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Dietary intake of specific fatty acids and breast cancer risk among postmenopausal women in the VITAL cohort

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Abstract

Studies of dietary fat intake and breast cancer have been inconsistent and few have examined specific fatty acids. We examined the association between specific monounsaturated (MUFA), polyunsaturated (PUFA), saturated (SFA), and trans-fatty acids (TFA) and breast cancer risk. Participants, 50–76y, were female members of the VITamins And Lifestyle (VITAL) Cohort, who were postmenopausal at baseline. In 2000–2002, participants completed a food frequency questionnaire. 772 incident, primary breast cancer cases were identified using a population-based cancer registry. Cox proportional hazard models estimated hazard ratios (HR) and 95% confidence intervals (95% CI) for the association between fatty acid intake and breast cancer risk. Intake of total MUFAs (Highest vs. lowest quintile: HR=1.61, 95% CI: 1.08–2.38, *P*-trend=0.02), particularly myristoleic and erucic acids, was associated with increased breast cancer risk. Whereas total SFA was suggestive of an increased risk (HR=1.47, 95% CI: 1.00–2.15, *P*-trend=0.09), strong associations were observed for palmitic, margaric, and stearic acids. Total TFA and PUFA intake were not associated with breast cancer. However, among TFAs, linolelaidic acid was positively associated with risk; among PUFAs, intake of eicosapentaenoic and docosahexaenoic acids were inversely associated with risk. Our findings show that fatty acids are heterogeneous in their association with postmenopausal breast cancer risk.

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INTRODUCTION

There has been interest in the relationship between dietary fat intake and breast cancer risk for decades. Support for a positive association began in the 1970's, based on the large variation in the global incidence of breast cancer (1), the variation in breast cancer risk with per capita fat intake by country (2), and evidence that immigrants from low to high risk countries experienced a higher risk of breast cancer within their lifetime (3–5). A meta-analysis of case-control studies conducted through the early 1990's also provided support for a positive association between individual fat intake and breast cancer risk (6). However, the majority of the prospective studies that followed have failed to show an association between dietary fat and breast cancer risk (7, 8). Among thirteen cohort studies which have reported on total fat intake and breast cancer risk, only four studies reported positive associations (9–12), while the remaining studies have found no association (13–21). Finally, the large Women's Health Initiative (WHI) randomized dietary modification trial of a low fat, high fruit and vegetable diet failed to provide a definitive answer to whether fat intake modifies breast cancer risk [Hazard Ratio (HR) = 0.91, 95% Confidence Interval (95% CI): 0.83–1.01 for intervention vs. control group after 8 years of follow-up] (22).

These inconsistent results described above may be because measurement error in food frequency questionnaires (FFQs) has obscured an association in most cohort studies. In fact, in the past 10 years, the few prospective studies of breast cancer that have corrected for measurement error (11) or used more accurate measures of intake (i.e., food records rather than FFQs) (23, 24), found significant associations with total fat intake.

It is also possible that the inconsistency across studies is due to differential effects by type of fatty acid, and different populations vary in the proportion of major fat groups contributing to total fat intake. Thus categories of fat and specific fatty acids need to be examined. Saadatian-Elahi et al. (25), conducted a meta-analysis of existing biomarker studies and found total monounsaturated fatty acids (MUFAs) to be significantly associated with breast cancer among postmenopausal women, however there was substantial variation in risk estimates across studies. A number of prospective cohort studies of self-reported diet have also found total MUFAs to be associated with breast cancer (10–12, 19, 26). Very few of them examined the specific MUFA, oleic acid, and those that did had inconsistent results (27, 28). Studies that have looked at total saturated fat (SFA) have had similarly disparate findings (9–12, 16, 18, 26, 27, 29, 30), and no prospective studies conducted thus far have examined the association between dietary intake of specific saturated fatty acids and breast cancer. Although most dietary studies have not observed an association between marine long-chain ω-3 PUFAs and breast cancer (31), inverse associations were reported among studies which measured blood biomarkers of long-chain ω-3 PUFAs (32).

Due to the scarcity of prospective studies that have looked at breast cancer in relation to intake of specific fatty acids, we conducted an investigation of these associations within the prospective VITamins And Lifestyle (VITAL) cohort study. The FFQ used in our study yields nutrients based on an updated nutrient composition database that contains data for a large number of fatty acids. Additionally, the FFQ was formulated to ask participants about their fat consumption and food preparation to provide more information on the quantity and types of fat consumed.

MATERIALS AND METHODS

Study Population

Participants in this study were female members of the VITAL cohort, a study of men and women, which was designed to investigate prospectively the association between

supplement use and cancer risk. Study methods have been detailed previously (33). Women, who were 50–76 years of age and living in the 13-county area covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry, were eligible to participate. Between October 2000 and December 2002 we mailed baseline questionnaires and post-card reminders two weeks later to 168,953 women, using names identified from a commercial mailing list. Of these, 40,337 (23.9%) were returned and deemed eligible. Women were excluded if they had a history of breast cancer at baseline (n=3,078) or if this information was missing (n=86), if they were premenopausal (n=1,347), perimenopausal (n =1,009), or were missing menopausal status (n=564). Women were considered postmenopausal if they had experienced a natural menopause with no menstruation in the year prior to the study, received hormone therapy, had undergone bilateral oophorectomy, or were ≥60 years at baseline. A woman who had experienced a hysterectomy without an oophorectomy was characterized as postmenopausal if she had ever received hormone therapy or if she was ≥55 years at baseline. In addition, we excluded women if they failed to successfully complete the baseline food-frequency questionnaire (n= 3,755). All participants gave informed consent and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Additional exclusions were made for women with post-baseline diagnoses of atypical breast cancer histologies, including sarcoma, phyllodes, or lymphoma (n=6), and women diagnosed with incident *in situ* breast cancer (n = 240). After these exclusions, 30,252 women were available for study.

Data Collection

Dietary intakes were assessed using a semi-quantitative FFQ, adapted from instruments developed for the WHI and other studies (34–36). Participants reported their usual frequency and portion size (small, medium or large relative to a given portion size and to photographs of portion sizes) of 120 foods and beverages consumed during the year prior to baseline. The questionnaire was formulated to improve measurement of fatty acid intake. This was accomplished in part by use of questions to delineate the amount of fats consumed (e.g., how often participants ate the skin when eating chicken), food preparation (e.g., fried fish vs. not fried) and types of fat added in cooking or at the table (e.g., 9 options for type of fat used in cooking). Also for 13 types of food, we used adjustment questions or multiple food items to differentiate the use of lower-fat from regular fat products (e.g. salad dressings, lunch meats, frozen desserts). The average daily intake of specific fatty acids was calculated by multiplying the adjusted serving size of each specific food by its fatty acid content. The fatty acid and nutrient composition of each food was determined by using the Minnesota Nutrient Data System for Research (37). The sum of fat intake within a category of fats [SFA, MUFA, PUFA, *trans* (TFA)] was determined by adding up the fatty acids specific to each category. Because fish oil supplements contain high doses of the ω-3 PUFAs eicosapentaenoic acid (EPA, PUFA 20:5) and docosahexaenoic acid (DHA, PUFA 22:6), we added supplemental intake to dietary intake to yield total EPA intake and total DHA intake. Participants were asked to report the frequency (days per week) and duration (years) of fish oil supplement use in the past 10 years. Because data on supplement dose was not available, we estimated doses of EPA and DHA based on the average suggested daily dose among the most popular brands of fish oil supplements (0.64 g/day and 0.35 g/day, respectively).

Participants also reported on personal characteristics, including known or suspected breast cancer risk factors. Participants answered questions on height and weight at baseline; from these data, body mass index (BMI, kg/m^2) was computed. Participants additionally responded to questions on their medical history, including breast cancer screening, having had a benign breast biopsy, hormone therapy use, reproductive history, and family history of breast cancer. Participants reported on their physical activity over the past 10 years,

including type of activity in minutes/day, days/week, and years in duration. From these data, average MET hours/week over the 10 years prior to baseline was computed. Use of any non-steroidal anti-inflammatory drug (NSAID), including low-dose and regular-strength aspirin, ibuprofen, naproxen, or COX-2 inhibitors, such as celecoxib (Celebrex), for ≥4 days/week for ≥4 years was considered regular use.

Case Ascertainment

Cohort members were followed for incident breast cancer diagnoses from baseline to December 31, 2007 with a mean follow-up time of 6 years. Incident, primary, invasive breast cancers were ascertained by linking the study cohort to the western Washington region of the SEER cancer registry, maintained by the Fred Hutchinson Cancer Research Center. This registry covers all incident cancer cases except non-melanoma skin cancer diagnosed within the 13-county area of western Washington State. Cases were ascertained through all area hospitals, offices of pathologists, oncologists, and radiotherapists, and from state death certificates. Extensive quality-control procedures ensure that registry data are accurate and complete. Linkage of participants in the VITAL and SEER databases is mostly automated and based on information such as name, social security number, date of birth. In the instance of a partial match, records were visually inspected. Between November 2000 and December 2007, 772 eligible cases of invasive breast cancer were ascertained.

Follow-up for Censoring

Other than the 2.5% of the cohort that developed breast cancer, the study participants were censored on the earliest of the following dates: requested removal from the study (0.04%), died (4.5%), moved out of the SEER catchment area (5.3%), or the date of complete endpoint ascertainment, December 31, 2007 (87.8%). Deaths were determined by linking VITAL data to the Washington State death files. Individuals who moved out of the area were identified by linkage to the National Change of Address System and follow-up telephone calls.

Statistical analysis

Cox proportional hazards models were used to estimate breast cancer hazard ratios (HR) and 95% confidence intervals (95% CI) associated with participant characteristics and fatty acids from diet. Age was used as the survival time metric, with participants entering regression models at the age they completed the baseline questionnaire and exiting at the age of a censoring event. Statistical analyses were performed using SAS v.9.1 (Cary, N.C.).

Dietary intake of specific fatty acids was categorized into quintiles. We selected for *a priori* potential confounding factors, including known and suspected risk factors for breast cancer. Models were adjusted for age (years), race (white, nonwhite), education (<college graduate, ≥college graduate), height (<1.60,.60 –<1.65, 1.65 –< 1.67, > 1.67 m), BMI (<25, 25–<30, ≥30 kg/m^2), age at menarche (≤11, 12, 13, 14+ years), age at first birth (≤19, 20–24, 25–34, ≥35 years, nulligravid), age at menopause (≤44, 45–49, ≥50 years), history of hysterectomy (none, simple hysterectomy, oophrectomy or total hysterectomy), combined hormonal therapy (never, 1–<5, 5–10, >10 years), estrogen-only hormonal therapy (never, 1–<5, 5–10, >10 years), number of first-degree relatives with a history of breast cancer (none, 1, ≥2), history of mammography (yes/no), history of benign biopsy (yes/no), use of non-steroidal anti-inflammatory drugs (irregular/regular), physical activity (0, 0–<2.39, 2.39–6.13, 6.13–< 14.10, >14.10 MET-hours/week), alcohol consumption (0–<0.5, 0.5–<1.5, 1.5–<5, 5–<10, ≥10 grams/day), total energy intake (< 1015, 1015 –< 1284, 1284 –< 1552, 1552 –< 1910 calories per day), vegetable intake (< 1.08, 1.08 – <1.62, 1.62 –< 2.23, 2.23 –< 3.26, > 3.26 servings per day), and fruit intake (< 0.70, 0.70 – <1.20, 1.20 –< 1.91, 1.91 –< 2.87, > 2.87

servings per day). All reported *P*-values are two-sided. *P*-values for trend (*P*-trend) were calculated by treating categorical variables as ordinal in the regression models.

RESULTS

Selected characteristics of VITAL participants and age-adjusted HRs and 95% CI for the association between these characteristics and breast cancer risk are given in Table 1. Consistent with the literature, increasing age, white race, older age at first birth (or nulliparity), increasing numbers of first-degree relatives with breast cancer, increasing body mass and alcohol intake were all associated with elevated risks of breast cancer.

The associations between dietary fats and breast cancer risk are presented in Table 2. None of the hazard ratios adjusted only for age were significant, but most became stronger after multivariable adjustment, primarily due to inclusion of energy intake in the model. After full adjustment, total fat intake was not associated with breast cancer risk (Quintile 5 vs. Quintile 1 HR 1.43, 95% CI: 0.95–2.14, *P*-trend = 0.10).

We further examined the association of the four main groups of fatty acids and specific fatty acids, listed in footnotes c, d, e, and f of Table 2 with breast cancer risk. Only the fatty acids that are the main dietary contributors to each category are given, with the exception of PUFAs EPA, DHA, and arachidonic acid, which are of particular interest in breast cancer research.

Dietary intake of total MUFAs was significantly associated with an increased risk of breast cancer; comparing the highest versus the lowest quintile of intake, the HR was 1.61 (95% CI: 1.08–2.38, *P*-trend 0.02; Table 2). Intake of the most abundant MUFA, oleic acid (MUFA 18:1) was suggestive of an increased risk of breast cancer, but the *P* for trend was not significant (P-trend = 0.08). Among the MUFAs consumed in smaller quantities (data not shown), myristoleic acid (MUFA 14:1) was associated with an increased breast cancer risk (Quintile 5 vs. Quintile 1 HR = 1.54, 95% CI: 1.16–2.05, *P*-trend < 0.01) and erucic acid (MUFA 22:1) was associated with a reduction in risk (Quintile 5 vs. Quintile 1 HR = 0.67, 95% CI: 0.52–0.87, *P*-trend < 0.01). Intake of other MUFAs was not significantly associated with breast cancer risk. In addition, none of the ten foods highest in total MUFAs in the food database were associated with breast cancer (Supplemental Table), with the exception of fried chicken (Quintile 5 vs. Quintile 1 HR = 1.28, 95% CI: 0.95–1.73, *P*-trend = 0.02).

For total SFA and TFA intake, some point estimates were elevated (Table 2), but the *P* values for trend did not reach statistical significance (*P*-trend = 0.09 and 0.08, respectively). The two fatty acids that contribute the most to SFA intake (mean g/day in VITAL women), palmitic acid (SFA 16:0) and stearic acid (SFA 18:0), were each significantly and linearly associated with increased breast cancer risk (Quintile 5 vs. Quintile 1 HR = 1.68, 95% CI: 1.13–2.50, *P*-trend = 0.02 and HR = 1.65, 95% CI: 1.12–2.43, *P*-trend = 0.03, respectively). Of the SFAs consumed in smaller quantities, only margaric acid (SFA 17:0) was associated with risk (HR = 1.36, 95% CI: 1.03–1.80, *P*-trend = 0.01) (data not shown). Among TFAs, only dietary intake of TFA 18:2 (trans-octadecadienoic acid, also known as linolelaidic acid) was significantly associated with breast cancer risk (HR = 1.53, 95% CI: 1.07–2.19, *P*-trend = 0.02).

We observed no association between total PUFA intake and breast cancer risk (Table 2); however, dietary plus supplemental intake of eicosapentaenoic acid (EPA; PUFA 20:5) and docosahexaenoic acid (DHA; PUFA 22:6) were inversely associated with breast cancer risk (Quintile 5 vs. Quintile 1 HR = 0.70, 95% CI: 0.54–0.90; and HR = 0.67, 95% CI: 0.52–0.87, respectively), and tests for linear trend were statistically significant. When only dietary

intake was considered, findings remained suggestive of an inverse association for EPA (HR = 0.79, 95% CI: 0.61–1.02) and DHA (HR = 0.85, 95% CI: 0.66–1.09) (data not shown). The short-chain ω-3 α-linolenic acid (PUFA 18:3) and ω-6 PUFAs linoleic acid (PUFA 18:2) and arachidonic acid (PUFA 20:4) were not associated with breast cancer risk (Table 2). Finally, the ratio of long-chain ω-3 PUFA intake (EPA+DHA, from diet+supplement) to ω-6 PUFA intake (linoleic+arachidonic acid) was not associated with breast cancer risk.

DISCUSSION

In this prospective study of postmenopausal women, we found associations between the intake of fatty acids within all four major categories of fats and breast cancer incidence. Specifically, intakes of total MUFA, the main contributors to SFA intake palmitic acid (SFA 16:0) and stearic acid (SFA 18:0), and the 18:2 *trans* fat, linolelaidic acid, were associated with increased risks of breast cancer. Dietary plus supplemental intakes of EPA (PUFA 20:5) and DHA (PUFA 22:6) were inversely associated with breast cancer risk. We also examined fatty acids consumed in only small amounts, which have not been examined in prior research. Among these, myristoleic (MUFA 14:1) and margaric (SFA 17:0) acids were associated with increased risks of breast cancer, while erucic acid (MUFA 22:1) was associated with decreased risk.

Authors of 10 cohort studies have investigated the association of total MUFAs from diet and breast cancer risk (10–12, 18, 19, 24, 26, 29, 38–40) with inconsistent results. Consistent with our study, 6 reported significant increased risks of breast cancer associated with MUFA consumption (10–12, 19, 24, 26), while others reported inverse associations (18, 38) or no association (29, 39, 40), including a very large pooled analysis of 8 cohort studies with 7,329 cases (40). Two reports using measurement methods that may be more accurate than FFQs found a significant increased risk with MUFA intake. A nested case-control study within the WHI in which a 4 day diet record was used to assess diet reported a relative risk of 1.96 (95% CI: 1.11–3.45, *P*-trend = 0.02) for the highest vs. lowest quintile of intake of MUFAs (24). In a meta-analysis of prospective studies of blood measures of MUFAs by Saadatian-Elahi et al. (25), the authors reported a doubling of post-menopausal breast cancer risk for those in the highest quartile of MUFAs in blood compared to the lowest (RR 2.20, 95% CI: 1.93–2.52).

Our finding for total MUFA intake was primarily driven by a statistically non-significant increased risk associated with intake of oleic acid (MUFA 18:1), the most abundant MUFA in food. One cohort study found an increased risk of postmenopausal breast cancer with increasing oleic acid consumption only among women without a history of benign breast disease (Quintile 5 vs. 1: RR 1.82, 95% CI: 0.89–3.71; *P*-trend = 0.03) (27). Furthermore, in a case-control analysis nested within a cohort of postmenopausal women in northern Italy, Pala et al. (28), reported that the highest tertile of oleic acid (MUFA 18:1) measured in blood erythrocytes was associated with a near-tripling of breast cancer risk (OR 2.79, 95% CI: 1.24–6.28; *P*-trend = 0.01). Numerous cohort studies have reported on the association between dietary saturated fat and breast cancer risk (9–12, 16, 18, 24, 26, 27, 29, 30, 39, 40). Six studies reported significant positive associations (9, 11, 12, 24, 39, 40), including the WHI study based on diet records (24) and the very large pooled analysis of 8 cohort studies, in which saturated fat intake was associated with breast cancer risk in the multivariate nutrient density model only (40). Seven studies found no association between saturated fat and breast cancer risk (10, 16, 18, 26, 27, 29, 30); this inconsistency between studies may be due to measurement errors inherent in FFQs and the resulting need for large sample sizes to observe significant associations. While our results for intake of SFAs did not reach statistical significance, we did observe significant positive associations between intakes of the two most consumed SFAs, palmitic (SFA 16:0) and stearic (SFA 18:0) fatty acids, and

breast cancer risk. To our knowledge, no prospective study has reported on the association of dietary intake of these fatty acids with breast cancer risk. In the meta-analysis of prospective studies of fatty acids measured in blood, Saadatian-Elahi et al. (25), reported that high levels of palmitic acid (SFA 16:0) were associated with an 89% increased risk of postmenopausal breast cancer (Quartile 4 vs. 1: RR 1.89, 95% CI: 1.70–2.10). In contrast to our finding, however, the authors reported a significant inverse association for stearic acid (Quartile 4 vs. 1: RR 0.68, 95% CI: 0.61–0.76) (25).

We found suggestive associations between intakes of total TFAs and breast cancer risk, with intake of linolelaidic acid (TFA 18:2) associated with a significant increase in risk. However, our results do not have support from earlier studies. Of the two prior prospective studies that examined the association between TFA intake and breast cancer risk (16, 41), neither reported a significant association. In a recent analysis of the Beta-Carotene and Retinol Efficacy Trial (CARET), Takata et al. (42), reported no association between total TFA 18:2 measured in blood and breast cancer risk.

We previously reported that fish oil use was associated with a 32% reduction in breast cancer risk in the VITAL cohort (43). In this report, total (diet+supplemental) EPA and DHA was additionally associated with a reduction in risk. The association between fish or ω-3 PUFA intake from diet and breast cancer has been examined in several cohort studies (44–53). Generally, no association has been reported (31); however, results of a prospective study of women in Singapore, where fish intake is much higher than that of the US, showed an inverse association between dietary ω-3 PUFA from marine sources and breast cancer risk (RR 0.72, 95% CI: 0.53–0.98) (49). A similar finding was observed for high intake of marine ω-3 PUFA in the Shanghai Women's Health Study (Quintile 5 vs. 1: RR 0.74, 95% CI: 0.52–1.06) (53). In the meta-analysis of blood biomarkers of fatty acids, inverse associations similar in magnitude to our own were reported for EPA (RR 0.69, 95% CI: 0.45–1.05) and DHA (RR 0.68, 95% CI: 0.44–1.04) (32). Thus, an association between long-chain ω-3 PUFAs and breast cancer appears to only be observed in studies in which the population has a high intake (e.g., in high fish intake areas or high supplement use) or when biomarkers of ω-3 PUFA are used.

Dietary fat intake could affect the progression of breast cancer through several potential mechanisms (54, 55). Higher fat intake is associated with adiposity, which can increase *de novo* estrogen synthesis leading to increased cell proliferation and breast cancer risk (56, 57). However, our results were adjusted for BMI, to estimate the association of fat intake to breast cancer independent of body mass. It is also possible that a low fat diet *per se* modifies blood hormone concentrations. Some randomized trials of a low-fat diet, including the large WHI dietary modification trial, reported reductions in estradiol and other hormones (58–60). However many low-fat interventions also included increased intake of fruits, vegetables and/or fiber and most led to some weight loss, so the direct effect of fat intake on circulating hormones remains uncertain.

An alternative hypothesis more related to types of fat consumed is that fatty acid intake could shift the balance of saturated to unsaturated fatty acids in the breast cell membrane, thereby altering the fluidity of the cell membrane. This in turn could alter the composition of proteins in the cell membrane or their behavior, perhaps by affecting a cell's response to growth factors or its ability to adhere to neighboring cells (61–63). It is also possible that certain fatty acids may promote cell invasiveness or metastasis, as has been suggested by *in vitro* (64, 65) and *in vivo* studies (66). Additionally, it is well known that myristoylation or palmitoylation of specific proteins can cause them to be preferentially localized and anchored to the membrane. Thus, it is possible that increased dietary intake of specific fatty acids may be causing key changes in the localization and function of proteins important for

tumor suppression. Dietary fats may also affect breast cancer risk by altering the membranes of the cells of the immune system (55).

Finally, there is evidence from human and animal studies that marine ω-3 PUFAs have anti-inflammatory properties. Experimental studies in rodents have shown a reduction in prostaglandin E_2 levels and mammary tumor incidence when rodents were fed diets high in marine ω-3 PUFAs (67–69). In humans, dietary intake of ω-3 PUFAs or fish has been associated with reductions in blood concentrations of several inflammatory markers including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (70, 71). Moreover, authors of a recent randomized trial of ω-3 PUFA supplements reported that the supplements reduced circulating CRP and TNF-α (72); these markers have been associated with breast cancer risk in some epidemiologic studies (73–75).

The strengths of this study are the relatively large size of the cohort, the prospective design which minimizes selection bias and differential measurement error, and detailed FFQ which was designed for more complete ascertainment of amounts and types of fat consumed over prior versions. In addition, we were able to ascertain fish oil supplement data to include in our assessment of intake of ω-3 PUFAs.

One of the main limitations of this study is the measurement error due to self-reported food consumption. However, any error would be non-differential in relation to disease status and would have led to attenuation of results. Another limitation in the interpretation of our results is that while we found associations between intake of several fatty acids and breast cancer risk, it is possible that other constituents of the foods high in the fatty acids of interest, including other fatty acids, could be responsible for the increased risk. Foods that are highest in total MUFAs per serving include fried chicken, beef/pork/ham/lamb eaten with the fat, peanut butter and nuts, fried fish, doughnuts/pies/pastries, regular (not low-fat) hot dogs and sausage, pizza, olive oil, and ground meat. MUFAs, as well as PUFAs, are inherently more sensitive to oxidation at high heat during frying because of their double bonds. Thus any harmful effect may be due to chemical alterations to MUFAs during cooking. This is supported by our analysis of the foods highest in MUFAs: only fried chicken was associated with breast cancer risk (Supplemental Table). It is possible that our findings reflect associations with other constituents of these foods. In addition, although the individual SFAs that were associated with breast cancer risk in this study are found in a large number of foods, they tend to occur together in the same foods, so one cannot separate their independent effects. However, it is unlikely that all SFAs have the same association with breast cancer risk because the two most abundant SFAs (palmitic and stearic acids) only accounted for about one–half of intake of total SFAs, and the other SFAs (except for margaric acid) were not associated with breast cancer risk.

Another concern is residual confounding due to mismeasured or missing covariates in our analyses of fatty acids and foods. Also, our significant results only appeared after multivariate adjustment, primarily due to adjustment for energy intake. Adjustment for energy intake serves two purposes 1) it “calibrates” intake based on the amount of energy consumed (which in turn would be correlated with body mass), which may be more biologically relevant than absolute intake, and 2) it corrects for one component of measurement error in a FFQ, i.e., the tendency of some people to over-report and others to under-report intake across most foods on a FFQ. Thus the difference between the age-adjusted and fully adjusted results these two types of corrections.

In summary, in this cohort study of postmenopausal women, we found total MUFA intake and intake of specific MUFAs, SFAs, and TFAs to be associated with an increased risk of breast cancer, and long-chain ω-3 PUFAs associated with reduced risks of breast cancer.

Although further study of specific fatty acids is needed, this study provides further support for the hypothesis that fat consumption is associated with breast cancer risk, and suggests that risk varies by type of fatty acid.

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ABBREVIATIONS

BMI	body mass index
CARET	Carotene and Retinol Efficacy Trial
CRP	C-reactive protein
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
HR/95% CI	hazard ratio, 95% confidence interval
MUFA	monounsaturated fatty acid
PUFA	polyunsaturated fatty acid
SEER	Surveillance, Epidemiology, and End Results
SFA	saturated fatty acid
TFA	*trans*-fatty acid
VITAL	VITamins And Lifestyle
WHI	Women's Health Initiative

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Table 1

Associations between participant characteristics and breast cancer risk among female VITAL study participants (n = 30,252).

Characteristic	Cases n = 772 N (%)	Non-Cases n = 29480 N (%)	Age Adjusted HR (95% CI)[a]
Age at Baseline (years)			
50–<55	81 (10.49)	5831 (19.78)	N/A
55–<60	173 (22.41)	7519 (25.51)	
60–<65	164 (21.24)	5699 (19.33)	
65–<70	159 (20.60)	4792 (16.26)	
70–<77	195 (25.26)	5639 (19.13)	
Race			
White	734 (95.70)	27531 (93.79)	1.00 (reference)
Non-white	33 (4.30)	1823 (6.21)	0.70 (0.49, 0.99)
Age at First Birth (years)			
<19	116 (15.10)	5304 (18.09)	1.00 (reference)
20–24	328 (42.71)	12239 (41.74)	1.17 (0.95, 1.46)
25–29	134 (17.45)	5728 (19.53)	1.09 (0.85, 1.40)
30–34	47 (6.12)	1871 (6.38)	1.26 (0.90, 1.77)
35+	23 (2.99)	574 (1.96)	2.03 (1.30, 3.18)
Nulliparious	120 (15.63)	3606 (12.30)	1.70 (1.31, 2.20)
P trend			0.039
First Degree Relatives with Breast Cancer			
0	596 (79.15)	24679 (84.90)	1.00 (reference)
1	137 (18.19)	3979 (13.69)	1.40 (1.17, 1.69)
2	20 (2.66)	409 (1.41)	1.92 (1.23, 3.00)
P trend			< 0.0001
Mammogram Within Last 2 Years			
No	66 (8.56)	2467 (8.39)	1.00 (reference)
Yes	705 (91.44)	26951 (91.61)	0.96 (0.75, 1.25)
Combined HT[d] (years)			
0–<1	396 (54.55)	16960 (60.78)	1.00 (reference)
1–<5	80 (11.02)	4101 (14.70)	0.96 (0.75, 1.23)
5–<10	108 (14.88)	3322 (11.91)	1.47 (1.18, 1.82)
≥10	142 (19.56)	3520 (12.62)	1.62 (1.33, 1.97)
P trend			< 0.0001
BMI[d] (kg/m^2)			
<25	278 (37.52)	11429 (40.64)	1.00 (reference)
25–<30	266 (35.90)	9500 (33.78)	1.18 (0.98, 1.41)
≥30	197 (26.59)	7196 (25.59)	1.13 (0.96, 1.34)
P trend			0.070
Physical Activity (MET-hrs/week)			

Characteristic	Cases n = 772 N (%)	Non-Cases n = 29480 N (%)	Age Adjusted HR (95% CI)[a]
0	123 (16.08)	4328 (14.86)	1.00 (reference)
>0 – <2.39	177 (23.14)	6172 (21.20)	1.00 (0.80, 1.26)
2.39 – <6.13	152 (19.87)	6250 (21.46)	0.83 (0.66, 1.06)
6.13 – <14.20	149 (19.48)	6186 (21.24)	0.83 (0.65, 1.05)
≥14.20	164 (21.44)	6183 (21.23)	0.90 (0.72, 1.14)
P trend			0.175
Alcohol Intake (g/day)			
0 – < 0.5	320 (41.45)	13227 (44.87)	1.00 (reference)
0.5 – < 1.5	79 (10.23)	3812 (12.93)	0.89 (0.69, 1.13)
1.5 – < 5	98 (12.69)	4338 (14.72)	0.96 (0.76, 1.20)
5 – < 10	88 (11.40)	3180 (10.79)	1.17 (0.92, 1.48)
≥10	187 (24.22)	4923 (16.70)	1.58 (1.31, 1.89)
P trend			<0.0001
Total Energy Intake (kcal/day)			
≤1015	167 (21.63)	5884 (19.96)	1.00 (reference)
1015 –< 1284	133 (17.23)	5916 (20.07)	0.80 (0.64, 1.00)
1284 –< 1552	163 (21.24)	5887 (19.97)	1.00 (0.80, 1.24)
1552 –< 1910	159 (20.60)	5891 (19.98)	0.97 (0.78, 1.21)
≥1910	149 (19.30)	5902 (20.02)	0.93 (0.74. 1.15)
P trend			0.925

[a] HT, Hormone Therapy: HR, Hazards Ratio; CI, Confidence Interval; BMI, Body Mass Index

Table 2

Associations between fatty acid intake and breast cancer risk among female VITAL study participants (n = 30,252).

Fat Category	Cases n = 772 N (%)	Non-Cases n = 29480 N (%)	Age-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[a,b]
Total Fat (g/day)				
< 32.6	155 (20.08)	5896 (20.00)	1.00 (reference)	1.00 (reference)
32.6 – < 43.9	152 (19.69)	5897 (20.00)	0.99 (0.80, 1.25)	1.16 (0.90, 1.49)
43.9 – < 56.2	143 (18.52)	5908 (20.04)	0.94 (0.75, 1.18)	1.12 (0.83, 1.51)
56.2 – < 73.9	163 (21.11)	5887 (19.98)	1.08 (0.87, 1.35)	1.30 (0.92, 1.81)
≥73.9	159 (20.60)	5892 (19.99)	1.08 (0.86, 1.34)	1.43 (0.95, 2.14)
P Trend			0.37	0.10
Total MUFA[a,c] (g/day)				
< 12.1	144 (18.65)	5907 (20.04)	1.00 (reference)	1.00 (reference)
12.1 – < 16.4	159 (20.60)	5890 (19.98)	1.12 (0.89, 1.41)	1.32 (1.02, 1.70)
16.4 – < 21.0	146 (18.91)	5905 (20.02)	1.03 (0.82, 1.30)	1.28 (0.95, 1.72)
21.0 – < 27.8	164 (21.24)	5886 (19.97)	1.17 (0.93, 1.46)	1.49 (1.07, 2.08)
≥27.8	159 (20.60)	5892 (19.99)	1.16 (0.92, 1.45)	1.61 (1.08, 2.38)
P Trend			0.20	0.02
MUFA 18:1 oleic acid (g/day)				
< 11.2	146 (18.91)	5905 (20.03)	1.00 (reference)	1.00 (reference)
11.2 – < 15.1	161 (20.85)	5889 (19.98)	1.12 (0.90, 1.40)	1.30 (1.01, 1.67)
15.1 – < 19.4	143 (18.52)	5907 (20.04)	1.00 (0.79, 1.25)	1.19 (0.89, 1.59)
19.4 – < 25.7	166 (21.50)	5884 (19.96)	1.16 (0.93, 1.45)	1.41 (1.02, 1.95)
≥25.7	156 (20.21)	5895 (20.00)	1.12 (0.89, 1.40)	1.44 (0.97, 2.12)
P Trend			0.32	0.08
Total SFA[a,d] (g/day)				
< 9.9	152 (19.69)	5898 (20.01)	1.00 (reference)	1.00 (reference)
9.9 – < 13.6	157 (20.34)	5893 (19.99)	1.05 (0.84, 1.31)	1.15 (0.90, 1.48)
13.6 – < 17.8	146 (18.91)	5906 (20.03)	0.99 (0.79, 1.25)	1.14 (0.85, 1.52)
17.8 – < 24.0	152 (19.69)	5897 (20.00)	1.04 (0.83, 1.30)	1.22 (0.88, 1.69)
≥24.0	165 (21.37)	5886 (19.97)	1.15 (0.93, 1.44)	1.47 (1.00, 2.15)
P Trend			0.28	0.09
SFA 16:0 palmitic acid (g/day)				
< 5.5	148 (19.17)	5903 (20.02)	1.00 (reference)	1.00 (reference)
5.5 – < 7.4	161 (20.85)	5889 (19.98)	1.10 (0.86, 1.38)	1.26 (0.98, 1.63)
7.4 – < 9.6	141 (18.26)	5909 (20.04)	0.98 (0.78, 1.24)	1.20 (0.89, 1.62)
9.6 – < 12.7	157 (20.34)	5893 (19.99)	1.10 (0.88, 1.38)	1.40 (1.00, 1.95)
≥12.7	165 (21.37)	5886 (19.97)	1.18 (0.95, 1.48)	1.68 (1.13, 2.50)
P Trend			0.20	0.02
SFA 18:0 stearic acid (g/day)				
< 2.5	146 (18.91)	5905 (20.03)	1.00 (reference)	1.00 (reference)

Fat Category	Cases n = 772 N (%)	Non-Cases n = 29480 N (%)	Age-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[a,b]
2.5 – < 3.5	165 (21.37)	5884 (19.96)	1.15 (0.92, 1.43)	1.26 (0.98, 1.61)
3.5 – < 4.6	140 (18.13)	5912 (20.05)	0.98 (0.77, 1.23)	1.17 (0.88, 1.57)
4.6 – < 6.2	155 (20.08)	5895 (20.00)	1.09 (0.87, 1.37)	1.37 (0.99, 1.89)
≥6.2	166 (21.50)	5884 (19.96)	1.20 (0.96, 1.49)	1.65 (1.12, 2.43)
P Trend			0.22	0.03
Total TFA[a,e] (g/day)				
< 1.64	145 (18.78)	5906 (20.03)	1.00 (reference)	1.00 (reference)
1.64 – < 2.36	147 (19.04)	5902 (20.02)	1.01 (0.81, 1.28)	1.11 (0.86, 1.42)
2.36 – < 3.22	165 (21.37)	5887 (19.97)	1.13 (0.90, 1.41)	1.35 (1.04, 1.75)
3.22 – < 4.58	165 (21.37)	5885 (19.96)	1.13 (0.90, 1.41)	1.33 (1.00, 1.77)
≥4.58	150 (19.43)	5900 (20.01)	1.03 (0.82, 1.30)	1.27 (0.92, 1.78)
P Trend			0.45	0.08
TFA 18:1 (g/day)				
< 1.40	144 (18.65)	5907 (20.04)	1.00 (reference)	1.00 (reference)
1.40 – <2.03	147 (19.04)	5903 (20.02)	1.02 (0.81, 1.28)	1.14 (0.89, 1.46)
2.03 – <2.78	165 (21.37)	5886 (19.97)	1.13 (0.91, 1.42)	1.37 (1.06, 1.78)
2.78 – <4.00	167 (21.63)	5882 (19.95)	1.15 (0.92, 1.44)	1.36 (1.02, 1.81)
≥4.00	149 (19.30)	5902 (20.02)	1.03 (0.82, 1.30)	1.30 (0.94, 1.80)
P Trend			0.48	0.07
TFA 18:2 [f] (g/day)				
< 0.19	139 (18.01)	5911 (20.05)	1.00 (reference)	1.00 (reference)
0.19 – < 0.27	150 (19.43)	5901 (20.02)	1.09 (0.86, 1.37)	1.23 (0.96, 1.59)
0.27 – < 0.35	170 (22.02)	5881 (19.95)	1.22 (0.97, 1.53)	1.52 (1.16, 2.00)
0.35 – < 0.49	158 (20.47)	5891 (19.98)	1.14 (0.91, 1.43)	1.40 (1.03, 1.91)
≥0.49	155 (20.08)	5896 (20.00)	1.13 (0.90, 1.42)	1.53 (1.07, 2.19)
P Trend			0.28	0.02
Total PUFA[a,g] (g/day)				
< 7.10	152 (19.69)	5899 (20.01)	1.00 (reference)	1.00 (reference)
7.10 – < 9.70	160 (20.73)	5889 (19.98)	1.06 (0.85, 1.32)	1.13 (0.89, 1.45)
9.70 – < 12.40	142 (18.39)	5910 (20.05)	0.94 (0.75, 1.18)	1.06 (0.80, 1.39)
12.40 – < 16.60	169 (21.89)	5880 (19.95)	1.13 (0.90, 1.40)	1.19 (0.88, 1.60)
≥16.60	149 (19.30)	5902 (20.02)	1.00 (0.80, 1.26)	1.07 (0.76, 1.52)
P Trend			0.78	0.62
ω-3 PUFAs				
PUFA 18:3 alpha-linolenic acid (g/day)				
< 0.69	157 (20.34)	5893 (19.99)	1.00 (reference)	1.00 (reference)
0.69 – < 0.97	152 (19.69)	5898 (20.01)	0.97 (0.78, 1.21)	1.00 (0.78, 1.27)
0.97 – < 1.29	157 (20.34)	5895 (20.00)	1.00 (0.80, 1.25)	1.06 (0.82, 1.37)
1.29 – < 1.75	156 (20.21)	5894 (19.99)	1.00 (0.80, 1.25)	1.01 (0.77, 1.33)
≥1.75	150 (19.43)	5900 (20.01)	0.97 (0.78, 1.22)	0.97 (0.71, 1.32)

Fat Category	Cases n = 772 N (%)	Non-Cases n = 29480 N (%)	Age-Adjusted HR (95% CI)	Multivariable-Adjusted HR (95% CI)[a,b]
P Trend			0.93	
PUFA 20:5 eicosapentaenoic acid (diet + supplement, g/day)				
< 0.02	158 (20.49)	5870 (19.99)	1.00 (reference)	1.00 (reference)
0.02 – < 0.03	160 (20.75)	5867 (19.98)	1.00 (0.80, 1.24)	0.96 (0.77, 1.21)
0.03 – < 0.06	160 (20.75)	5867 (19.98)	1.00 (0.81, 1.25)	0.96 (0.76, 1.22)
0.06 – < 0.10	177 (22.96)	5854 (19.93)	1.12 (0.91, 1.39)	1.04 (0.83, 1.32)
≥0.10	116 (15.05)	5913 (20.13)	0.73 (0.57, 0.93)	0.70 (0.54, 0.90)
P Trend			0.03	0.04
PUFA 22:6 docosahexaenoic acid (diet + supplement, g/day)				
< 0.03	164 (21.27)	5865 (19.97)	1.00 (reference)	1.00 (reference)
0.03 – < 0.07	165 (21.40)	5864 (19.97)	1.00 (0.81, 1.25)	0.96 (0.77, 1.20)
0.07 – < 0.12	163 (21.14)	5865 (19.97)	0.99 (0.80, 1.23)	0.93 (0.74, 1.17)
0.12 – < 0.21	159 (20.62)	5870 (19.99)	0.98 (0.79, 1.21)	0.92 (0.72, 1.16)
≥0.21	120 (15.56)	5907 (20.11)	0.73 (0.58, 0.93)	0.67 (0.52, 0.87)
P Trend			0.02	0.01
ω-6 PUFAs				
PUFA 18:2 linoleic acid (g/day)				
< 6.09	152 (19.69)	5899 (20.01)	1.00 (reference)	1.00 (reference)
6.09 – < 8.36	152 (19.69)	5898 (20.01)	1.00 (0.80, 1.26)	1.09 (0.85, 1.40)
8.36 – < 10.85	151 (19.56)	5900 (20.01)	1.00 (0.80, 1.26)	1.12 (0.86, 1.48)
10.85 – < 14.58	163 (21.11)	5886 (19.97)	1.08 (0.87. 1.35)	1.19 (0.89, 1.60)
≥14.58	154 (19.95)	5897 (20.00)	1.04 (0.83, 1.30)	1.18 (0.84, 1.66)
P Trend			0.56	0.30
PUFA 20:4 arachidonic acid (g/day)				
< 0.05	151 (19.56)	5899 (20.01)	1.00 (reference)	1.00 (reference)
0.05 – < 0.07	153 (19.82)	5897 (20.00)	1.02 (0.81, 1.28)	1.00 (0.79, 1.27)
0.07 – < 0.10	162 (20.98)	5890 (19.98)	1.09 (0.88, 1.37)	1.11 (0.87, 1.42)
0.10 – < 0.13	163 (21.11)	5887 (19.97)	1.11 (0.89, 1.39)	1.10 (0.85, 1.41)
≥0.13	143 (18.52)	5907 (20.04)	1.00 (0.79, 1.26)	0.97 (0.74, 1.29)
P Trend			0.72	0.88
ω-3 / ω-6 PUFAs				
PUFA 20:5n-3 + PUFA 22:6n-3 / PUFA 18:2n-6 + PUFA 20:4n-6 (g/day)				
< 0.005	151 (19.56)	5899 (20.01)	1.00 (reference)	1.00 (reference)
0.005 – < 0.01	163 (21.11)	5887 (19.97)	1.07 (0.86, 1.34)	1.03 (0.81, 1.29)
0.01 – < 0.02	163 (21.11)	5889 (19.98)	1.06 (0.85, 1.33)	1.04 (0.83, 1.31)
0.02 – < 0.03	162 (20.98)	5888 (19.97)	1.07 (0.86, 1.34)	1.02 (0.81, 1.30)
≥0.03	133 (17.23)	5917 (20.07)	0.87 (0.69, 1.10)	0.84 (0.65, 1.09)
P Trend			0.32	0.27

[a]HR, Hazards Ratio; CI, Confidence Interval; MUFA, Monounsaturated Fatty Acid; SFA, Saturated Fatty Acid, TFA, Trans Fatty Acid; PUFA, Polyunsaturated Fatty Acid;

[b] adjusted for age, race, education, height, body mass index, age at menarche, age at first birth, age at menopause, history of hysterectomy, years of combined hormone therapy, years of estrogen hormone therapy, family history of breast cancer, mammography, history of benign breast biopsy, regular use of non-steroidal anti-inflammatory drugs, exercise, alcohol consumption, vegetable intake, fruit intake, and total energy

[c] MUFAs: 14:1, myristoleic acid; 16:1, palitoleic acid; 18:1, oleic acid; 20:1, gadoleic acid; 22:1, erucic acid

[d] SFAs: SFA 4:0 butyric acid, SFA 6:0 caproic acid, SFA 8:0 caprylic acid, SFA 10:0 capric acid, SFA 12:0 lauric acid, SFA 14:0 myristic acid, SFA 16:0 palmitic acid, SFA 17:0 margaric acid, SFA 18:0 stearic acid, SFA 20:0 arachidic acid, SFA 22:0 behenic acid

[e] Trans Fatty Acids: 16:1, trans-hexadecenoic acid, 18:1, trans-octadecenoic acid (elaidic acid), 18:2 trans-octadecadienoic acid (linolelaidic acid) includes c-t, t-c, t-t

[f] 18:2 trans-octadecadienoic acid (linolelaidic acid) includes c-t, t-c, t-t

[g] PUFAs: 18:2, linoleic acid; 18:3, alpha-linolenic acid (ALA); 18:4, parinaric acid; 20:4, arachidonic acid; 20:5, eicosapentaenoic acid (EPA); 22:5, docosapentaenoic (DPA); 22:6, docosahexaenoic acid (DHA)