Nutrition and Cancer, 60(4), 492–504

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635580801956485

Routledge
Taylor & Francis Group

Dietary Fat, Cooking Fat, and Breast Cancer Risk in a Multiethnic Population

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Our objective was to examine the association between dietary fat intake, cooking fat usage, and breast cancer risk in a population-based, multiethnic, case-control study conducted in the San Francisco Bay area. Intake of total fat and types of fat were assessed with a food frequency questionnaire among 1,703 breast cancer cases diagnosed between 1995 and 1999 and 2,045 controls. In addition, preferred use of fat for cooking was assessed. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). High fat intake was associated with increased risk of breast cancer (highest vs. lowest quartile, adjusted OR = 1.35, 95% CI = 1.10–1.65, $P_{trend} < 0.01$). A positive association was found for oleic acid (OR = 1.55, 95% CI = 1.14–2.10, $P_{trend} < 0.01$) but not for linoleic acid or saturated fat. Risk was increased for women cooking with hydrogenated fats (OR = 1.58, 95% CI = 1.20–2.10) or vegetable/corn oil (rich in linoleic acid; OR = 1.30, 95% CI = 1.06–1.58) compared to women using olive/canola oil (rich in oleic acid). Our results suggest that a low-fat diet may play a role in breast cancer prevention. We speculate that monounsaturated trans fats may have driven the discrepant associations between types of fat and breast cancer.

INTRODUCTION

Diet, especially dietary fat, has been widely investigated as a potential risk factor for breast cancer. Extensive evidence from animal experiments supports the hypothesis that fat contributes to breast cancer initiation and promotion (1) as do large ecologic studies and international comparisons (2). Results from analytic epidemiologic studies, however, are mixed. Meta-analyses of case-control studies have found a positive association between high fat intake and breast cancer risk (3,4), whereas most prospective studies have failed to find an association (5,6). A recent randomized, controlled, intervention trial, the Women's Health Initiative (WHI), failed to find a statistically significant reduction of breast cancer risk after 8 yr of a low-fat dietary intervention, although in subgroup analyses, reduced risk was observed for women with certain subtypes of breast cancer defined by hormone receptor status (7). That study, however, was not able to evaluate the effects of specific types of fat on breast cancer risk. More recently, a large prospective cohort study with a wide range of dietary fat intake linked both total fat and the major fat subtypes, including saturated fat, monounsaturated fat, and polyunsaturated fat, to increased risk of postmenopausal breast cancer (8). Different effects have been reported for different types of fatty acids in a meta-analysis of animal studies, with n-6 polyunsaturated fats having a strong and saturated fats having a weaker promoting effect in mammary carcinogenesis, whereas monounsaturated fats have no statistically significant effects (1).

In the population-based, case-control study reported here, we used 2 complementary approaches to assess the effects of different types of dietary fats on breast cancer risk. To capture the multiple food sources that contribute to each dietary fat subtypes (i.e., saturated fat, monounsaturated fat, and polyunsaturated fat), we estimated intake of specific fat components from a food frequency questionnaire (FFQ). In addition, we examined preferred use of cooking fat to assess the effects of naturally occurring complex mixtures of different fatty acids on breast cancer risk. Unlike most epidemiologic studies of dietary fat and breast cancer risk that included women from a single ethnic group only, in this study, we included comparable numbers of Whites, African Americans,

Submitted 15 June 2007; accepted in final form 30 December 2007.
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and Latinas. The multiethnic study population allowed us to examine dietary intake over a wide range of exposures and compare dietary effects across ethnicities.

MATERIALS AND METHODS

Study Population

Study subjects were participants in a population-based, case-control study conducted in the San Francisco Bay area (9,10). A total of 10,159 women aged 35 to 79 yr with a first primary invasive breast cancer (case) diagnosed between 1995 and 1999 were identified through the Greater Bay Area Cancer Registry. Of these, 1,204 could not be contacted (392 were deceased, 151 had physician refusals, 55 were not Latina, African American, or White according to the physician, 600 were lost or had moved, and 6 declined participation in any research study). Of 8,955 cases contacted, 90% completed a screening telephone interview that established study eligibility and assessed self-reported race/ethnicity. All Latina and African-American cases and a 10% random sample of White cases were eligible for the in-person interview, which was completed by 1,788 (87%) cases including 649 (88%) Latinas, 543 (87%) African Americans, and 596 (86%) whites.

Controls were identified through random digit dialing (82% response to household enumeration) and were frequency matched to cases according to the expected race/ethnicity and 5-yr age distribution of cases. Of 2,999 women selected as controls, 184 could not be contacted (14 were deceased and 170 were lost or had moved). Among those contacted, 91% completed the telephone screening interview, and of those meeting the eligibility criteria (no history of breast cancer; White, African American, or Latina by self-report; age 35–79 yr, and Bay area resident), 2,129 (84%) completed the in-person interview including 885 (87%) Latinas, 598 (82%) African Americans, and 646 (83%) Whites.

Data Collection and Dietary Assessment

Trained professional interviewers administered in English or Spanish a structured questionnaire at a home visit to collect information on demographic background, lifestyle factors, menstrual and reproductive history, and medical history up to the reference year, defined as the calendar year prior to diagnosis for cases or the calendar year prior to selection into the study for controls. Usual dietary intake during the reference year was assessed using a FFQ adapted from the 1995, 106-item Block Health History and Habits Questionnaire (11,12). Additional foods commonly consumed by African-American and Latina women in California were included, and the intake of phytoestrogen-rich foods and plant foods was expanded. The FFQ assessed for each food item the frequency of consumption and portion size, using food models and utensils, and included questions on consumption of low-fat food (i.e., dairy products) and fats used for cooking, as these variables can have large effects on estimated fat intake. Daily intake of specific nutrients was estimated for protein, carbohydrate, total fat, and specific types of fat, including saturated fat, oleic acid (the most abundant monounsaturated fat), and linoleic acid (the most abundant polyunsaturated fat), using the DIETSYS software that linked the FFQ data to a nutrient database, which was adapted from nutrient databases developed for the Block 1995 FFQ and the FFQ used for the Study of Women's Health Across the Nation (13). Oleic acid and linoleic acid include both cis- and trans-isoforms, but the nutrient database did not distinguish between them. The choices of cooking fats include olive or canola oil, vegetable or corn oil, lard, butter, margarine, low-fat margarine, and vegetable oil shortening. Subjects were asked to choose up to 2 types of fat as their most commonly used cooking fat(s).

The interviewers also took 3 measurements of standing height and 2 measurements of weight, which were averaged. Height was measured to the nearest mm using a stadiometer after the study participants removed their shoes. Weight was measured to the nearest 0.2 kg using a portable scale, with study participants wearing light clothing. Body mass index (BMI) as a measure of adiposity was computed as measured weight (kg) divided by measured height (m) squared (or self-reported height and self-reported weight for the 11% of cases and 10% of controls who declined the measurements). Menopausal status was defined as described elsewhere (9). A positive history of benign breast disease was defined as having a biopsy for benign breast disease at least 2 yr prior to diagnosis (cases) or selection into the study (controls).

Statistical Analysis

Of the 3,917 women who completed the in-person interview, 106 women (2.7%) with daily total energy intake lower than 500 kcal or higher than 5,000 kcal (possibly indicating unreliable data) were excluded from analysis. We also excluded 63 women (1.6%) with missing data on other risk factors. The final analysis was based on 3,748 women (1,703 cases and 2,045 controls).

Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer were estimated by unconditional logistic regression (14). All tests of significance were 2-sided with $P < 0.05$ as the significant cutoff point. All analyses were adjusted for total energy intake using 2 energy-adjustment methods, the residual method and the multivariate nutrient density method (15). Because the results from the residual model and the multivariate nutrient density model were similar, we only presented the results from the latter model in which the ORs associated with fat intake can be interpreted as the effect of substituting calories from fat for the same percentage of calories from carbohydrates and protein. For each type of fat (saturated fat, linoleic acid, and oleic acid), 2 models were tested: 1 with each type of fat put into the model separately and the other with all 3 types of fat put into the model for simultaneous adjustment. Nutrients were modeled using continuous variables as well as using quartiles. We only presented the results from models using quartiles because of the

highly concordant results from these two analyses. Quartiles were determined according to the distribution among all controls, and the lowest quartile was used as the referent. Trend tests were conducted across the quartile medians. In tests of effect modification, total fat (or types of fat) were modeled linearly in units of 5% of total energy intake. For the cooking fat analysis, olive/canola oil was used as the referent. Butter and lard were combined as a single item, as both are rich in saturated fat. Margarine, low-fat margarine, and vegetable shortening were combined as a single item of hydrogenated fats. Potentially confounding variables adjusted in the multivariate models included age in reference year (continuous), race/ethnicity (White, African American, Latina), country of birth (U.S. born, foreign born), years of education (<12, 12, 13–15, ≥16), menopausal status (premenopausal, postmenopausal, undetermined), family history of breast cancer in first-degree relatives (yes, no), personal history of benign breast disease (yes, no), age at menarche (<12, 12–13, ≥14 years), parity (0, 1, 2, 3, 4, ≥5), lifetime duration of breast feeding (0, <12, ≥12 months), height (continuous), BMI (<25, 25–29.9, ≥30), and alcohol consumption (0, 0–4.9, ≥5 g per day). We considered race/ethnicity, menopausal status, family history of breast cancer, and history of benign breast disease as potential effect modifiers. Formal tests for effect modification were performed by including the appropriate interaction terms in the logistic regression models. To compare risks for breast cancer subtypes defined by stage, histological grade, estrogen receptor (ER) status, and progesterone receptor (PR) status, we used polytomous logistic regression to estimate the OR for each subtype and to test for the heterogeneity between subtypes.

STATA version 8.0 (Stata Corporation, College Station, TX) was used for polytomous logistic regression. All other analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC).

RESULTS

Characteristics of the Study Population

The study population (1,703 cases and 2,045 controls) included 32% Whites, 29% African Americans, and 39% Latinas (Table 1), and 63% of women were classified as postmenopausal. Cases and controls were of similar age and menopausal status within each racial/ethnic group. The majority of Whites (91%) and African Americans (97%) were born in the United States, whereas 59% of Latinas were foreign born. Nearly half of controls had college education or above. The proportion was highest among Whites (73%), intermediate among African Americans (56%), and lowest among Latinas (26%). Of all breast cancer cases, 76% were infiltrating ductal, 8% were lobular, 5% were ductal and lobular carcinomas, and the remaining were rare types. A total of 33% of cases had advanced breast cancer (regional or distant stage disease). Compared with African Americans and Latinas, fewer White cases were diagnosed at advanced stages (28% vs. 35%) or with histological grade greater than 2 (25% vs. 38%). Examination of well-established breast cancer risk factors including family history of breast cancer, previous history of benign breast disease, education, age at menarche, age at menopause, parity, age at first full-term pregnancy, breast feeding, height, and alcohol intake showed significant associations in the expected direction (Table 1). BMI was negatively associated with cancer risk among premenopausal women but unrelated to cancer risk among postmenopausal women.

The median total energy intake among all controls was 1,914 kcal/day (Table 2). The median total energy from fat was 31%. Among the 3 racial/ethnic groups, Latinas had the highest total energy intake (median: 2,151 kcal/day) but the lowest median energy from fat (28%). There were strong correlations of total fat intake with both oleic acid ($r = 0.93$) and saturated fat ($r = 0.79$) intake. Oleic acid intake was also highly correlated with saturated fat intake ($r = 0.73$). Linoleic acid intake had a weaker correlation with total fat intake ($r = 0.61$) or types of fat intake (oleic acid, $r = 0.52$; saturated fat, $r = 0.19$). Carbohydrate and fat intakes were negatively correlated ($r = –0.81$).

Dietary Fat Intake and Breast Cancer Risk

Overall, total fat intake was positively associated with breast cancer risk when adjusted for age, race/ethnicity, and total energy intake [Quartile $(Q)_4$ vs. Q_1, OR = 1.48, 95% CI = 1.22–1.80]. Further adjustment for other risk factors slightly attenuated the association (Q_4 vs. Q_1, OR = 1.35, 95% CI = 1.10–1.65; Table 3), but a significant trend of increasing risk across the quartiles of intakes remained (P trend < 0.01). Among the fat components estimated from the FFQ (saturated fat, oleic acid, and linoleic acid), oleic acid was more strongly associated with breast cancer risk (Q_4 vs. Q_1, OR = 1.43, 95% CI = 1.17–1.76, $P_{trend} < 0.001$) than was linoleic acid (Q_4 vs. Q_1, OR: 1.27; 95% CI: 1.04–1.54, $P_{trend} = 0.04$). Saturated fat intake was not associated with breast cancer risk (Q_4 vs. Q_1, OR = 1.07, 95% CI = 0.88–1.30, $P_{trend} = 0.34$). After simultaneously adjusting each type of fat for the others, an association of similar magnitude remained for oleic acid ($P_{trend} < 0.01$), whereas the association with linoleic acid disappeared ($P_{trend} = 0.68$). Different patterns of association were seen in the 3 racial/ethnic groups. For total fat and oleic acid, a trend of increasing risk with increasing intake was observed among Whites and Latinas but not among African Americans (Table 4). The differences by race/ethnicity, however, were not statistically significant ($P_{int} > 0.05$); thus, further analyses were conducted with all racial/ethnic groups combined.

Neither family history of breast cancer nor personal history of benign breast disease (BBD) modified the association between total fat and breast cancer risk (Table 5). There was, however, a significant interaction between linoleic acid and BBD ($P_{int} < 0.01$). A positive association was found only among women with a history of BBD (OR = 1.85, 95% CI = 1.15–2.96). Associations did not vary by tumor characteristics (Table 5). Premenopausal but not postmenopausal breast cancer

TABLE 1
Basic Characteristics and Breast Cancer Risk Factors by Case-Control Status[a]

	No. Cases (%)[b]	No. Controls (%)[c]	OR (95% CI)[d]
Age in reference year (yr)			
35–49	527 (31)	660 (32)	
50–64	695 (41)	820 (40)	
65–79	481 (28)	565 (28)	
Race/ethnicity			
White	581 (34)	633 (31)	
African American	502 (29)	566 (28)	
Latina	620 (36)	846 (41)	
Menopausal status			
Premenopausal	505 (30)	601 (29)	1.0
Postmenopausal	1073 (63)	1279 (63)	0.96 (0.76–1.23)
Undetermined	125 (7)	165 (8)	0.86 (0.65–1.14)
Country of birth			
U.S. born	1329 (78)	1417 (69)	1.0
Foreign born	374 (22)	628 (31)	0.62 (0.51–0.74)
Education (yr)			
<12	367 (22)	613 (30)	1.0
12	353 (21)	425 (21)	1.39 (1.14–1.70)
13–15	558 (33)	577 (28)	1.63 (1.35–1.97)
≥16	425 (25)	430 (21)	1.69 (1.37–2.08)
Family history of breast cancer[e]			
No	1437 (84)	1817 (89)	1.0
Yes	266 (16)	228 (11)	1.44 (1.19–1.74)
History of benign breast disease			
No	1342 (79)	1727 (84)	1.0
Yes	361 (21)	318 (16)	1.43 (1.21–1.70)
Age at menarche			
8–11	400 (23)	433 (21)	1.0
12–13	880 (52)	1037 (51)	0.90 (0.77–1.07)
≥14	423 (25)	575 (28)	0.80 (0.66–0.96)
Age at menopause (among postmenopausal women)			
<44	222 (25)	290 (28)	1.0
45–54	544 (61)	659 (63)	1.06 (0.86–1.32)
≥55	119 (13)	105 (10)	1.46 (1.06–2.03)
Parity[f]			
1	263 (15)	273 (13)	1.0
2	452 (27)	484 (24)	0.97 (0.79–1.20)
3	321 (19)	430 (21)	0.78 (0.62–0.97)
4	187 (11)	245 (12)	0.79 (0.61–1.02)
≥5	195 (11)	368 (18)	0.55 (0.43–0.70)
Nulliparous	285 (17)	245 (12)	1.21 (0.95–1.54)
Age at first full-term pregnancy			
<20	344 (20)	504 (25)	1.0
20–24	545 (32)	676 (33)	1.19 (0.99–1.43)
25–29	306 (18)	367 (18)	1.23 (1.00–1.52)
≥30	222 (13)	243 (12)	1.36 (1.07–1.71)
Nulliparous	285 (17)	245 (12)	1.68 (1.34–2.10)

(Continued on next page)

TABLE 1
Basic Characteristics and Breast Cancer Risk Factors by Case-Control Status[a] *(Continued)*

	No. Cases (%)[b]	No. Controls (%)[c]	OR (95% CI)[d]
Breast feeding (mo)			
0	649 (38)	673 (33)	1.0
<12	413 (24)	533 (26)	0.81 (0.68–0.96)
≥12	356 (21)	594 (29)	0.64 (0.53–0.76)
Nulliparous	285 (17)	245 (12)	1.19 (0.97–1.46)
Use of oral contraceptives			
Never	584 (37)	769 (38)	1.0
Ever	978 (63)	1254 (62)	1.02 (0.87–1.20)
Use of HRT (among postmenopausal women)			
Never	419 (39)	486 (38)	1.0
Ever	644 (61)	778 (62)	0.92 (0.77–1.09)
Height (cm, quartiles)			
<155	340 (20)	519 (25)	1.0
155–159	395 (23)	531 (26)	1.12 (0.92–1.36)
160–164	476 (28)	486 (24)	1.47 (1.21–1.8)
≥165	492 (29)	509 (25)	1.45 (1.17–1.78)
BMI (kg/m^2)			
Premenopausal			
<25	171 (34)	162 (27)	1.0
25–29	147 (29)	196 (33)	0.70 (0.51–0.96)
≥30	187 (37)	243 (40)	0.71 (0.52–0.95)
Postmenopausal			
<25	279 (26)	307 (24)	1.0
25–29	349 (33)	444 (35)	0.92 (0.74–1.14)
≥30	445 (41)	528 (41)	0.99 (0.80–1.22)
Total energy intake (kcal/day, quartiles)			
<1,438	408 (24)	510 (25)	1.0
1,438–1,914	445 (26)	512 (25)	1.10 (0.92–1.33)
1,914–2,609	444 (26)	512 (25)	1.12 (0.93–1.35)
>2609	406 (24)	511 (25)	1.05 (0.87–1.27)
Alcohol intake (g/day)			
0	869 (51)	1167 (57)	1.0
0–5	411 (24)	455 (22)	1.22 (1.03–1.43)
≥6	423 (25)	423 (21)	1.32 (1.11–1.56)

[a] Subjects for some variables may not add up to 3,748 due to missing data. Abbreviations are as follows: OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; BMI, body mass index.
[b] $n = 1, 703$.
[c] $n = 2, 045$.
[d] OR and 95% CI adjusted for age and race/ethnicity.
[e] In first-degree relatives.
[f] Number of full-term pregnancies.

appeared to be negatively associated with linoleic acid intake ($P_{\text{int}} = 0.04$). Saturated fat intake showed a negative association with localized breast cancer but not with advanced breast cancer ($P < 0.01$ for heterogeneity test). Some heterogeneity by ER status was also suggested. Oleic acid was positively (and saturated fat was negatively) associated with ER negative but not ER positive breast cancer ($P_{\text{int}} = 0.05$).

Cooking Fat Usage and Breast Cancer Risk

Among controls, 51% reported cooking with vegetable or corn oil, 45% chose olive or canola oil, and 24% chose hydrogenated fat (including margarine, low-fat margarine, and vegetable oil shortening). Compared to women cooking only with olive/canola oil, those cooking only with vegetable/corn oil were at 30% increased risk of breast cancer (OR = 1.30, 95%

TABLE 2
Daily Intake of Total Energy and Percentage of Energy from Dietary Components Among Controls by Race/Ethnicity

Nutrient	Mean (± SD)			
	All Controls	Whites	African Americans	Latinas
Total energy, kcal/day				
Mean (± SD)	2,090 (± 889)	1,920 (± 745)	2,001 (± 970)	2,276 (± 898)
Median (25–75%)	1,914 (1,438–2,609)	1,777 (1,407–2,355)	1,793 (1,246–2,539)	2,151 (1,594–2,844)
Total fat, % energy				
Mean (± SD)	31.3 (± 7.6)	32.6 (± 7.5)	34.1 (± 7.7)	28.5 (± 6.5)
Median (25–75%)	31.0 (26.1–36.3)	32.2 (27.6–37.4)	33.9 (29.1–39.1)	28.3 (23.8–33.0)
Saturated fat, % energy				
Mean (± SD)	10.9 (± 3.2)	11.7 (± 3.5)	11.2 (± 3.0)	10.1 (± 2.9)
Median (25–75%)	10.7 (8.8–12.7)	11.2 (9.3–13.6)	11.0 (9.2–13.0)	10.0 (8.2–11.9)
Linoleic acid, % energy				
Mean (± SD)	5.4 (± 1.9)	5.8 (± 2.1)	6.0 (± 2.0)	4.8 (± 1.4)
Median	5.1 (4.1–6.3)	5.4 (4.3–6.7)	5.7 (4.6–7.1)	4.5 (3.8–5.5)
Oleic acid, % energy				
Mean (± SD)	11.1 (± 2.9)	11.5 (± 2.7)	12.1 (± 2.9)	10.0 (± 2.7)
Median (25–75%)	11.1 (9.1–12.9)	11.4 (9.7–13.4)	12.2 (10.2–14.0)	9.9 (8.2–11.8)
Protein, % energy				
Mean (± SD)	17.7 (± 3.6)	17.1 (± 3.5)	18.0 (± 4.2)	17.8 (± 3.3)
Median (25–75%)	17.4 (15.2–19.7)	16.8 (14.7–19.3)	17.8 (15.2–20.4)	17.5 (15.6–19.8)
Carbohydrates, % energy				
Mean (± SD)	49.8 (± 9.0)	48.3 (± 8.5)	46.8 (± 9.7)	52.9 (± 7.9)
Median (25–75%)	49.9 (43.6–56.0)	48.4 (42.2–53.7)	46.9 (40.2–52.9)	53.2 (47.5–58.2)

CI = 1.06–1.58; Table 6). Using only hydrogenated fats conferred an even higher risk (OR = 1.58, 95% CI = 1.20–2.10). For women reporting two types of cooking fats, risk was intermediate between the two component ORs. For example, those using both hydrogenated fat and olive/canola oil had a risk (OR = 1.27, 95% CI = 0.95–1.69) higher than those using only olive/canola oil and lower than those using only hydrogenated fat. For women using both vegetable/corn oil and hydrogenated fat, the risk (OR = 1.41, 95% CI = 1.10–1.82) was intermediate between those using only vegetable/corn oil or only hydrogenated fat. Although the popularity of the cooking fats varied across ethnicities, with Whites reporting use of olive/canola oils more often than other fats and African Americans and Latinas using vegetable/corn oil most commonly, the associations for cooking fat usage were similar in each racial/ethnic group. Compared to women cooking only with olive/canola oil, using hydrogenated fat in cooking was associated with increased risk of breast cancer among Whites (OR = 1.41, 95% CI = 1.04–1.92) and Latinas (OR = 1.54, 95% CI = 1.08–2.20). For African-American women, the association was weaker and nonsignificant (OR = 1.27, 95% CI = 0.87–1.85).

Finally, evaluating the effects of the three specific types of dietary fat and cooking fat usage in a single model did not change the results (data not shown).

DISCUSSION

In this population-based, multiethnic, case-control study, we found an association between high fat intake and increased breast cancer risk, which is consistent with other case-control studies (3,4,16–25). To determine which components of dietary fat might be responsible, we used two different approaches. First, estimating fat intake by FFQ, we found oleic acid (monounsaturated fat) to be associated with increased risk, whereas no associations were found for linoleic acid and saturated fat intake. In contrast, when analyzing cooking fat usage, increased risk was associated with using hydrogenated fat or vegetable/corn oil (rich in n-6 polyunsaturated fat). Women using olive/canola oil (rich in monounsaturated fat) were at lower risk, similar to those who used no fats for cooking.

This apparent discrepancy—that monounsaturated fat as measured by FFQ increases breast cancer risk, yet certain foods rich in monounsaturated fat (i.e., edible oils such as olive or canola oil) are associated with lower risk than fats rich in n-6 polyunsaturated fats and hydrogenated fats—is reflected in the epidemiologic literature. Most dietary studies (including a meta-analysis of 16 case-control studies published between 1978 and 1991 [4]) found either a positive association (16–22,26–28) or no association (25,29–44) between monounsaturated fat intake and breast cancer. A meta-analysis of fatty acid biomarkers

TABLE 3
Breast Cancer Risk and Total Energy Intake and Percentage of Energy from Total Fat, Specific Fats, Protein, and Carbohydrates Among All Cases and Controls[a]

	Quartile (Q) of Intake				
Nutrient	Q1	Q2	Q3	Q4	P_{trend}
Total energy					
No. of cases	408	445	444	406	
No. of controls	510	512	512	511	
OR (95% CI)[b]	1.0 (ref)	1.14 (0.94–1.37)	1.16 (0.96–1.41)	1.13 (0.93–1.38)	0.27
Total fat					
No. of cases	339	388	460	516	
No. of controls	507	514	520	504	
OR (95% CI)[c]	1.0 (ref)	1.10 (0.90–1.34)	1.20 (0.98–1.46)	1.35 (1.10–1.65)	<0.01
Saturated fat					
No. of cases	369	417	453	464	
No. of controls	501	528	495	521	
OR (95% CI)[c]	1.0 (ref)	1.02 (0.84–1.24)	1.14 (0.94–1.39)	1.07 (0.88–1.30)	0.39
OR (95% CI)[d]	1.0 (ref)	0.89 (0.72–1.11)	0.92 (0.72–1.17)	0.82 (0.63–1.07)	0.16
Linoleic acid					
No. of cases	339	408	465	491	
No. of controls	520	497	507	521	
OR (95% CI)[c]	1.0 (ref)	1.22 (1.01–1.49)	1.33 (1.10–1.61)	1.27 (1.04–1.54)	0.04
OR (95% CI)[d]	1.0 (ref)	1.15 (0.95–1.41)	1.20 (0.98–1.48)	1.10 (0.88–1.37)	0.68
Oleic acid					
No. of cases	325	413	423	542	
No. of controls	514	521	490	520	
OR (95% CI)[c]	1.0 (ref)	1.19 (0.98–1.45)	1.23 (1.01–1.51)	1.43 (1.17–1.76)	<0.001
OR (95% CI)[d]	1.0 (ref)	1.21 (0.97–1.52)	1.29 (0.99–1.68)	1.55 (1.14–2.10)	<0.01
Protein					
No. of cases	456	399	422	426	
No. of controls	508	520	501	516	
OR (95% CI)[c]	1.0 (ref)	0.90 (0.75–1.09)	0.99 (0.82–1.19)	0.96 (0.80–1.16)	0.91
Carbohydrates					
No. of cases	501	466	405	331	
No. of controls	511	507	519	508	
OR (95% CI)[c]	1.0 (ref)	0.96 (0.80–1.15)	0.92 (0.76–1.11)	0.80 (0.65–0.98)	0.04

[a] Abbreviations are as follows: OR, odds ratio; CI, confidence interval.
[b] Adjusted for age, race/ethnicity, menopausal status, country of birth, education, family history of breast cancer, history of benign breast disease, age at menarche, parity, breast feeding, BMI, height, and alcohol intake.
[c] Model 1: Adjusted for covariates in footnote *b* and total energy intake.
[d] Model 2: Adjusted for covariates in Model 1 and saturated fat, linoleic acid, and oleic acid in a single model.

studies also found a positive association between oleic acid levels and risk of breast cancer in cohort studies, although not in case-control studies (45). However, despite this potential link, monounsaturated fat is generally considered to be a "good" fat with respect to cancer risk, mostly based on evidence from reports on the Mediterranean diet. Olive oil, which is the principal source of fat in Mediterranean diets, contains over 70% monounsaturated fat (mostly oleic acid) and has been reported to be protective against breast cancer (33,34,46). Our finding, within a single study, that oleic acid as measured by FFQ increases risk, whereas cooking fats high in oleic acid reduce risk, highlights the question of whether the underlying risk factor is oleic acid per se or something else related to its various sources.

Oleic acid is substantially present in a variety of fats of both plant and animal origin, composing 40–50% of animal adipose fat, 20–40% of animal structural fats, 25% of dairy fat, and 20–70% of most commonly used cooking oils (e.g., 70% in olive oil,

TABLE 4
Breast Cancer Risk and Percentage of Energy from Total Fat and Specific Fat Intake by Race/Ethnicity[a]

Nutrient	Race/Ethnicity		Quartile (Q) of Intake				P_{trend}
			Q1	Q2	Q3	Q4	
Total fat	Whites	No. of cases	98	140	151	192	
		No. of controls	123	150	175	185	
		OR (95% CI)[b]	1.0 (ref)	1.23 (0.86–1.77)	1.17 (0.82–1.69)	1.45 (1.01–2.09)	0.06
	African Americans	No. of cases	72	90	130	210	
		No. of controls	79	118	147	222	
		OR (95% CI)[b]	1.0 (ref)	0.81 (0.53–1.24)	0.93 (0.61–1.40)	0.98 (0.66–1.45)	0.72
	Latinas	No. of cases	169	158	179	114	
		No. of controls	305	246	198	97	
		OR (95% CI)[b]	1.0 (ref)	1.14 (0.85–1.54)	1.31 (0.96–1.78)	1.53 (1.06–2.21)	0.02
Saturated fat	Whites	No. of cases	112	141	144	184	
		No. of controls	119	151	155	208	
		OR (95% CI)[b]	1.0 (ref)	1.03 (0.72–1.47)	1.06 (0.74–1.52)	1.02 (0.72–1.45)	0.93
		OR (95% CI)[c]	1.0 (ref)	0.85 (0.57–1.26)	0.77 (0.50–1.20)	0.66 (0.42–1.05)	0.07
	African Americans	No. of cases	100	108	149	145	
		No. of controls	111	142	152	161	
		OR (95% CI)[b]	1.0 (ref)	0.79 (0.54–1.16)	1.03 (0.71–1.49)	0.92 (0.64–1.33)	0.98
		OR (95% CI)[c]	1.0 (ref)	0.86 (0.55–1.34)	1.13 (0.69–1.86)	1.01 (0.59–1.73)	0.84
	Latinas	No. of cases	157	168	160	135	
		No. of controls	271	235	188	152	
		OR (95% CI)[b]	1.0 (ref)	1.11 (0.83–1.50)	1.24 (0.90–1.70)	1.19 (0.85–1.66)	0.24
		OR (95% CI)[c]	1.0 (ref)	0.97 (0.69–1.35)	0.97 (0.67–1.42)	0.89 (0.58–1.37)	0.62
Linoleic acid	Whites	No. of cases	92	150	147	192	
		No. of controls	130	133	166	204	
		OR (95% CI)[b]	1.0 (ref)	1.67 (1.16–2.40)	1.27 (0.89–1.80)	1.34 (0.95–1.90)	0.52
		OR (95% CI)[c]	1.0 (ref)	1.55 (1.07–2.24)	1.08 (0.74–1.56)	1.03 (0.70–1.52)	0.38
	African Americans	No. of cases	71	84	168	179	
		No. of controls	89	111	155	211	
		OR (95% CI)[b]	1.0 (ref)	0.91 (0.60–1.41)	1.33 (0.90–1.97)	1.00 (0.69–1.47)	0.99
		OR (95% CI)[c]	1.0 (ref)	0.98 (0.63–1.53)	1.43 (0.93–2.21)	1.09 (0.70–1.69)	0.92
	Latinas	No. of cases	176	174	150	120	
		No. of controls	301	253	186	106	
		OR (95% CI)[b]	1.0 (ref)	1.08 (0.81–1.43)	1.28 (0.94–1.73)	1.48 (1.05–2.09)	0.01
		OR (95% CI)[c]	1.0 (ref)	1.01 (0.75–1.35)	1.14 (0.82–1.57)	1.26 (0.87–1.83)	0.18
Oleic acid	Whites	No. of cases	92	144	155	190	
		No. of controls	117	162	171	183	
		OR (95% CI)[b]	1.0 (ref)	1.24 (0.86–1.79)	1.31 (0.90–1.89)	1.59 (1.09–2.33)	0.02
		OR (95% CI)[c]	1.0 (ref)	1.39 (0.92–2.11)	1.64 (1.02–2.63)	2.26 (1.31–3.90)	<0.01
	African Americans	No. of cases	74	100	115	213	
		No. of controls	81	116	144	225	
		OR (95% CI)[b]	1.0 (ref)	0.88 (0.58–1.35)	0.83 (0.55–1.25)	0.95 (0.64–1.40)	0.98
		OR (95% CI)[c]	1.0 (ref)	0.86 (0.52–1.40)	0.77 (0.43–1.36)	0.82 (0.44–1.53)	0.69
	Latinas	No. of cases	159	169	153	139	
		No. of controls	316	243	175	112	
		OR (95% CI)[b]	1.0 (ref)	1.28 (0.95–1.72)	1.43 (1.03–1.97)	1.70 (1.18–2.45)	<0.01
		OR (95% CI)[c]	1.0 (ref)	1.27 (0.91–1.78)	1.39 (0.91–2.11)	1.65 (1.01–2.72)	0.05

[a] Abbreviations are as follows: OR, odds ratio; CI, confidence interval.
[b] Adjusted for covariates in Model 1 of Table 3, with exclusion of race/ethnicity.
[c] Adjusted for covariates in Model 2 of Table 3, with exclusion of race/ethnicity.

TABLE 5
Breast Cancer Risk for a 5% Increase in Percent of Calories from Fat and Fat Subtypes by Other Risk Factors and Tumor Characteristics[a]

Modifier	Dietary Fat (OR and 95% CI per 5% Increase of Energy)			
	Total Fat[b]	Saturated Fat[c]	Linoleic Acid[c]	Oleic Acid[c]
Family history of breast cancer[d]				
No	1.05 (1.00–1.11)	0.90 (0.76–1.07)	1.01 (0.80–1.27)	1.26 (1.00–1.59)
Yes	1.21 (1.06–1.38)	1.22 (0.78–1.91)	1.27 (0.70–2.28)	1.22 (0.68–2.19)
History of benign breast disease				
No	1.07 (1.01–1.13)	0.95 (0.80–1.14)	0.87 (0.68–1.11)[e]	1.32 (1.04–1.68)
Yes	1.10 (0.99–1.23)	0.96 (0.66–1.39)	1.85 (1.15–2.96)	1.02 (0.62–1.67)
Menopausal status				
Premenopausal	1.05 (0.96–1.16)	0.95 (0.68–1.32)	0.72 (0.48–1.10)[f]	1.42 (0.94–2.16)
Postmenopausal	1.09 (1.02–1.15)	0.96 (0.79–1.17)	1.18 (0.90–1.53)	1.18 (0.91–1.54)
ER status				
Positive	1.08 (1.02–1.14)	1.05 (0.87–1.25)	1.08 (0.85–1.38)	1.10 (0.87–1.41)
Negative	1.08 (1.00–1.18)	0.77 (0.57–1.03)[g]	0.93 (0.64–1.34)	1.63 (1.13–2.35)[g]
PR status				
Positive	1.07 (1.01–1.13)	0.96 (0.79–1.15)	1.03 (0.80–1.32)	1.23 (0.95–1.58)
Negative	1.09 (1.02–1.17)	1.02 (0.80–1.30)	1.06 (0.76–1.44)	1.18 (0.86–1.63)
Histological grade				
Low (1/2)	1.07 (1.01–1.13)	0.99 (0.81–1.20)	1.21 (0.93–1.56)	1.08 (0.83–1.40)
High (3/4)	1.09 (1.02–1.17)	0.93 (0.73–1.17)	0.88 (0.65–1.21)	1.45 (1.07–1.97)
Stage				
Local	1.07 (1.01–1.13)	0.84 (0.70–1.01)	1.04 (0.82–1.32)	1.39 (1.09–1.76)
Advanced	1.11 (1.04–1.19)	1.20 (0.96–1.50)[e]	1.05 (0.77–1.43)	1.06 (0.78–1.44)

[a] Abbreviations are as follows: OR, odds ratio; CI, confidence interval, ER, estrogen receptor; PR, progesterone receptor.
[b] Adjusted for covariates in Model 1 of Table 3, with exclusion of stratified variables.
[c] Adjusted for covariates in Model 1 of Table 3 and simultaneously adjusted for saturated fat, linoleic acid, and oleic acid intake as continuous variables (5% of energy).
[d] In first-degree relatives.
[e] $P_{int} < 0.01$.
[f] $P_{int} = 0.04$.
[g] $P_{int} = 0.05$.

20% in soybean and sunflower oils) (47). The source of dietary monounsaturated fat varies depending on dietary patterns. In the Mediterranean diet, olive oil is the principle source of total fat and oleic acid (48,49). In contrast, in the United States, where the consumption of olive oil is low, monounsaturated fat mainly comes from animal and dairy products and more important, from processed foods. Substantial amounts of monounsaturated fats in margarine, shortening, baked products, confectionary products, deep-fried products, and processed snack foods have, until very recently, been present in the form of trans isomers. For example, 30–40% of monounsaturated fats in French fries are trans fats (47).

In the nutrient database used for this study (and in most other epidemiologic studies), trans fats were not differentiated from their cis isoforms. Therefore, the estimated intake of oleic acid based on FFQ data included contributions of both cis- and trans-oleic acid. The estimated trans fat intake in the United States diet is 4.7–13.3 g/day (50–52). If this range is also representative of the trans fat intake in our study, trans fat may have accounted for 7–20% of total fat intake or 21–58% of oleic acid intake, thus suggesting the possibility that the observed positive association between oleic acid and breast cancer is at least partially attributable to its trans isomer coming from hydrogenated fat. Indeed, we found that among all types of cooking fat, hydrogenated fat conferred the highest risk of breast cancer.

The effects of trans fat on mammary carcinogenesis have been rarely investigated, and the mechanisms are currently not clear. Animal studies in general did not find extra adverse effects of trans fat in promoting mammary tumorigenesis in comparison with their cis isoforms (53). There are some indications of a positive association between adipose level of trans fatty acid and breast cancer risk (54,55). However, the results have not been consistent (56). Examination of dietary trans fat intake and

TABLE 6
Breast Cancer Risk and Use of Fat in Cooking[a]

Type of Cooking Fat	Cases	Controls	OR (95% CI)[b]
Olive or canola oil only	412	513	1.00 (ref)
Butter or lard only	43	59	1.03 (0.67–1.58)
Vegetable or corn oil only	444	558	1.30 (1.06–1.58)
Hydrogenated fat only[c]	150	134	1.58 (1.20–2.10)
Pam or no oil	26	36	0.89 (0.52–1.51)
Olive or canola oil + butter or lard	91	105	1.05 (0.76–1.44)
Olive or canola oil + vegetable or corn oil	118	166	0.91 (0.69–1.20)
Olive or canola oil + hydrogenated fat	124	124	1.27 (0.95–1.69)
Butter or lard + vegetable or corn oil	72	111	1.02 (0.72–1.43)
Butter or lard + hydrogenated fat	21	29	0.96 (0.53–1.74)
Vegetable or corn oil + hydrogenated fat	190	198	1.41 (1.10–1.82)
Whites			
Olive or canola oil only	212	258	1.00 (ref)
Vegetable or corn oil but not hydrogenated fat[d]	137	136	1.25 (0.92–1.71)
Hydrogenated fat[e]	146	135	1.41 (1.04–1.92)
Others[f]	81	100	1.05 (0.73–1.49)
African Americans			
Olive or canola oil only	70	94	1.00 (ref)
Vegetable or corn oil but not hydrogenated fat[d]	193	220	1.18 (0.81–1.71)
Hydrogenated fat[e]	201	214	1.27 (0.87–1.85)
Others[f]	35	34	1.29 (0.72–2.29)
Latinas			
Olive or canola oil only	130	161	1.00 (ref)
Vegetable or corn oil but not hydrogenated fat[d]	304	479	1.14 (0.85–1.55)
Hydrogenated fat[e]	138	136	1.54 (1.08–2.20)
Others[f]	44	66	0.85 (0.53–1.37)

[a] A total of 12 cases and 12 controls had missing data on cooking fat. Abbreviations are as follows: OR, odds ratio; CI, confidence interval.

[b] Adjusted for the same covariates as Model 1 in Table 3, with exclusion of race/ethnicity in race/ethnicity specific analysis.

[c] Hydrogenated fat included margarine, low-fat margarine, and vegetable oil shortening.

[d] Includes subjects choosing vegetable or corn oil only, vegetable or corn oil and olive or canola oil, and vegetable or corn oil and butter or lard.

[e] Includes subjects choosing hydrogenated fat only, hydrogenated fat and olive or canola oil, hydrogenated fat and vegetable or corn oil, and hydrogenated fat and butter or lard.

[f] Includes subjects choosing Pam or no oil, butter or lard only, and butter or lard and olive or canola oil.

breast cancer risk in the Nurses' Health Study did not reveal any significant associations (42,57).

Alternatively, the observed protective effect of cooking fats high in monounsaturated fats may be related to other attributes of the fat source in addition to its fatty acid composition such as vitamins, flavonoids, and phenolic compounds found in olive oil and alpha-linolenic acid (an n-3 polyunsaturated fat) found at a relatively high level (>10%) in canola oil. In support of this explanation, in a study involving 5 European study centers, tissue stores of oleic acid only showed a strong inverse association with breast cancer risk in southern Spain, where olive oil is the primary source of oleic acid, but not in Germany, Northern Ireland, the Netherlands and Switzerland where fats from animal sources contribute much more to oleic acid intake (58). We also could not exclude the possibility that choosing olive/canola oil for cooking may reflect a general healthy lifestyle among these women that has lead to a reduced risk of breast cancer. On the other hand, there is some evidence showing that cis monounsaturated fats may actually promote mammary tumorigenesis (59,60). Finally, because the FFQ used in this study has not been validated in our multiethnic population, it is possible that some undefined degree of measurement error may have influenced our results for oleic acid.

This study included three major U.S. racial/ethnic groups—Whites, African Americans, and Latinas—with more than 1,000 subjects in each group. Few studies of dietary fat intake and

breast cancer risk, even in the ethnically diverse United States, have included multiple ethnicities in the same study. The only two case-control studies that included both Whites and Asians from Hawaii had small numbers in each ethnic group (61,62). Other multiethnic studies with larger sample sizes have not yet reported any results on dietary fats (63,64). In this study, the median fat intake among Whites (32% of energy) was comparable to that reported for Whites by other studies (43,65), whereas African Americans had slightly higher (34%) and Latinas had lower (28%) median fat intake than Whites in this study population. The median fat intakes in the lowest and highest quartiles of our study population were 22% and 40% of total energy intake, respectively—an 18% difference that is wider than that in some large cohorts (66–68) and would allow for a more modest effect of fat to be detected. Our study also provided the opportunity to examine the consistency of the diet-cancer association across three racial/ethnic groups, which has not been previously explored. We found a positive association between total or monounsaturated fat and breast cancer risk only among Whites and Latinas but not among African Americans. The reason for this inconsistency is not clear. It is unlikely to be explained by recall bias because there is no reason that African Americans would recall usual dietary intake differently from Whites and Latinas. The Block FFQ, which was adapted for this study, has been validated in other White and African-American populations (69–71), and was modified by adding food items commonly eaten by African Americans and Latinos, most of which were also included in the Block FFQ adapted for another multiethnic study (13). Therefore, it is unlikely that the FFQ is a major source of bias responsible for the inconsistent results across race/ethnicity. Whites, African Americans, and Latinas differ in many lifestyle factors and dietary habits. Although we adjusted the analyses for the major known breast cancer risk factors, the inconsistency may reflect important confounding issues that have not been identified or that were not easy to adjust for. For example, 10% of BMI data came from self-report, which might have caused some misclassification and resulted in residual confounding. Although a similar association between cooking fats and breast cancer risk was found in all three racial/ethnic groups, it is also possible that some unmeasured components in diet, such as trans fats, are responsible for the inconsistent findings for oleic acid intake measured by the FFQ.

Effects of dietary fat on subtypes of breast cancer defined by hormone receptor status have been investigated in several studies, and the findings so far are inconsistent. The Nurses' Health Study reported a stronger positive association with animal fat for ER positive breast cancer among premenopausal women (57). In two studies among postmenopausal women, one found total fat as a risk factor only for ER positive and PR positive breast cancer (72), whereas the other study found no difference by ER or PR status regarding effects of total fat or subtypes of fat (73). In fact, the latter study found a significant elevation in risk in the lowest fat-intake group for ER positive and PR negative cancer, opposite to the results from the WHI, which showed a stronger risk-reducing effect of a low-fat diet for ER positive and PR negative tumors. In this study, total fat intake showed similar associations regardless of ER or PR status, whereas the associations for specific subtypes of fat appeared to differ by ER status, with oleic acid being positively and saturated fat negatively associated with ER negative breast cancer. The inconsistent results from these studies suggest that most of the findings are likely to be due to chance. Similarly, we cannot exclude the possibility that our finding of differential effects of saturated fat by stage of cancer was a chance finding.

A meta-analysis reported the association between dietary fat and breast cancer risk to be stronger among postmenopausal than premenopausal women (3). In this study, we did not find that menopausal status modified the association with total fat intake. However, there was an indication that linoleic acid tended to be positively associated with postmenopausal breast cancer but negatively with premenopausal breast cancer. A pooled analysis of prospective studies have reported an interaction between total fat intake and previous history of BBD, with a positive association observed among women with a history of BBD (74). In our study, there was no evidence of interaction between total fat intake and BBD. However, we observed an interaction between linoleic acid and BBD, with linoleic acid increasing cancer risk only among women with a history of BBD.

Although our study could not avoid certain limitations common to all case-control studies, such as potential recall bias and measurement errors when estimating dietary intake via the FFQ, these limitations are unlikely to explain the observed positive association between breast cancer risk and dietary oleic acid intake and the inverse association of cooking with oils high in monounsaturated fats. We speculate that the positive association between oleic acid and breast cancer risk based on FFQ data may be driven by a causal effect of hydrogenated fats on breast cancer risk. This study, however, has the limitation of not being able to directly examine the effects of trans fat due to the lack of trans fat data in our nutrient database. Therefore, our conjecture on the effects of hydrogenated fat needs to be further investigated by studies in which the trans fat content of foods can be quantified in studies with appropriately collected and stored biologic tissue. Such studies may also shed light on the inconsistency among previous publications, as in most published epidemiologic studies, trans fats were not differentiated from their cis isoforms.

In conclusion, our findings add to the literature suggesting that adoption of a low-fat diet may play a role in reducing breast cancer risk. The potential implications of the adverse effects of hydrogenated fats need further evaluation.

ACKNOWLEDGMENTS

This research was supported by Grants R01 CA63446 (to E. M. John) and R01 CA77305 (to E. M. John) from the National Cancer Institute, DAMD17–96–6071 (to E. M. John) from the United States Army Medical Research Program, and IRB0125

(to P. L. Horn-Ross) and 7WB-0110 (to S. A. Ingles) from the California Breast Cancer Research Program.

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