Dietary fat and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition[1–3]

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ABSTRACT

Background: Epidemiologic studies have produced conflicting results with respect to an association of dietary fat with breast cancer.

Objective: We aimed to investigate the association between fat consumption and breast cancer.

Design: We prospectively investigated fat consumption in a large (n = 319 826), geographically and culturally heterogeneous cohort of European women enrolled in the European Prospective Investigation into Cancer and Nutrition who completed a dietary questionnaire. After a mean of 8.8 y of follow-up, 7119 women developed breast cancer. Cox proportional hazard models, stratified by age and center and adjusted for energy intake and confounders, were used to estimate hazard ratios (HRs) for breast cancer.

Results: An association between high saturated fat intake and greater breast cancer risk was found [HR = 1.13 (95% CI: 1.00, 1.27; P for trend = 0.038) for the highest quintile of saturated fat intake compared with the lowest quintile: 1.02 (1.00, 1.04) for a 20% increase in saturated fat consumption (continuous variable)]. No significant association of breast cancer with total, monounsaturated, or polyunsaturated fat was found, although trends were for a direct association of risk with monounsaturated fat and an inverse association with polyunsaturated fat. In menopausal women, the positive association with saturated fat was confined to nonusers of hormone therapy at baseline [1.21 (0.99, 1.48) for the highest quintile compared with the lowest quintile; P for trend = 0.044; and 1.03 (1.00, 1.07) for a 20% increase in saturated fat as a continuous variable].

Conclusions: Evidence indicates a weak positive association between saturated fat intake and breast cancer risk. This association was more pronounced for postmenopausal women who never used hormone therapy. *Am J Clin Nutr* 2008;88:1304–12.

INTRODUCTION

Breast cancer is the most common cancer affecting women worldwide. For women living in low-risk countries, the risk of developing breast cancer increases upon immigration to a high-risk country (1), which suggests that this cancer is influenced by modifiable lifestyle or environmental factors.

Epidemiologic studies have produced conflicting results regarding an association of dietary fat with breast cancer. Although strong associations between high fat intake and greater breast cancer incidence have been found in international correlation studies (2) and animal studies (3–6), most case-control studies indicate only a weak association (7), and prospective cohort studies have usually shown little (8) or no (9–12) association. A recent prospective study on postmenopausal US women found that dietary fat intake was weakly but significantly associated with the risk of invasive breast cancer, whereas intakes of saturated, monounsaturated, and polyunsaturated fat each were significantly related to breast cancer risk (13). A pooled analysis of data from cohort studies found a weak increase in breast cancer risk when carbohydrates were "substituted" by saturated fats in an isocaloric diet (14), and a meta-analysis of 45 epidemiologic studies (14 cohort studies and 31 case-control studies) found a weak but statistically significant relation between high fat intake and greater breast cancer risk (15). It is interesting that fat intake was significantly associated with breast cancer risk in European but not

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in Canadian or US studies, possibly in relation to greater variation in dietary fat intake among European than North American women (15). The recently published results of the randomized Women's Health Initiative found that low-fat diets were associated with a 9% reduction in the risk of invasive breast cancer (16).

Conflicting results with respect to monounsaturated fat have also been reported. Some cohort studies reported a protective effect of monounsaturated fat intake on breast cancer risk (12, 17–19), whereas others reported no effect or even a positive association with breast cancer (9, 11, 13–15, 20). The conflicting results of analytic epidemiologic studies are likely to be due to the known difficulties in obtaining precise estimates of intakes of various types of fat (21) and also to the limited heterogeneity of fat intake within geographically confined populations. The aim of the present study was to investigate prospectively, in a large, geographically and culturally heterogeneous cohort of European women, the association between dietary fat and breast cancer risk.

SUBJECTS AND METHODS

Subjects

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a prospective study being conducted in 23 centers in 10 European countries: Norway, Sweden, Denmark, the United Kingdom, Germany, the Netherlands, France, Spain, Italy, and Greece. The design and methods of EPIC were described in detail elsewhere (22, 23). Briefly, the study recruited 519 978 volunteers (men and women), who completed dietary and lifestyle questionnaires and whose anthropometric measurements were recorded. Most participants were recruited from the general population of a town or province, with the following exceptions: the French cohort was recruited from female members of the teachers' health insurance organization; the Utrecht (Netherlands) and Florence (Italy) cohorts were recruited from women presenting for breast cancer screening; the Ragusa and Turin (Italy) cohort and part of the Spanish cohort were recruited from blood donors and their spouses. The Cambridge cohort and one-half of the Oxford cohort (United Kingdom) were recruited by general practitioners, and they formed the general population group. The rest of the Oxford cohort was recruited by mail in collaboration with vegetarian societies and was considered separately as a "health-conscious" group.

The study was conducted in 328 238 women aged 20–70 y after exclusion of those with cancer at recruitment and those who did not complete the dietary or lifestyle questionnaires (n = 3320). To reduce the effect of implausible extreme values on the analysis, we also excluded women in whom the ratio of total energy intake to basal metabolic rate (24) was at either extreme of the distribution (cutoffs were the first and last percentiles; n = 6764). We also excluded 8412 women with missing values for the potentially confounding variables of smoking and education. Thus, the analyses were conducted in 319 826 women, and the mean duration of follow-up was 8.8 y (2 812 609.6 person-years).

All participants provided written informed consent. The present study was approved by the ethics review boards of the International Agency for Research on Cancer (Lyon, France) and of all local recruiting institutions.

Ascertainment of cancer cases

Cases were ascertained by population-based cancer registries in 7 of the participating countries (Denmark, Italy, the Netherlands, Spain, Sweden, the United Kingdom, and Norway). In France, Germany, Greece, and the Italian center of Naples, various methods were used to identify cases, including consulting health insurance records and regional or national pathology registries, and active follow-up was conducted by contacting participants or next-of-kin. By February 2007, all centers had provided follow-up data for cancer cases up to December 1998, and more recent follow-up data (up to December 2005) was provided in many cases. The International Classification of Diseases for Oncology (ICD 10-O-2) was used to code cases. At the latest central audit (end of February 2007), 7298 invasive breast cancer cases had been identified (ICD code C50). After we applied the exclusions described above, a total of 7119 cases of invasive breast cancer were investigated.

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Dietary measurements

Diet was assessed by using country-specific (or in some cases center-specific) dietary questionnaires designed to capture local dietary habits. Eight countries used self-administered dietary questionnaires, whereas, in Greece, Spain, and southern Italy (Naples and Ragusa), the questionnaires were administered by interviewers. In most countries, the questionnaires were extensive quantitative instruments (containing up to 260 food items). In Denmark, Norway, Sweden (Umeå), and Italy (Naples), semiquantitative food-frequency questionnaires (FFQs) were administered. In Sweden (Malmö), an interview-based diet history method combining a questionnaire with a 7-d menu book was used. In the United Kingdom, an FFQ and a 7-d dietary record were used, but all results are from the FFQ (22, 23). All dietary questionnaires had been validated (25–32). For most centers, validation employed 12 monthly 24-h recall interviews. Pearson correlation coefficients between the mean consumption of total fat, reported in the dietary questionnaire, and the mean from the 24-h recalls varied, for women, from ≈0.4 to 0.7. For saturated, monounsaturated, and polyunsaturated fat, correlation coefficients were in the range of 0.5–0.7, 0.4–0.8, and 0.4–0.7, respectively (25–31). A separate standardized 24-h dietary recall (24-hDR) interview was carried out in a random sample (8%) of the entire EPIC cohort (33) to correct measurement errors in the dietary questionnaire; the random sample was stratified by sex and 5-y age strata in proportion to the expected numbers of total cancer cases in those categories. The EPIC Nutrient Database (34) was used to convert the quantities of food consumed into daily energy and total, saturated, monounsaturated, and polyunsaturated fat intakes.

Statistical analysis

We used multivariate Cox proportional hazard models to assess the association of fat and fat subtype intake with breast cancer risk, with stratification by center, to control for center effects and age (1-y categories). In all models, age was the primary time variable. Statistical adjustments were performed for menopausal status [premenopausal, perimenopausal, postmenopausal, or uncertain, as defined by Lahmann et al (35)], alcohol intake (none or <12, 12–24, or >24 g/d), height, weight, smoking status (never, former, or current), and educational attainment (years of schooling). Information on family history of breast cancer was not available in all centers and was not included in the analyses. Age at first delivery, age at menarche, the number of full-term pregnancies, and oral contraceptive use (not available for 35 852 women including 882 cases) were included as potential confounders in preliminary models but had no influence on the results, and these data were excluded from final models.

Because macronutrient intake correlates strongly with energy intake, we used various models to adjust for the confounding effect of energy intake. We first applied a standard model that included absolute fat intake (in g) and total nonalcoholic energy intake (36). We next applied a residual model in which we regressed each type of fat intake on total nonalcohol energy by using country-specific regression models; the residual of the nutrient intake together with nonalcohol energy intake was then included in the model (36). Third, we applied a density model, in which energy from fat as a proportion of total nonalcohol energy intake, together with nonalcohol energy, was included. The fourth model was an energy partition model (36), in which nonalcohol energy from the specific nutrient was modeled as one variable, and nonalcohol energy from other sources (eg, protein, carbohydrates, or other fat subtypes as appropriate) was the second energy variable. The first 3 models estimated the hazard ratio (HR) of breast cancer associated with isocaloric replacement of other macronutrients with the nutrient of interest (fat). The fourth model estimated the HR associated with the addition of energy from fat to the diet, while keeping the quantities of other macronutrients constant. We also used a fifth model, a multivariate nutrient density model, to evaluate the effect of replacing nonalcohol energy from carbohydrate (20% decrease) with energy from fat (20% increase) in an isocaloric diet with mutual adjustment for protein intake, nonalcohol energy, and other fat subtypes as appropriate.

Fat intakes were analyzed as both categorical and continuous variables. For the former, quintiles of fat intake were determined from the distribution in the whole cohort. Tests of linear trend were performed by modeling the median of each quintile. When intakes of total fat, fat subtype, and energy components were modeled as continuous variables, they were transformed to logarithms to the base 1.2, so that HRs represent the risk associated with a 20% increase in intake.

We also examined whether the association between fat and breast cancer risk was modified by body mass index (BMI; in kg/m^2) (≥25 or <25), baseline menopausal status (postmenopausal or premenopausal), and menopausal hormone replacement therapy (HRT) use (sometime HRT use or no use). This evaluation was achieved by modeling product terms of dichotomized variables multiplied by the median of the fat intake quintile to which the subject belonged or multiplied by the subject's fat intake when fat was considered a continuous variable. The significance of interactions was assessed by comparing the likelihood ratio test statistics of the models with and without the product term to a chi-square distribution with 1 df.

To correct for error in food intake measurement, we used a center-specific multivariate calibration approach (37), in which reference values of each fat type (according to the type of energy adjustment model used) and nonalcohol energy, obtained from the 24-hDR, were regressed on the dietary questionnaire measurements, and the resulting coefficients were used to estimate intake values. Adjustments for weight, height, age at recruitment, alcohol consumption categories, smoking status, educational attainment, and study center were included. In addition, the models were adjusted for unequal seasonal and weekday distribution (weekday or weekend) of the 24-hDR interviews, and the ratio of the expected to the observed number of interviews at each center was applied as weighting.

The Q test statistic with 9 df was used to assess statistical heterogeneity and investigate the hypothesis that associations between dietary components and breast cancer risk were the same in all countries (38). We tested the proportional hazard assumption for each fat and fat subtype in relation to breast cancer risk by using the method of Grambsch and Therneau (39). In all cases, the proportional hazards assumption was satisfied for total fat and fat subtypes ($P > 0.22$).

All analyses were performed with STATA software (version 7.0; Stata Corp, College Station, TX). All tests were 2-tailed, and 95% CIs were calculated and used to determine statistical

TABLE 1
Daily energy intake from fat and fat subtypes in women participating in the European Prospective Investigation into Cancer and Nutrition

Country	Cases	Person-years of follow-up	Total fat	Saturated fat	Monounsaturated fat	Polyunsaturated fat
	n	*n*	%	%	%	%
Denmark	822	214 842	33.3 ± 5.22[1]	13.1 ± 2.76	11.1 ± 2.04	5.5 ± 1.48
France	2272	691 567	36.7 ± 5.82	14.4 ± 3.13	12.9 ± 2.54	6.6 ± 2.23
Greece	103	93 832	46.9 ± 4.73	13.1 ± 2.57	22.7 ± 4.11	7.0 ± 2.98
Germany	457	226 510	35.5 ± 5.54	14.8 ± 2.91	12.2 ± 2.12	6.2 ± 1.75
Italy	670	255 538	35.3 ± 5.58	12.4 ± 2.54	16.6 ± 3.40)	4.3 ± 1.22
Netherlands	567	227 662	35.9 ± 5.45	15.3 ± 2.81	12.0 ± 2.29	7.0 ± 1.80
Norway	441	198 456	34.9 ± 4.83	13.7 ± 2.46	11.1 ± 1.85	6.5 ± 1.56
Spain	319	240 836	37.6 ± 6.06	11.6 ± 3.08	15.7 ± 3.60	6.0 ± 2.33
Sweden	648	257 185	35.8 ± 6.07	15.5 ± 3.54	12.6 ± 2.24	5.4 ± 1.56
United Kingdom						
General population	423	130 141	33.5 ± 6.07	12.6 ± 3.24	11.1 ± 2.17	7.1 ± 2.19
Health-conscious group	397	276 038	32.3 ± 6.54	11.6 ± 3.39	10.4 ± 2.34	7.6 ± 2.44
Total	7119	2 812 609	35.7 ± 6.31	13.7 ± 3.25	13.0 ± 3.76	6.3 ± 2.17

[1] $\bar{x}$ ± SD (all such values).

significance; interactions and heterogeneity were considered significant at $P < 0.05$.

RESULTS

The mean daily proportion of nonalcohol energy intake from total fat and fat subtypes obtained from the dietary questionnaires, by country, is shown in **Table 1**. Mean energy from total fat ranged from 32.2% in the UK health-conscious group to 46.9% in Greece; mean energy from saturated fats ranged from 11.6% in Spain and the UK health-conscious group to 15.5% in Sweden and the Netherlands. Mean energy from monounsaturated fats was highest in Greece (22.7%) and lowest, less than half that (10.4%), in the UK health-conscious group. Mean energy from polyunsaturated fat ranged from 4.3% in Italy to >7.6% in the United Kingdom.

Adjusted HRs for breast cancer by intake of total fat, obtained by using the 4 energy-adjustment models, are shown in **Table 2**. Irrespective of whether total fat intake was analyzed as a categorical or continuous variable, HRs indicated no statistically significant association of total fat intake with breast cancer risk. No significant between-country heterogeneity was found in any of these models.

Adjusted HRs of developing breast cancer by quintile of saturated, monounsaturated, or polyunsaturated fat for each of the 4 energy-adjustment models are shown in **Table 3**. Women in the highest quintile of saturated fat intake had a significantly greater risk of developing breast cancer than did those in the lowest quintile, according to the standard (HR: 1.13; 95% CI: 1.00, 1.27), density (HR: 1.10; 95% CI: 1.01, 1.19), and partition (1.11; 95% CI: 1.00, 1.23) models. The test for trend was statistically significant for the standard ($P = 0.038$) and partition ($P = 0.045$) models. No significant between-country heterogeneity (Q test) was found in any of these models ($P = 0.904$, 0.761, 0.902, and 0.927 for standard, residual, density, and partition models, respectively).

When fat intake was considered as a continuous variable, an increase in saturated fat intake was associated with greater risk in all models (HR: 1.02; 95% CI: 1.00, 1.04 for the standard and density models; HR: 1.02; 95% CI: 1.00, 1.03 for the residual and partition models). After calibration, HRs for saturated fat intake remained statistically significant in most models and were slightly greater than those from the continuous model with the use of noncalibrated data.

No association of the other types of fat intake with breast cancer risk was observed, although HR estimates for monounsaturated fat were in the same direction as those for saturated fats, whereas HR estimates for polyunsaturated fat tended to go in the opposite direction (ie, were <1). After calibration, HRs for monounsaturated fat intake became statistically significant in most models.

When all types of fat were included simultaneously in the model together with protein intake (multivariate density model) to estimate the effect of isocalorically substituting the intake of a given fat subtype for carbohydrate, HRs indicated no statistically significant association between fat intake of any kind and breast cancer risk; however, the trends for saturated and monounsaturated fat remained (data not shown). We conducted a further subanalysis to exclude early cases (<2-y follow-up) because of the possible influence of subclinical disease on dietary fat intake, but the results did not change.

The association between fat consumption and breast cancer was not modified by BMI or menopausal status (data not shown). However, among menopausal women, the results obtained with the standard model differed according to reported HRT use (**Table 4**). Specifically, tests for an HRT × fat interaction were statistically significant for intakes of total fat ($P = 0.039$), monounsaturated fat ($P = 0.011$), and saturated fat ($P = 0.018$) but not for polyunsaturated fat ($P = 0.763$). Among women who never used HRT, greater breast cancer risk was associated with greater consumption of saturated fat (HR: 1.03; 95% CI: 1.00, 1.07 for 20% higher use). Among HT users, there was no association between saturated fat intake and breast cancer risk (HR: 0.99; 95% CI: 0.96, 1.03). Similar results were obtained for total and monounsaturated fat, but none were statistically significant. The other energy-adjustment methods gave similar results for all types of fat (data not shown). No significant between-country heterogeneity was found for the interaction between HRT and fat subtypes.

TABLE 2
Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) for invasive breast cancer risk in association with total fat intake by quintile (Q) in the European Prospective Investigation into Cancer and Nutrition[1]

Energy adjustment model	Intake					*P* for trend[2]	Intake as a continuous variable[3]	Calibrated data (Intake as continuous variable)[4]
	Q1	Q2	Q3	Q4	Q5			
Standard[5]								
Median (g/d)	46.0	61.3	74.0	88.6	113.4			
Cases/person-years (*n*)	1274/534 091	1375/547 764	1444/561 608	1522/576 957	1504/592 190			
HR	1	1.01 (0.93, 1.10)[6]	1.03 (0.93, 1.13)	1.05 (0.94, 1.17)	1.02 (0.90, 1.17)	0.601	1.02 (0.99 1.04)	1.04 (0.98, 1.10)
Residual[7]								
Median (g/d)	61.5	71.2	77.2	83.4	94.0			
Cases/person-years (*n*)	1352/559 634	1473/551 288	1432/553 818	1429/568 379	1433/579 490			
HR	1	1.10 (1.01, 1.19)	1.07 (0.99, 1.17)	1.06 (0.98, 1.16)	1.06 (0.97, 1.16)	0.378	1.02 (0.99, 1.04)	1.03 (0.98, 1.09)
Density[8]								
Median (% of energy/d)	28.9	33.5	36.7	39.8	44.9			
Cases/person-years (*n*)	1347/548 716	1391/553 292	1516/559 319	1439/573 902	1426/577 379			
HR	1	1.00 (0.93, 1.08)	1.07 (0.99, 1.15)	0.99 (0.92, 1.07)	1.04 (0.96, 1.13)	0.432	1.02 (0.99, 1.04)	1.04 (0.98, 1.09)
Partition[9]								
Median (g/d)	46.0	61.3	74.0	88.6	113.4			
Cases/person-years (*n*)	1274/534 090	1375/547 764	1444/561 616	1522/576 960	1504/592 178			
HR	1	1.01 (0.93, 1.09)	1.02 (0.94, 1.11)	1.04 (0.96, 1.14)	1.02 (0.92, 1.12)	0.575	1.01 (0.99, 1.03)	1.03 (0.99, 1.07)

[1] Values were stratified by age and center and adjusted for educational attainment, smoking status, height, weight, alcohol intake, and menopausal status. $n = 7119$ breast cancer cases.
[2] Test for linear trend was performed on median intake for each quintile.
[3] Values were $\log_{1.2}$ transformed (equivalent to an increase of 20%).
[4] Calibrated data were obtained by linear regression models that compared observed nutrient questionnaire measurements with 24-h dietary recall.
[5] Standard models contain log-transformed total fat intake and log-transformed nonalcohol energy intake.
[6] 95% CIs in parentheses (all such values).
[7] Residual models contain the residual of the regression of log-transformed total fat intake on log-transformed nonalcohol energy intake and log-transformed nonalcohol energy intake.
[8] Density models contain log-transformed nonalcohol energy intake from total fat and log-transformed nonalcohol energy intake.
[9] Partition models contain log-transformed total fat and log-transformed nonalcohol energy intake.

DISCUSSION

In this prospective study in 319 826 women, 7119 of whom developed invasive breast cancer, we found a weak but significant association of breast cancer risk with dietary saturated fat intake but no association with total fat intake. Monounsaturated fat was positively associated with breast cancer incidence; HRs were similar to those for saturated fat and were statistically significant only after calibration. Previous observational studies, reviewed in the Introduction, provided conflicting evidence of such an association. The randomized Women's Health Initiative Dietary Modification Trial (16) suggested that reducing fat intake may lower breast cancer risk: the incidence was 9% lower (not significant) in the low-fat dietary pattern group than in control subjects after 8.1 y of follow-up. Furthermore, the most recent meta-analysis of case-control and cohort studies found a statistically significant relation between high saturated fat intake and greater breast cancer risk (15). The present analysis considered 12 cohort studies and 3783 cancer cases. The EPIC study included nearly twice as many breast cancer cases and achieved similar results. The recently published National Institutes of Health–AARP study of a large cohort of postmenopausal US women found a direct association between breast cancer risk and saturated fat consumption (13). That study also found that intakes of total, monosaturated, and polyunsaturated fat were significantly related to breast cancer risk, although only saturated fat remained significantly associated when all fat subtypes were mutually adjusted. The lack of a significant association between total fat and breast cancer risk in the present study could be due to the fact that saturated (and to some extent monounsaturated) fat directly increases breast cancer risk, whereas polyunsaturated fat is inversely related to that risk. When fat subtypes were mutually adjusted, saturated and monounsaturated fat consumption remained directly but not significantly associated with risk. In this mutual adjustment (ie, multivariate density model), analysis of fat type is complicated because the main dietary sources of monounsaturated fat and saturated fat are often the same, so it is difficult to separate the effect of one from another. Nevertheless, the results of this model support direct effects of both saturated and monounsaturated fats on risk. A direct effect of monounsaturated intake on breast cancer risk is supported by some studies (13, 20, 40), although others found no association (9, 11, 12) or an inverse association (17–19).

TABLE 3

Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) of invasive breast cancer risk associated with subtypes of fat intake by quintile (Q) in the cohort of the European Prospective Investigation into Cancer and Nutrition[1]

Fat subtype	Intake					*P* for trend[2]	Intake as continuous variable[3]	Calibrated data (intake as continuous variable)[4]
	Q1	Q2	Q3	Q4	Q5			
Saturated fat								
Standard[5]								
Median (g/d)	16.2	22.6	27.9	34.1	45.0			
Cases/person-years (*n*)	1160/538 852	1341/545 846	1451/557 165	1536/571 949	1631/598 798			
HR	1	1.08 (0.99, 1.17)[6]	1.12 (1.02, 1.22)	1.14 (1.03, 1.26)	1.13 (1.00, 1.27)	0.038	1.02 (1.00, 1.04)	1.03 (1.00, 1.07)
Residual[7]								
Median (g/d)	21.1	26.1	29.3	32.6	38.1			
Cases/person-years (*n*)	1274/565 391	1342/547 796	1370/547 072	1454/560 043	1679/592 308			
HR	1	1.06 (0.98, 1.15)	1.06 (0.97, 1.15)	1.05 (0.97, 1.15)	1.06 (0.98, 1.16)	0.233	1.02 (1.00, 1.03)	1.03 (0.99, 1.07)
Density[8]								
Median (% of energy/d)	9.9	12.3	13.9	15.5	18.2			
Cases/person-years (*n*)	1185/555 735	1374/547 967	1412/552 679	1474/565 272	1674/590 956			
HR	1	1.07 (0.99, 1.16)	1.06 (0.98, 1.15)	1.05 (0.96, 1.13)	1.10 (1.01, 1.19)	0.068	1.02 (1.00, 1.04)	1.04 (1.00, 1.07)
Partition[9]								
Median (kcal/d)	145.8	203.3	250.9	306.5	404.6			
Cases/person-years (*n*)	1160/538 852	1341/545 852	1451/557 159	1536/571 961	1631/598 786			
HR	1	1.07 (0.98, 1.16)	1.11 (1.02, 1.21)	1.12 (1.02, 1.23)	1.11 (1.00, 1.23)	0.045	1.02 (1.00, 1.03)	1.03 (1.00, 1.06)
Monounsaturated fat								
Standard[5]								
Median (g/d)	15.3	21.0	26.0	32.3	44.1			
Cases/person-years (*n*)	1273/525 283	1352/546 266	1515/568 799	1584/58 914	1395/583 116			
HR	1	0.98 (0.91, 1.07)	1.05 (0.95, 1.15)	1.07 (0.96, 1.18)	1.05 (0.92, 1.20)	0.254	1.02 (0.99, 1.04)	1.05 (1.00, 1.10)
Residual[7]								
Median (g/d)	20.2	24.2	27.0	30.3	38.1			
Cases/person-years (*n*)	1310/536 795	1469/551 560	1499/569 583	1552/586 099	1289/568 573			
HR	1	1.09 (1.00, 1.18)	1.03 (0.95, 1.12)	1.10 (1.00, 1.20)	1.08 (0.98, 1.21)	0.150	1.02 (0.99, 1.04)	1.04 (0.99, 1.10)
Density[8]								
Median (% of energy/d)	9.5	11.3	12.7	14.5	18.2			
Cases/person-years (*n*)	1291/532 384	1472/548 551	1483/570 103	1579/590 546	1294/571 026			
HR	1	1.07 (0.99, 1.15)	1.02 (0.95, 1.11)	1.06 (0.98, 1.15)	1.05 (0.96, 1.16)	0.323	1.02 (0.99, 1.04)	1.05 (1.00, 1.10)
Partition[9]								
Median (kcal/d)	137.9	189.0	234.4	291.0	397.2			
Cases/person-years (*n*)	1273/525 283	1352/546 266	1515/568 799	1584/589 146	1395/583 116			
HR	1	0.98 (0.90, 1.06)	1.04 (0.95, 1.14)	1.06 (0.96, 1.17)	1.04 (0.93, 1.18)	0.253	1.01 (0.99, 1.03)	1.04 (1.00, 1.09)
Polyunsaturated fat								
Standard[5]								
Median (g/d)	7.2	9.8	12.3	15.4	21.3			
Cases/person-years (*n*)	1403/550 518	1409/547 583	1376/555 864	1445/570 597	1486/588 046			
HR	1	1.00 (0.93, 1.08)	0.95 (0.88, 1.04)	0.95 (0.87, 1.04)	0.97 (0.88, 1.07)	0.372	0.99 (0.98, 1.01)	0.99 (0.95, 1.03)
Residual[7]								
Median (g/d)	8.4	10.9	12.7	15.0	19.5			
Cases/person-years (*n*)	1523/572 752	1390/556 567	1377/552 245	1470/559 334	1359/571 712			
HR	1	0.97 (0.90, 1.06)	1.02 (0.94, 1.10)	1.00 (0.92, 1.08)	0.99 (0.91, 1.08)	0.967	0.99 (0.98, 1.01)	0.99 (0.96, 1.03)
Density[8]								
Median (% of energy/d)	4.0	5.1	6.1	7.2	9.4			
Cases/person-years (*n*)	1533/573 440	1389/557 490	1374/552 199	1472/558 845	1351/570 636			
HR	1	0.99 (0.91, 1.07)	0.95 (0.88, 1.03)	0.99 (0.92, 1.07)	0.96 (0.88, 1.04)	0.390	0.99 (0.98, 1.01)	0.99 (0.95, 1.02)
Partition[9]								
Median (kcal/d)	64.4	88.6	110.7	138.6	191.5			
Cases/person-years (*n*)	1403/550 518	1409/547 583	1376/555 864	1445/570 598	1486/588 046			
HR	1	1.00 (0.93, 1.08)	0.95 (0.88, 1.04)	0.95 (0.87, 1.04)	0.97 (0.88, 1.07)	0.370	0.99 (0.98, 1.01)	0.99 (0.95, 1.02)

[1] Values were stratified by age and center and were adjusted for educational attainment, smoking status, height, weight, alcohol intake, and menopausal status. $n = 7119$ breast cancer cases.
[2] Test for linear trend was performed on median intake for each quintile.
[3] Values were $\log_{1.2}$ transformed (equivalent to a 20% increase).
[4] Calibrated data were obtained by linear regression models that compare observed nutrient questionnaire measurements with 24-h dietary recall.
[5] Standard models contain log-transformed fat subtype intake and nonalcohol energy intake.
[6] 95% CIs in parentheses (all such values).
[7] Residual models contain residual of regression of log-transformed fat subtype intake and nonalcohol energy intake.
[8] Density models contain log-transformed energy from fat subtypes and nonalcohol energy.
[9] Partition models contain log-transformed fat subtype intake and energy intake from other sources excluding alcohol.

TABLE 4
Multivariate-adjusted hazard ratios (HRs) (and 95% CIs) for invasive breast cancer risk in association with subtypes of fat intake by quintile (Q) in postmenopausal women stratified by hormone replacement therapy (HRT)[1]

Subtypes of fat and quintile of intake	HRT (n = 1909)	No HRT (n = 1553)	P for interaction
Total fat			
Q1	1	1	
Q2	0.91 (0.78, 1.06)[2]	1.12 (0.95, 1.32)	
Q3	1.011.01 (0.86, 1.19)	0.98 (0.82, 1.17)	
Q4	0.87 (0.73, 1.05)	1.02 (0.84, 1.23)	
Q5	0.85 (0.69, 1.05)	1.09 (0.88, 1.36)	
P for trend[3]	0.127	0.74	0.053
Intake as continuous variable	0.98 (0.94, 1.02)	1.02 (0.98, 1.06)	0.039
Saturated fat			
Q1	1	1	
Q2	1.14 (0.98, 1.34)	0.98 (0.83, 1.16)	
Q3	1.11 (0.95, 1.31)	1.10 (0.92, 1.30)	
Q4	1.02 (0.86, 1.22)	1.08 (0.90, 1.30)	
Q5	1.01 (0.83, 1.23)	1.21 (0.99, 1.48)	
P for trend[3]	0.698	0.044	0.020
Intake as a continuous variable	0.99 (0.96, 1.03)	1.03 (1.00, 1.07)	0.018
Monounsaturated fat			
Q1		1	
Q2	0.92 (0.79, 1.07)	1.09 (0.92, 1.29)	
Q3	0.98 (0.84, 1.15)	1.09 (0.92, 1.31)	
Q4	0.94 (0.79, 1.12)	1.06 (0.88, 1.29)	
Q5	0.90 (0.73, 1.11)	1.17 (0.94, 1.46)	
P for trend[3]	0.426	0.239	0.05
Intake as a continuous variable	0.98 (0.95, 1.02)	1.03 (0.99, 1.06)	0.011
Polyunsaturated fat			
Q1	1	1	
Q2	1.01 (0.87, 1.19)	1.13 (0.96, 1.32)	
Q3	0.91 (0.78, 1.07)	1.02 (0.86, 1.21)	
Q4	0.90 (0.76, 1.06)	0.99 (0.83, 1.18)	
Q5	0.97 (0.82, 1.16)	0.95 (0.79, 1.15)	
P for trend[3]	0.460	0.298	0.763
Intake as a continuous variable	0.99 (0.97, 1.02)	0.99 (0.96, 1.01)	0.808

[1] The standard model was used. Values were stratified by age and center and were adjusted for educational attainment, smoking status, height, weight, alcohol intake, and menopausal status. Likelihood ratio test on the median intake level in each quintile with 1 df and likelihood ratio test on the continuous scale with 1 df.

[2] HR; 95% CI in parentheses (all such values).

[3] Test for linear trend was performed by using the median intake in each quintile.

Various biological data support a relation between high fat intake and greater breast cancer risk. Why, then, have many studies found no association of fat with breast cancer? One possible explanation is that the populations investigated were characterized by uniform dietary fat intake. In the EPIC study, which was designed to obtain data from populations that varied considerably in quantity of fat consumed, the interquintile range for the entire cohort was 54.5–98.3 g/d. Intakes of saturated and monounsaturated fats (expressed as % of energy) also varied markedly across cohorts: in Greece, Italy, and Spain, more calories were obtained from monounsaturated than saturated fat, whereas, in all other countries, more calories were obtained from saturated than monounsaturated fat.

A second possible explanation is that there is no generally agreed-upon method of adjustment for the influence of total energy intake (which is closely related to total macronutrient intake). Various energy-adjustment methods have been used, including the multivariate nutrient density (8, 9, 13, 41), residual (13, 42–45), energy partition (13, 45–47), and nutrient density (8, 13, 41) methods. We used 4 adjustment methods (ie, standard, residual, density, and energy partition), which are similar to those used in the National Institutes of Health–AARP study (13). In that study, fat intake was found to be associated with breast cancer risk irrespective of the type of energy adjustment used. In the present study, when exposures were considered as continuous variables, all models gave similar results. These considerations suggest that the type of energy adjustment does not influence the detection or nondetection of an effect.

A third possible explanation is that errors in measuring dietary fat and energy intake obscure a fat-cancer association. This possibility is supported by that fact that 2 studies that assessed fat intake by using 2 independent methods found a stronger association of fat with breast cancer with a measurement method that was potentially more precise than the FFQ (48, 49). Unfortunately, the calibration procedure used by EPIC does not completely solve the problem of measurement error, because errors inherent in the calibration instrument (24-hDR) and the dietary questionnaire are not completely independent of each other (50). Nonetheless, after calibration, HRs for saturated fat intake were slightly greater than uncalibrated data when intake was a continuous variable (the only situation in which calibration can be applied).

Despite inconsistencies across studies, ≥2 biological mechanisms lend support to the dietary fat–breast cancer hypothesis. First, fat intake may raise endogenous estrogen concentrations (51). Intervention studies indicate that reduced fat intake lowers the concentrations and bioavailability of serum sex hormones (52–54). Most established epidemiologic risk factors for breast cancer are related to alterations in hormone metabolism, and high concentrations of circulating sex hormones increase the risk of breast cancer (55, 56). In the present study, sex hormone involvement was suggested by significant interactions of the intakes of total, monounsaturated, and saturated fats with HRT use in postmenopausal women. Similar associations were reported in the National Institutes of Health–AARP cohort (13).

Other studies (57, 58) have also found that HRT influences the association between body fat (as BMI or adult weight gain) and breast cancer risk: the risk was increased only in obese postmenopausal women not using HRT. An earlier meta-analysis of 9 prospective studies also found a significant association between serum concentrations of estrogens and postmenopausal breast cancer, which, again, was confined to HRT nonusers at the time of blood donation (59). HRT use is such a strong risk factor for breast cancer (60) that it may conceal the effect of other factors that influence breast cancer risk by altering endogenous hormones. In particular, the increase in sex hormone concentrations due to high fat intake may be small compared with the already high concentrations due to HRT, and a high-fat diet is unlikely to confer additional risk for HRT users. In contrast, high fat intake in postmenopausal women not using HRT may increase estrogen bioavailability beyond the threshold that is likely to increase breast cancer risk. Consumption of fat, especially saturated fat, may also increase breast cancer risk by worsening insulin resistance (61). Several studies suggest associations of plasma concentrations of insulin, C peptide, and insulin growth factor-I with breast cancer (62). A previous EPIC report showed that high insulin growth factor-I and insulin growth factor–binding protein-3 were associated with a greater risk of breast cancer that was diagnosed after (but not before) age 50 y in women not using HRT or oral contraceptives at blood sampling (63).

Strengths of the present study are its large size (>7000 cases), prospective cohort design, wide variation in fat intake between centers, and extensive availability of information on potential confounders. Limitations common to most observational dietary studies are also apparent. In particular, the estimation of food and nutrient intake by questionnaires is associated with large random error that tends to attenuate relative risk estimates.

In conclusion, the data from the present study add to the accumulating evidence of a weak positive association between saturated fat intake and breast cancer risk. This association was more pronounced in postmenopausal women who never used HRT. It seems that a large cohort characterized by wide variation in fat consumption is necessary to show this weak effect, which may have limited significance from the public health point of view.

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