	Disease stage, age at diagnosis, BMI, parity, HRT, alcohol use, multivitamin use, energy

^a Abbreviations: BMI, body mass index; ER, estrogen receptor; FA, fatty acid; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; LA, linoleic acid; NCI, National Cancer Institute; RCT, randomized controlled trial; RR, rate ratio.

Table 4
Studies evaluating postdiagnosis dietary fat subtypes in relation to breast cancer and all-cause mortality^a

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR for all-cause mortality	Covariates
Saturated fat (SF)/animal fat								
Rohan et al. 1993 (50)	Australia	Prospective cohort study (follow-up of cases from a case-control study)	412 cases Age: 20–74 years 112 breast cancer deaths	FFQ	SF(g) Quintile 5 versus 1	1.65 (0.73–3.75)	Not available	Energy, age at menarche, BMI
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,982 women with invasive breast cancer	FFQ	Animal fat (g) Quintile 5 versus 1 SF(g) Quintile 5 versus 1	Not available 1.23 (0.89–1.69)	1.01 (0.73–1.38) 1.23 (0.89–1.69)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HRT, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy
Goodwin et al. 2003 (22)	Canada	Prospective cohort study	477 women with surgically resected breast cancer Age <75 years	FFQ	Quadratic form: SF(g/d) Quintile 1 versus 5	Not available	4.3 (p = 0.10)	Age, energy, BMI, tumor and nodule stage, adjuvant hormone therapy, adjuvant chemotherapy
Beasley et al. 2011 (9)	United States	Prospective cohort study	4,441 women with history of invasive breast cancer and no history of recurrence Age: 29–70 years 525 deaths; 26% due to breast cancer	FFQ	SF (% energy) Quintile 5 versus 1	1.55 (0.88–2.75)	1.41 (1.06–1.87)	Age, state of residence, menopausal status, smoking, disease stage, alcohol, history of HRT, energy, treatment, BMI, and physical activity
Trans fats								

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR for all-cause mortality	Covariates
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,982 women with invasive breast cancer	FFQ	18:2 <i>trans</i> fat (g) Quintile 5 versus 1	Not available	1.45 (1.06–1.99)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HRT, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy
Beasley et al. 2011 (9)	United States	Prospective cohort	4,441 women with history of invasive breast cancer and no history of recurrence Age: 29–70 years 525 deaths; 26% due to breast cancer	FFQ	<i>Trans</i> fat(% energy) Quintile 5 versus 1	1.42 (0.80–2.52)	1.78 (1.35–2.32)	Age, state of residence, menopausal status, smoking, disease stage, alcohol, history of HRT, energy, cancer treatment, BMI, physical activity
Monounsaturated fat (MUFA)								
Rohan et al. 1993 (50)	Australia	Prospective cohort study (follow-up of cases from a case-control study)	412 cases Age: 20–74 years 112 breast cancer deaths	FFQ	MUFA intake (g) Quintile 5 versus 1	1.33 (0.56–3.13)	Not available	Energy, age at menarche, BMI
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,982 women with invasive breast cancer	FFQ	Oleic acid (g) Quintile 5 versus 1 MUFA (g) Quintile 5 versus 1	Not available 1.34 (0.96–1.86)	1.23 (0.89, 1.70)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HRT, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy
Goodwin et al. 2003 (22)	Canada	Prospective cohort study	477 women with surgically	FFQ	Quadratic form: Oleic acid (g/d)	Not available	3.1 (p = 0.03)	Age, energy, BMI, tumor and nodule

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR for all-cause mortality	Covariates
			resected breast cancer Age <75 years		Quintile 1 versus 5			stage, HRT, adjuvant chemotherapy
Beasley et al. 2011 (9)	United States	Prospective cohort study	4,441 women with history of invasive breast cancer and no history of recurrence Age: 29–70 years 525 deaths; 26% due to breast cancer	FFQ	MUFA (% energy) Quintile 5 versus 1	0.89(0.49–1.60)	1.14 (0.86–1.52)	Age, state of residence, menopausal status, smoking, disease stage, alcohol, history of HRT, energy, treatment, BMI, physical activity
Polyunsaturated fat (PUFA)								
Nomura et al. 1991 (43)	United States (Hawaii)	Prospective cohort study (follow-up of cases from a case-control study)	161 Caucasian Age: 45–74 years	Diet history interview	High versus low PUFA intake	1.72 (0.74–4.00)	Not available	Disease stage, menopausal status, obesity index, estrogen use
Rohan et al. 1993 (50)	Australia	Prospective cohort study (follow-up of cases from a case-control study)	412 cases Age: 20–74 years 112 breast cancer deaths	FFQ	PUFA intake (g) Quintile 5 versus 1	1.57 (0.78–3.14)	Not available	Energy, age at menarche, BMI
Holmes et al. 1999 (25)	United States	Prospective cohort study	1,982 women with invasive breast cancer 686 premenopausal 1,267 postmenopausal	FFQ	Omega-3 FA (g) Quintile 5 versus 1 LA(g) Quintile 5 versus 1 EPA(g) Quintile 5 versus 1 PUFA (g) Quintile 5 versus 1	Not available	0.77 (0.56–1.07) 1.05 (0.77–1.44) 0.78 (0.57–1.07) 1.05 (0.77–1.43)	Age, diet interval, calendar year of diagnosis, BMI, oral contraceptive use, menopausal status, HRT, smoking, age at first birth and parity, number of metastatic lymph nodes, tumor size, energy

Reference	Location	Design	Sample (n)	Dietary assessment method	Contrast	RR/HR (95% CI) for breast cancer mortality	RR/HR for all-cause mortality	Covariates
Goodwin et al. 2003 (22)	Canada	Prospective cohort study	477 women with surgically resected T1 to T3, NO/I, MO breast cancer Age <75 years	FFQ	Quadratic form: LA(g/d) Quintile 1 versus 5	Not available	1.3 (p = 0.59)	Age, energy, BMI, tumor and nodule stage, HRT, adjuvant chemotherapy
Beasley et al. 2011 (9)	United States	Prospective cohort study	4,441 women with history of invasive breast cancer and no history of recurrence Age: 29–70 years 525 deaths; 26% due to breast cancer	FFQ	PUFA (% energy) Quintile 5 versus 1	0.90 (0.52–1.55)	0.91 (0.70–1.19)	Age, state of residence, menopausal status, smoking, disease stage, alcohol, history of HRT, energy, treatment, BMI, physical activity
Patterson et al. 2011 (45)	United States	Prospective cohort study (cohort analysis from RCT)	3,081 women diagnosed and treated for early-stage breast cancer Age: 18–70 years	24-hour recalls	EPA and DHA (mg/day) Food only: Tertile 3 versus 1 Food adjusted for supplements: Tertile 3 versus 1 Food plus supplements: Tertile 3 versus 1	Not available	0.59 (0.43–0.82) 0.60 (0.44–0.83) 0.68 (0.51–0.90)	Age, obesity, physical activity, intervention group, entry cohort

^a Abbreviations: BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; LA, linoleic acid; RCT, randomized controlled trial; RR, rate ratio.