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Dietary fat intake in relation to lethal breast cancer in two large prospective cohort studies

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Abstract

Purpose—Whether fat intake influences risk of developing more aggressive, lethal breast tumors is unknown. We evaluated intakes of total fat, specific types of fat, and cholesterol prior to diagnosis in relation to lethal breast cancer risk in 88,759 women in the Nurses' Health Study (NHS; 1980–2010) and 93,912 women in the Nurses' Health Study II (NHSII; 1991–2010).

Methods—Diet was assessed every four years using a semi-quantitative food frequency questionnaire. Breast cancers were confirmed with pathology reports; deaths were confirmed by next of kin or the National Death Index. We defined lethal cases as women with invasive breast cancer who died of breast cancer. We pooled the cohorts and used multivariable Cox proportional hazards models.

Results—We identified 1,529 lethal breast cancer cases (1,279 in NHS and 250 in NHSII). Higher total fat intake was associated with a slightly lower lethal breast cancer risk (top vs. bottom quintile hazard ratio [HR] 0.85; 95 % CI 0.72, 1.01; p trend = 0.05). Specific types of fat were generally not associated with lethal breast cancer risk. For example, compared with those in the lowest quintile of saturated fat intake, those in the highest quintile had a HR of 0.98 (95 % CI

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0.75, 1.26; p trend = 0.96). Among women diagnosed with breast cancer, pre-diagnosis fat intake was not associated with survival.

Conclusions—Higher pre-diagnosis fat intake was not associated with greater risk of lethal breast cancer in these large prospective cohort studies, consistent with the weight of the evidence against a causal role for fat intake and breast cancer incidence.

Keywords

fat; breast cancer; mortality; survival; cholesterol; lethal

INTRODUCTION

The hypothesis that dietary fat is an important cause of breast cancer originated in the mid-20th century from early studies in which rodents consuming high fat diets developed more induced mammary tumors, theoretically through increased endogenous estrogen exposure. [1,2] However, because the high-fat diets were often also higher in calories, excess calorie consumption could have been responsible for these findings. [3] In early ecologic and case-control studies, positive associations were observed between total fat intake and risk of breast cancer [4,5], but these types of studies can be affected by biases including ecologic fallacy, confounding, recall bias, and selection bias. Most prospective studies, on the other hand, have not observed an association, even at very low or very high levels of total fat intake, as in the Pooling Project of eight prospective cohort studies with over 350,000 women, the largest study of dietary fat and breast cancer to date. [6] Furthermore, two randomized trials of total fat reduction showed no significant effect on breast cancer incidence. [7,8] Yet dietary fats are heterogeneous, and a few prospective studies suggested a positive association between intake of saturated/animal fat, particularly from red meat and high-fat dairy, and breast cancer incidence, [6,9,10] as well as an inverse relation between monounsaturated/vegetable fat and breast cancer risk. [6]

One critical issue is that many breast cancers diagnosed today are early stage tumors that may not have been diagnosed without intensive mammography. In a recent analysis using Surveillance, Epidemiology, and End Results data from 1976 to 2008, Bleyer and Welch demonstrate that the number of early stage breast cancer diagnoses has doubled since the introduction of mammography; they suggest that a large number of breast cancers are “overdiagnosed” and would never lead to advanced disease or death if left untreated. [11] This concept of breast cancer overdiagnosis has only more recently been discussed with breast cancer, but has been extremely relevant in the field of prostate cancer, [12–14] in which risk factors have been shown to vary for total prostate cancer vs. lethal prostate cancer. [15] In addition, the concept of breast cancer heterogeneity has become a driving force for breast cancer epidemiology. Recent research suggests that breast cancer tumor subtypes such as luminal A, luminal B, triple-negative, and others, which are differentially related to disease prognosis, [16,17] have distinct etiologies [18–21]. Therefore, a potentially important new research direction is to identify risk factors for the most aggressive, lethal breast tumors. Whether dietary fat intake influences development of lethal breast cancer is unknown.

We therefore assessed whether fats are important in the development or prevention of the most clinically relevant breast cancer tumors using data from two large prospective studies, the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII). We examined the intakes of total fat, specific types of fat, and cholesterol before cancer diagnosis in relation to risk of lethal breast cancer. Among women diagnosed with breast cancer, we also examined pre-diagnosis fat intake in relation to death from breast cancer.

METHODS

The NHS was established in 1976 when 121,701 US female registered nurses ages 30–55 completed an initial questionnaire. The NHSII was established in 1989 with 116,430 nurses ages 25–42 years. Information on lifestyle factors and new disease diagnoses is collected every two years through mailed questionnaires. The active follow-up among these cohorts is over 90%.

For the current analysis, we initiated follow-up when diet was first measured, in 1980 in NHS and 1991 in NHSII. From the 187,898 (92,468 in NHS and 95,430 in NHSII) women who returned the initial dietary questionnaire with reasonable energy intake (≥500 kcal or ≤3500 kcal/day in NHS, ≥600 kcal or ≤3500 kcal/day in NHSII), we excluded women who reported a previous diagnosis of cancer, except non-melanoma skin cancer, women with non-invasive breast cancer, and women with an unknown date of breast cancer diagnosis. After exclusions, data from 88,759 NHS participants and 93,912 NHSII participants were available for analysis (total N=182,671).

Dietary Assessment

Women reported dietary information on semi-quantitative food frequency questionnaires (FFQs) administered in 1980, 1984, 1986, 1990, 1994, 1998, 2002, and 2006 for the NHS and in 1991, 1995, 1999, 2003, and 2007 for the NHSII. Details about the reproducibility and reliability of the FFQs have been described elsewhere. [22,23] Fat intake for each individual was calculated as the sum of the contributions from all foods on the basis of U.S. Department of Agriculture food composition data, [24] taking into account types of margarine and fats used in cooking and baking. To calculate the percentage of energy contributed by each type of fat, we divided energy intake from each fat by total energy intake. We calculated energy-adjusted cholesterol intake using the nutrient residual method. [3] Updated cumulative average fat and cholesterol intakes were calculated by averaging intake over time since the baseline questionnaires. For example, the 1980 intake was used for the 1980–1984 follow-up period, and the average of the 1980 and 1984 intake was used for 1984–1986 follow-up to maintain a strictly prospective analysis. If an individual was missing dietary intake for a certain year, we used the updated cumulative average intake from the previous years.

The fat and cholesterol measurement on the FFQ have been shown to be valid and reproducible. In a group of 92 participants in the NHS, the correlation between total fat intake assessed by FFQ (average in 1980, 1984, and 1986) and weeklong diet records (average of 1980 and 1986) was 0.83; for saturated fat r=0.95 and for cholesterol r=0.90. [25] In 115 postmenopausal US women, the Spearman correlation between FFQ intake and

subcutaneous adipose tissue aspirates was 0.51 for trans fatty acids, 0.48 for n-3 fatty acids of marine origin, and 0.37 for polyunsaturated fatty acids. [26]

Breast cancer case ascertainment

All women reporting incident diagnoses of breast cancer on the biennial questionnaires were asked for permission to review their medical records to confirm the diagnosis and to classify cancers by invasiveness and hormone receptor status. Following medical record review, we were able to confirm 99% of self-reported breast cancers. To identify cases of cancer in non-respondents who died, we obtained death certificates and medical records for the incident cancers.

Death ascertainment

Deaths were identified by next of kin, the post office, or the National Death Index. Physician reviewers blinded to exposure information ascertained cause of death from death certificates, which were supplemented with medical records or interviews with the family or health care providers if necessary. In the case of death due to a cancer metastasis, the primary cancer was recorded as the cause of death.

Lethal breast cancer cases

We defined lethal breast cancer cases as women with confirmed diagnosis of invasive breast cancer during follow-up who died from breast cancer by June 1, 2012.

Covariate Assessment

We calculated participant age at each cycle using birth date and questionnaire return date. At baseline, participants reported height, age at menarche, weight at age 18 (assessed in 1980 in NHS), and reproductive history. Biennially, women reported weight, new pregnancies, oral contraceptive (OC) and postmenopausal hormone use, menopausal status, age at menopause, and diagnosis of benign breast disease. In 1986 in the NHS and biennially (through 2003) in the NHSII, we assessed breastfeeding duration. Every four years, women reported family history of breast cancer and alcohol consumption. We calculated updated cumulative average alcohol intake. Every 2–6 years, the questionnaires assessed average time per week spent engaged in different types of physical activity; we used this information to calculate metabolic equivalent task hours per week as described previously. [27]

Statistical analysis

The primary analysis assessed cumulative average fat intake in relation to lethal breast cancer. Person-time for each participant was calculated from the date of return of the baseline questionnaire until the date of breast cancer diagnosis, date of any other cancer diagnosis, death from any cause, or June 1, 2010, whichever came first. We used the date of breast cancer diagnosis rather than the date of death because women with breast cancer are likely to change their diets as a result of the diagnosis or its treatment. For this analysis, we used rates of lethal breast cancer with person-months in the denominator. For each woman, person-months were allocated to each exposure category, beginning at baseline and updated every two to four years. We used Cox proportional hazards models to estimate hazard ratios

(HRs) and 95% confidence intervals (CIs). We examined quintiles of dietary intake to allow for non-linearity and used the median values in each quintile as a continuous variable to test for linear trend.

Multivariate analysis included family history of breast cancer in a first-degree relative, personal history of benign breast disease, BMI at age 18, weight change since age 18, age at menarche, birth index (a variable combining parity and age at first birth, as described previously [28,29]), alcohol consumption, menopausal status and postmenopausal hormone use, age at menopause, and lactation history. Covariates were updated where possible. To simulate energy substitution for carbohydrates, we created a multivariable nutrient density model by adjusting for total energy intake and percent calories from protein; in analyses of specific types of fat, we additionally adjusted for percent calories from other types of fat.

Sensitivity Analyses

We assessed the associations using baseline diet only, simple updated diet, and a latency analysis [3] and including only breast cancers that were lethal within 5, 10, or 15 years of diagnosis. We also conducted a sensitivity analysis in which follow-up started in 1984 in the NHS because the FFQ administered in 1980 to NHS participants was a shorter version (61 vs. ~130 questions).

Because mammographic screening is associated with risk factors for breast cancer and breast cancer diagnosis, we fit logistic regression models for mammography and used inverse probability weighting to adjust the model, as described previously. [30]

To determine whether exposures were differentially associated with lethal and nonlethal breast cancer, we used competing risks models [31,32] incorporating the data augmentation method described by Lunn and McNeil. [33] We created a separate observation for each subject for each type of outcome (lethal breast cancer, non-lethal breast cancer, no breast cancer) and then stratified on event type, allowing for estimation of separate associations of each risk factor with the relative hazard of each type of outcome. The date of cancer diagnosis was used as the event date for lethal and nonlethal breast cancers. Likelihood ratio tests were conducted to compare models assuming different associations of exposures with each type of outcome to models assuming the same association with all types. We also used this type of model in a sensitivity analysis with four potential outcomes: women with breast cancer who died of their disease, women with breast cancer who died of other causes, women with breast cancer who did not die, and women without breast cancer.

Finally, among women with breast cancer, we examined pre-diagnosis fat intake in relation to breast cancer mortality, taking into account tumor characteristics and basic treatment regimens extracted from patient medical records. Women diagnosed with stage IV tumors were excluded from this analysis. We used cumulative average intake up to the questionnaire prior to breast cancer diagnosis as the main exposure for pre-diagnostic diet. We also adjusted for ER/PR status from medical records and tissue microarray specimens when medical records were not available, as described previously [34,35] and disease stage, as well as treatment (chemotherapy, radiation, and hormone therapy). Post-diagnosis diet,

defined as continuous change in intake of each type of fat (change = intake in most recent cycle - cumulative average intake before diagnosis), was incorporated into the model.

All analyses were conducted with SAS version 9.3 (SAS, Cary, NC, USA). All statistical tests were two sided, and p-values<0.05 were considered statistically significant. This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital and the Office of Human Research Administration at Harvard School of Public Health.

RESULTS

Over the course of follow-up, 9,979 invasive breast cancer cases developed, of which 1,529 went on to become lethal (1,279 in NHS and 250 in NHSII). On average, women with higher total fat intake consumed less alcohol, exercised less, had higher BMIs, and were less likely to get mammograms than women with low total fat intake (Table 1).

There was a borderline significant inverse association between cumulative average total fat intake and lethal breast cancer that appeared to be driven by trans fat intake, as trans fats were associated with a lower risk of lethal breast cancer (Table 2). Comparing the highest to the lowest quintile of intake, the relative risk was 0.85 (95% CI: 0.72, 1.01; p-trend=0.05) for total fat and 0.76 (95% CI: 0.61, 0.96; p-trend=0.01) for trans fat. However, the association was not entirely linear and was attenuated in the sensitivity analyses we conducted (e.g., baseline exposure only). Furthermore, the association of trans fat with lethal breast cancer was attenuated when we included deaths due to other causes (n=1184; e.g. myocardial infarction) after breast cancer diagnosis as a separate outcome in a model where the reference group included only nonlethal breast cancers (women without breast cancers were included separately as another outcome). Overall, intakes of other specific types of fat and dietary cholesterol were not associated with risk of total or lethal breast cancer in multivariable-adjusted models. For example, the HR for the highest vs. lowest quintile of saturated fat intake and lethal breast cancer was 0.98 (95% CI: 0.75, 1.26; p-trend=0.96). Women in the highest quintile of vegetable fat intake had a significantly lower risk of lethal breast cancer, although the p-value for trend was not significant (HR: 0.81, 95% CI: 0.67, 0.97; p-trend=0.18). There were not substantial differences between the two cohorts (data not shown).

Among women with breast cancer, pre-diagnosis intakes of fats and cholesterol were not associated with breast cancer survival, whether or not we adjusted for change in fat intake after diagnosis and tumor and treatment characteristics (Table 3). For example, for women in the highest vs. lowest quintile of pre-diagnosis total fat, the HR for breast cancer-specific mortality was 0.97 (95% CI: 0.78, 1.19; p-trend=0.62) in multivariable adjusted models. Upon further adjustment for change in total fat intake after diagnosis and tumor and treatment characteristics, the HR was 0.97 (95% CI: 0.76, 1.24; p-trend=0.85). The association with trans fat intake appeared suggestively inverse (quintile 5 vs. quintile 1 HR: 0.76; 95% CI: 0.55, 1.04; p-trend=0.05) but was not statistically significant. When trans fat intake was cross-classified into tertiles of pre-diagnosis intake and tertiles of intake after diagnosis (9 categories total), the association appeared to be driven by post-diagnosis trans

fat intake, which was associated with increased risk; compared to women with the highest trans fat intake before diagnosis and the lowest intake after diagnosis, those with the lowest intake before diagnosis and the highest after diagnosis had a HR of 1.37 (95% CI: 1.04, 1.80) of breast cancer-specific mortality (p-interaction=0.35).

These results were consistently null in different sensitivity analyses conducted including lagged analyses, defining baseline and current fat as the exposure, and adjusting for the probability of mammographic screening (data not shown).

DISCUSSION

Dietary intakes of fats and cholesterol were not associated with risk of lethal breast cancer in these two large prospective cohort studies. The results were null and consistent throughout numerous sensitivity analyses. We observed a borderline inverse association of total fat and lethal breast cancer, which appeared to be driven by trans fat intake. While trans fat intake was inversely associated with lethal breast cancer risk, this association was attenuated when we included deaths due to other causes in the model, including cardiovascular disease. These findings suggest that the apparent inverse association between trans fat and lethal breast cancer may be explained by competing risk of death due to other causes. Among women with breast cancer, pre-diagnosis fat and cholesterol intakes were not related to breast cancer-specific mortality, even after adjusting for change in fat intake after cancer diagnosis as well as tumor stage at diagnosis and treatment characteristics.

To our knowledge, this is the first prospective cohort study assessing pre-diagnosis dietary fat intake in relation to lethal breast cancer, and our null results were consistent with those of previous large prospective cohorts examining total invasive breast cancer incidence. In the Pooling Project of eight pooled prospective cohort studies with over 350,000 women and more than 7,000 cases, total fat intake was not associated with breast cancer incidence [RR for a 5% increment: 1.00 (95% CI: 0.98, 1.03)] [6], and in most survival analyses among women with breast cancer, total fat intake post-diagnosis was not associated with survival. [36] However, fatty acids are heterogeneous, with varied chemical structures, functions, and effects on the human body, so investigating the impacts of individual types of fat is important.

Our finding that high trans fat intake was associated with a significantly lower risk of lethal breast cancer was counter to our hypothesis, as trans fats are related to poor health outcomes like obesity and heart disease [37–39] and there is little evidence of their health benefits. We suspected that our results might be explained by women with high trans fat consumption being more likely to die due to heart disease, thus removing them from the population at risk for breast cancer mortality. When we included death due to other causes as an additional outcome in the model, the association between trans fat intake and lethal breast cancer was attenuated. This sensitivity analysis suggests that trans fats appear to be inversely related to breast cancer deaths because they increase risk of cardiovascular disease deaths. Trans fat intake was not associated with total breast cancer incidence in this study, nor was it significantly associated with disease-specific survival among women with breast cancer.

We did not observe associations between other specific types of fat and lethal breast cancer. Animal and saturated fat were not associated with lethal breast cancer risk, although a modest positive association (RR: 1.09; 95% CI: 1.00, 1.19 for a 5% increment in saturated fat replacing carbohydrate intake) was observed for incidence of total breast cancer in the Pooling Project [6] and animal fat intake was associated with a higher risk of premenopausal breast cancer (RR: 1.33; 95% CI: 1.02–1.73 for top vs. bottom quintile) in the NHSII. [10] In a study among 4,441 breast cancer survivors, Beasley et al. observed positive associations between saturated fat and trans fat and total mortality; [36] however, a recent meta-analysis that included results from the Pooling Project and more recent prospective studies observed no association between animal fat intake and breast cancer risk. [40] The positive association between animal fat and breast cancer in some studies could be explained by a possible positive association between red meat/dairy intake and breast cancer incidence and/or survival. In the Life After Cancer Epidemiology study, high-fat dairy intake after diagnosis was associated with higher breast cancer mortality; [41] however, in the Pooling Project and two recent meta-analyses using prospective data, the authors did not find a consistent positive association between red meat or dairy intake and incidence of breast cancer. [42–44]

Despite a modest, albeit not statistically significant association in the Pooling Project (RR: 0.93; 95% CI: 0.84, 1.03 for a 5% increment in vegetable fat replacing carbohydrate intake), [6] we did not observe an inverse association between vegetable fat and lethal breast cancer. Vegetable fat intake after diagnosis was not associated with mortality among 11,390 women in the After Breast Cancer Pooling Project. [45]

This study is limited by its observational nature. However, error was reduced by using the average of many repeated questionnaires, and type of fat intake using these data have robustly predicted risk of coronary heart disease. [46] Also, numerous prospective studies with detailed dietary data have consistently found no association between total fat and breast cancer risk, [6] which fits with our findings. Strengths of this study include the detailed, prospective dietary information over several decades, high rates of follow-up, thorough assessment of invasive breast cancer incidence and death follow-up, and careful control for confounders including post-diagnosis diet and tumor and treatment characteristics.

In summary, in these two large prospective cohorts, pre-diagnosis intakes of total fat and types of fat were not associated with lethal breast cancer or breast cancer survival. Our findings are consistent with the weight of the evidence, which argues against a causal role for high fat intake and incidence of breast cancer. Certain types of fat such as monounsaturated and polyunsaturated fats, especially long chain n-3 polyunsaturated fatty acids, appear to be beneficial for long-term health. [47] Healthy fats are an important part of a balanced diet and do not appear to increase breast cancer risk or mortality.

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Table 1

Age and age-standardized participant characteristics in 1990 (Nurses' Health Study, NHS) and 1991 (Nurses' Health Study II, NHSII), by quintile of total fat intake.

	NHS			NHSII		
	Percent Calories from Total Fat					
	Q1	Q3	Q5	Q1	Q3	Q5
N	8,489	17,421	21,516	26,519	18,502	10,989
Mean (SD)						
Percent energy from fat	25.7(2.6)	33.2(0.8)	41.8(3.4)	24.9(3.0)	33.1(0.8)	41.1(2.7)
Age, years	58.4(7.0)	56.2(7.1)	55.1(7.1)	36.0(4.7)	36.1(4.7)	36.5(4.6)
Physical activity, MET-hours/week	20.8(26.5)	16.0(22.7)	12.2(18.4)	26.8(34.7)	18.6(23.7)	15.4(23.6)
BMI, kg/m^2	24.9(4.5)	25.7(4.7)	26.5(5.4)	23.7(4.6)	24.8(5.3)	26.1(6.5)
BMI at age 18, kg/m^2	21.3(3.0)	21.3(2.9)	21.5(3.2)	21.0(3.2)	21.3(3.4)	21.8(3.8)
Parity[a]	3.0(1.4)	3.1(1.5)	3.2(1.5)	2.1(0.9)	2.2(0.9)	2.1(0.9)
Age at first birth[a], years	24.9(4.4)	24.9(4.1)	24.7(4.2)	26.1(4.3)	25.8(4.1)	25.1(4.1)
Total energy intake, kcal/day	1588(427)	1699(428)	1715(467)	1784(544)	1810(544)	1733(572)
Cholesterol, mg/day	237(73)	272(67)	318(91)	209(64)	253(61)	283(77)
Percent energy from saturated fat	9.3(1.4)	12.2(1.1)	15.8(2.2)	8.7(1.5)	11.8(1.2)	14.8(2.0)
Percent energy from polyunsaturated fat	9.5(1.2)	12.7(0.7)	16.5(2.0)	9.2(1.4)	12.6(0.8)	15.9(1.5)
Percent energy from monounsaturated fat	4.7(1.0)	5.8(1.0)	6.6(1.5)	4.7(1.0)	5.8(1.1)	7.0(1.8)
Percent energy from trans fat	1.2(0.4)	1.7(0.4)	2.2(0.5)	1.2(0.4)	1.7(0.5)	2.3(0.7)
Percent energy from long-chain omega 3 polyunsaturated fatty acids	0.1(0.1)	0.1(0.1)	0.1(0.1)	0.1(0.1)	0.1(0.1)	0.1(0.1)
Alcohol intake, g/day	9.2(14.1)	6.4(9.2)	4.5(7.2)	3.6(7.5)	3.0(5.5)	2.2(4.4)
Percent						
Ever used oral contraceptives	50	50	50	81	83	84
Age at menarche < 12 years	24	22	22	25	24	26
Nulliparous	8	5	6	33	24	25
Ever breastfed[a]	66	65	61	83	80	73
Family history of breast cancer	10	10	9	6	6	6
History of benign breast disease	16	16	14	35	33	33

	NHS			NHSII		
	Percent Calories from Total Fat					
	Q1	Q3	Q5	Q1	Q3	Q5
Mammogram in the past 2 years	81	80	73	43	42	40
Postmenopausal	76	75	74	4	3	3
Ever used postmenopausal hormones[b]	61	61	60	94	93	95

[a] Among parous women only

[b] Among postmenopausal women only

Table 2

Pooled hazard ratios and 95% confidence intervals of quintiles of dietary fat intake in relation to total breast cancer (n=9,979 cases) and lethal breast cancer only (n=1,529 cases) in the Nurses' Health Study and the Nurses' Health Study II.[a]

	Q1	Q2	Q3	Q4	Q5	
	Hazard Ratio (95% Confidence Interval)					p-trend
Total Fat						
Total breast cancer	1.00	1.04 (0.97, 1.10)	0.98 (0.92, 1.04)	0.99 (0.93, 1.06)	1.02 (0.96, 1.10)	0.88
Lethal breast cancer	1.00	0.95 (0.80, 1.14)	1.04 (0.88, 1.23)	0.94 (0.79, 1.12)	0.85 (0.72, 1.01)	0.05
Saturated fat						
Total breast cancer	1.00	0.97 (0.91, 1.04)	1.00 (0.93, 1.08)	0.96 (0.89, 1.04)	0.95 (0.86, 1.05)	0.29
Lethal breast cancer	1.00	0.96 (0.79, 1.16)	1.06 (0.87, 1.29)	1.09 (0.89, 1.34)	0.98 (0.75, 1.26)	0.96
Monounsaturated fat						
Total breast cancer	1.00	1.01 (0.94, 1.08)	1.00 (0.92, 1.08)	1.05 (0.97, 1.15)	1.00 (0.89, 1.12)	0.81
Lethal breast cancer	1.00	0.93 (0.77, 1.12)	1.00 (0.82, 1.23)	1.00 (0.80, 1.25)	0.84 (0.64, 1.12)	0.31
Polyunsaturated fat						
Total breast cancer	1.00	0.99 (0.93, 1.06)	0.98 (0.91, 1.05)	1.00 (0.93, 1.07)	0.94 (0.87, 1.02)	0.16
Lethal breast cancer	1.00	1.10 (0.93, 1.30)	1.20 (1.01, 1.42)	1.18 (0.99, 1.41)	1.11 (0.92, 1.35)	0.28
Trans fat						
Total breast cancer	1.00	1.02 (0.95, 1.09)	0.98 (0.91, 1.05)	1.03 (0.95, 1.11)	0.99 (0.91, 1.09)	0.94
Lethal breast cancer	1.00	0.99 (0.82, 1.19)	0.97 (0.81, 1.17)	0.90 (0.74, 1.10)	0.76 (0.61, 0.96)	0.01
Long-chain n-3 fatty acids						
Total breast cancer	1.00	1.00 (0.93, 1.07)	0.98 (0.92, 1.06)	1.03 (0.96, 1.11)	1.04 (0.96, 1.12)	0.16
Lethal breast cancer	1.00	1.00 (0.85, 1.18)	1.03 (0.87, 1.23)	1.16 (0.97, 1.39)	1.06 (0.86, 1.32)	0.40
Animal fat						
Total breast cancer	1.00	0.94 (0.88, 1.01)	1.00 (0.94, 1.07)	1.01 (0.94, 1.08)	0.98 (0.91, 1.06)	0.88
Lethal breast cancer	1.00	0.92 (0.76, 1.12)	0.92 (0.76, 1.11)	1.06 (0.88, 1.27)	0.89 (0.73, 1.09)	0.43
Vegetable fat						
Total breast cancer	1.00	0.96 (0.90, 1.03)	0.98 (0.91, 1.04)	1.01 (0.94, 1.08)	0.96 (0.89, 1.03)	0.58
Lethal breast cancer	1.00	0.99 (0.84, 1.16)	1.06 (0.90, 1.24)	1.14 (0.97, 1.35)	0.81 (0.67, 0.97)	0.18
Cholesterol						

	Q1	Q2	Q3	Q4	Q5	
	Hazard Ratio (95% Confidence Interval)					p-trend
Total breast cancer	1.00	1.01 (0.94, 1.08)	0.99 (0.93, 1.07)	1.03 (0.96, 1.11)	1.06 (0.98, 1.16)	0.10
Lethal breast cancer	1.00	0.99 (0.82, 1.20)	1.09 (0.90, 1.31)	1.18 (0.98, 1.42)	1.16 (0.94, 1.42)	0.08

[a]Exposure was quintiles of percent calories from fat. Models stratified on cohort, calendar year, and age in months and adjusted for family history of breast cancer (yes, no), height (<1.60, 1.60–1.65, 1.65–1.70, 1.70–1.75, and 1.75+ meters), age at menarche (<12, 12, 13, 14, 15+ years), physical activity (quintiles of MET-h per week, missing), history of benign breast disease (biopsy confirmed, not biopsy confirmed, no), birth index (continuous, missing indicator), lactation (none, <=6 months, >6 months, missing), BMI at 18 (<22, 22–<25, 25–<30, 30+, missing), weight change since age 18 (continuous, missing indicator), alcohol intake (0, 0–<5, 5–<15, 15+ grams/day), oral contraceptive recency and duration (never, past < 2 years, past 2+ years, current, missing), total energy intake, percent calories from other types of fat (monounsaturated, polyunsaturated, saturated, and trans included in the same model, animal and vegetable included in the same model) and protein, age at menopause (continuous, missing indicator), and menopausal status and postmenopausal hormone use (premenopausal, postmenopausal never, postmenopausal past, postmenopausal current estrogen user, postmenopausal current estrogen plus progesterone user, postmenopausal unknown hormone use, missing menopausal status).

Table 3

Pooled hazard ratios and 95% confidence intervals of quintiles of pre-diagnosis dietary fat intake among women diagnosed with breast cancer (n=8,580) in relation to breast cancer death (n=1,282) in the Nurses' Health Study and the Nurses' Health Study II.[a]

	Q1	Q2	Q3	Q4	Q5	
	Hazard Ratio (95% Confidence Interval)					p-trend
Total Fat						
Model 1	1.00	1.12 (0.91, 1.38)	1.13 (0.92, 1.38)	1.10 (0.89, 1.34)	0.97 (0.78, 1.19)	0.62
Model 2	1.00	1.05 (0.84, 1.32)	1.16 (0.92, 1.44)	1.08 (0.86, 1.35)	0.97 (0.76, 1.24)	0.85
Saturated fat						
Model 1	1.00	1.03 (0.83, 1.28)	1.01 (0.80, 1.28)	1.11 (0.86, 1.43)	0.91 (0.66, 1.26)	0.64
Model 2	1.00	1.06 (0.83, 1.34)	1.04 (0.81, 1.34)	1.20 (0.91, 1.59)	0.97 (0.68, 1.39)	0.98
Monounsaturated fat						
Model 1	1.00	1.04 (0.83, 1.30)	1.13 (0.89, 1.44)	1.04 (0.79, 1.37)	1.02 (0.72, 1.45)	0.98
Model 2	1.00	1.07 (0.84, 1.37)	1.25 (0.96, 1.63)	1.12 (0.83, 1.51)	1.19 (0.81, 1.75)	0.43
Polyunsaturated fat						
Model 1	1.00	1.07 (0.88, 1.30)	1.02 (0.83, 1.25)	1.01 (0.81, 1.25)	0.98 (0.77, 1.23)	0.70
Model 2	1.00	1.17 (0.94, 1.45)	0.96 (0.77, 1.21)	1.11 (0.87, 1.41)	1.08 (0.83, 1.40)	0.73
Trans fat						
Model 1	1.00	1.00 (0.81, 1.23)	0.92 (0.73, 1.14)	0.88 (0.70, 1.11)	0.82 (0.63, 1.08)	0.09
Model 2	1.00	0.99 (0.79, 1.25)	0.90 (0.71, 1.15)	0.86 (0.66, 1.11)	0.76 (0.55, 1.04)	0.05
Long chain n-3 fatty acids						
Model 1	1.00	0.99 (0.81, 1.21)	1.07 (0.86, 1.33)	1.20 (0.96, 1.51)	1.08 (0.83, 1.40)	0.41
Model 2	1.00	1.00 (0.80, 1.24)	1.16 (0.91, 1.48)	1.27 (0.98, 1.63)	1.16 (0.87, 1.55)	0.25
Animal fat						
Model 1	1.00	0.95 (0.76, 1.17)	1.03 (0.83, 1.27)	1.06 (0.86, 1.31)	0.92 (0.73, 1.16)	0.63
Model 2	1.00	1.02 (0.81, 1.29)	1.09 (0.87, 1.37)	1.05 (0.83, 1.33)	1.02 (0.77, 1.35)	0.90
Vegetable fat						
Model 1	1.00	0.89 (0.73, 1.09)	1.02 (0.84, 1.25)	1.01 (0.82, 1.24)	0.82 (0.65, 1.03)	0.23
Model 2	1.00	0.97 (0.78, 1.21)	1.06 (0.84, 1.33)	1.04 (0.82, 1.31)	0.85 (0.66, 1.10)	0.34
Cholesterol						

	Q1	Q2	Q3	Q4	Q5	
	Hazard Ratio (95% Confidence Interval)					p-trend
Model 1	1.00	1.22 (0.99, 1.51)	1.26 (1.02, 1.57)	1.20 (0.96, 1.51)	1.24 (0.97, 1.59)	0.23
Model 2	1.00	1.24 (0.98, 1.57)	1.36 (1.07, 1.73)	1.25 (0.97, 1.60)	1.24 (0.94, 1.64)	0.32

[a]Women with stage IV breast cancer were excluded from this analysis. Exposure was quintiles of percent calories from fat.

Model 1: Stratified on calendar year and age in months and adjusted for the same variables in Table 2.

Model 2: Additionally adjusted for change in intake of that type of fat after diagnosis, tumor stage (I, II, III, missing), ER/PR status (ER+/PR+, ER+/PR−, ER−/PR−, other/missing), chemotherapy (yes, no, missing), hormone therapy (yes, no, missing), radiation therapy (yes, no, missing), and month of diagnosis.