Serum Fatty Acids and Risk of Breast Cancer in a Nested Case-Control Study of the New York University Women's Health Study

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Abstract

Migrant and experimental animal studies suggest that differences in breast cancer incidence rates may be related, in part, to intake of dietary fat. The experimental evidence indicates that total fat, saturated, and n-6 polyunsaturated fatty acids (PUFAs) may stimulate both mammary tumor growth and metastasis, whereas n-3 PUFAs may have a tumor-inhibiting effect. Overall, epidemiological studies do not appear to confirm such observations. Within a cohort of women in the New York University Women's Health Study, the fatty acid composition of serum phospholipids was analyzed by gas chromatography among 197 pre- and postmenopausal clinically identified breast cancer subjects and their matched controls. Individual fatty acids in serum phospholipids were expressed as a percentage of total fatty acids. No significant difference was observed in the proportion of saturated fatty acids (SFAs), monounsaturated fatty acids, or n-6 and n-3 PUFAs between cases and controls. After menopause, total SFAs were positively associated with the risk of breast cancer [odds ratio (OR) = 1.96, 95% confidence interval (CI): 0.73–5.25; $P = 0.05$] after adjustment for potential confounding factors. Myristc acid (C14:0) was suggestive of a small increase in breast cancer risk in premenopausal women (OR = 2.22, 95% CI: 0.78–6.31), whereas palmitic acid (C16:0) showed similar trends in postmenopausal women (OR = 2.57, 95% CI: 0.99–6.61). Overall, total PUFAs (n-6 and n-3) were suggestive of a small protective effect (OR = 0.59, 95% CI: 0.31–1.09). No significant associations were found between other fatty acids and the risk of breast cancer. The study suggested evidence of an association between serum levels of SFAs and the risk of breast cancer in postmenopausal women. Neither individual n-3 fatty acids of marine origin, eicosapentaenoic acid (C20:5 n-3), and docosahexaenoic acid (C22:6 n-3), nor n-6 PUFAs were related to cancer risk in this study.

Introduction

Both migrant studies (1, 2) and experimental animal studies in rodents (3) suggest that differences in breast cancer rates are partly related to dietary fat intake and especially to the quantity and quality of fat ingested. Studies in rodents suggest that n-6 PUFAs[2] stimulate both mammary tumor growth and metastasis (4), whereas n-3 PUFAs, particularly those of marine origin (eicosapentaenoic acid, C20:5 n-3 and docosahexaenoic acid, C22:6 n-3) have a tumor-inhibiting effect (4, 5). SFAs have been associated with an increase in breast cancer risk in some experimental animal studies (4) and have suppressed the development of mammary tumors in others (6). However, supplementation with modest amounts of n-6 PUFA, particularly linoleic acid (C18:2 n-6), has been reported to suppress the inhibitory effect of SFA (7) and n-3 PUFA (8) during the promotion phase of chemically induced carcinogenesis, suggesting that dietary C18:2 n-6, rather than SFA or n-3 PUFA, is a more important modulator of mammary carcinogenesis. Results on the effect of MUFAs and especially oleic acid on mammary tumor development have been inconsistent (9).

In epidemiological studies in which questionnaires were used to assess fat intake, some case-control studies found a positive relationship between the risk of breast cancer and total fat intake (10–15) or saturated fat (14, 16–19). Dietary intake of monounsaturated fatty acids was shown to be positively related to breast cancer risk in a combined analysis of 12 case-control studies (20) and in a meta-analysis of 10 case-control studies (21), whereas dietary intake of PUFAs did not show any association with breast cancer risk (20, 21). Some cohort studies have also supported the finding of case-control studies on total fat (22–24), SFA (22, 25), MUFA (22, 23), and PUFA (26–28). However, no association between breast cancer risk and different types of fat was observed in statistical pooled analysis (29, 30) and in meta-analysis (21, 31) of cohort studies.

Studies involving biological measurement of dietary fat intake are scarce mainly because of the logistical difficulty of collecting and storing biological samples. The assessment of fat intake in these studies is based on the analysis of the fatty acid composition of adipose tissue, erythrocyte membrane, serum, or plasma. This methodology has the advantage of not being dependent on subjects' self-reported dietary habits, which can be affected by systematic and random measurement errors. As the half-life of fatty acids in adipose tissue is ~2 years (32), the

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[2] The abbreviations used are: PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; NYUWHS, New York University Women's Health Study; FAME, fatty acid methyl ester; RR, relative risk; CI, confidence interval; OR, odds ratio; IGF, insulin-like growth factor.

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Table 1 Characteristics of study subjects[a]

Variable	Premenopausal		Postmenopausal	
	Cases (n = 91)	Controls (n = 91)	Cases (n = 106)	Controls (n = 106)
Age at blood sampling	43.44 (4.67)	43.35 (4.66)	58.79 (3.45)	58.79 (3.45)
Age at menarche	12.36 (1.53)	12.47 (1.38)	12.42 (1.24)	12.61 (1.51)
Age at first full-term birth	25.75 (5.46)	24.14 (5.41)	25.78 (4.56)	25.49 (4.34)
Age at menopause			49.66 (5.62)	48.56 (5.91)
Height (cm)	163.42 (7.52)	163.6 (6.55)	162.17 (6.13)	161.44 (6.25)
Weight (kg)	64.34 (13.29)	66.14 (13.87)	69.85 (12.06)	67.20 (14.04)
Body mass index (kg/cm^2)	24.05 (4.27)	24.72 (5.02)	26.55 (4.32)	25.82 (5.19)
Nulliparous (%)	42.86	36.26	27.36	20.75
History of benign breast disease (%)	34.07	16.48	28.30	16.04
Family history of breast cancer (%)	34.07	19.78	22.64	19.81

[a] Mean (SD).

fatty acid composition of this tissue can provide precious information about long-term intake. s.c. fat aspiration, however, requires a local anesthetic and may be painful and time-consuming. Therefore, fatty acid fractions from blood samples are a more practical alternative. Triglyceride fatty acid fractions may depend on the type and amount of fat consumed during recent meals and are not the most appropriate markers of usual dietary habits. As the fatty acid composition of serum or plasma phospholipids reflects medium-term (weeks to months) intake of dietary fat (33), this blood fraction can be used as a biological marker of habitual availability and metabolism of fatty acids in large-scale epidemiological studies.

With the aim of elucidating the relationship between serum fatty acid profiles and breast cancer risk, we carried out a nested case-control study within the cohort of the NYUWHS. We analyzed the fatty acid composition of serum phospholipids of women with clinically identified breast cancer and their matched controls. We focused on 22 individual fatty acids belonging to the four major fatty acid families: SFAs; MUFAs; and n-6 and n-3 PUFAs. Individual fatty acids were expressed as the percentage of total fatty acids in serum phospholipids.

Materials and Methods

Subjects. Subjects were women ages 34–65 years who participated in a prospective cohort study on hormones, diet, and cancer, the NYUWHS between 1985 and 1991 (34, 35). They were classified as postmenopausal at entry if they had had no menstrual cycles during the 6 months preceding enrollment or if they had had a total bilateral oophorectomy. They completed self-administered questionnaires, including information on usual food consumption, lifestyle, anthropometric, and reproductive characteristics, and were asked to donate 30 ml of nonfasting peripheral venous blood at baseline and before breast examination. The times of last food intake and blood donation were recorded. Additional blood samples were drawn from approximately one-half of the participants at subsequent screening visits. After donation, the blood samples were kept at room temperature for 1 min, then at 4°C for 60 min to allow clot retraction, then centrifuged at 600 × g for 15 min. Serum obtained in this way was partitioned into 1-ml aliquots and stored at −80°C until laboratory analysis.

Study subjects were followed up to identify all cases of cancer occurring during the study period. Follow-up consisted of periodic direct contacts by mail, telephone, and record linkages with the state-wide tumor registries of New York, New Jersey, Connecticut, Florida, and with mortality databases. The vast majority of reported cancer cases were confirmed through an internal review of clinical and pathological documents. A capture-recapture analysis estimated that 95% of incident breast cancer cases in our cohort were identified (36). The last complete follow-up was carried out in December 1998. The time between recruitment and cancer diagnosis ranged from 0.6 to 8.9 years, with an average of 4.3 years (median, 4.3 years). Mean age at cancer diagnosis was 56 years (median, 57 years). Seventy-five percent of the case subjects were diagnosed 2.9 years after cohort recruitment, whereas 25% were diagnosed after 5.7 years.

Subjects diagnosed with breast cancer ≥6 months after cohort recruitment and before 1995 were included in this nested case-control study. Originally, 394 women (197 cases and 197 controls) were selected. Controls were cohort members free of cancer, randomly selected among those who matched a case by age at recruitment (±3 months), menopausal status at baseline (pre- or postmenopausal), date of baseline blood sampling (±3 months), and number of blood samplings before a case's date of diagnosis. If premenopausal, controls were also matched by phase and day of the menstrual cycle at the time of baseline blood collection. One control was identified for each case. Only the baseline blood samples were used for the analysis of serum fatty acids in this study.

Analysis of Fatty Acid Composition in Serum Samples. Samples were analyzed in the Unit of Nutrition and Cancer Laboratory at the International Agency for Research on Cancer (Lyon, France). Samples were identified by a code number and ordered randomly within a batch. Each batch included 8 subjects and 2 samples from a standard pool for quality control. Cases and their matched controls were analyzed in the same batch and on the same day.

Lipids were extracted from serum samples according to the method of Chajès *et al.* (37). Briefly, total lipids were extracted with 6 ml of chloroform-methanol 2:1 (v:v). Two phases were obtained after the addition of 1.5 ml of NaCl to the mixture. The chloroform layer, which contained total lipids, was transferred to a tube and evaporated to dryness under nitrogen. The lipid extract was dissolved in 200 μl of chloroform-methanol 2:1. Phospholipids were purified by adsorption chromatography on silica tubes and then converted to FAMEs using 25 μl of methyl-prep II.

FAMEs were separated on a gas chromatograph (Hewlett Packard, Palo Alto, CA) equipped with an on-column injector and a capillary column (length: 30 m, diameter: 0.32 mm; Supelco, Bellefonte, PA). The initial oven temperature was 65°C. It rose to 135°C at a rate of 5°C/min from 135 to 200°C at a rate of 2°C/min and from 200 to 220°C at a rate of 2°C/min.

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Table 2 Percentage ± (SD) of fatty acid composition of serum phospholipids in study subjects

Fatty acid (%)	Premenopausal		Postmenopausal	
	Cases (*n* = 91)	Controls (*n* = 91)	Cases (*n* = 106)	Controls (*n* = 106)
SFA				
14:0	0.2 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)
16:0	24.9 (1.5)	25.1 (1.6)	24.9 (1.6)	25 (1.3)
18:0	14.3 (1.0)	14.2 (1.2)	14.7 (1.2)	14.7 (1.0)
Total SFA[a]	40 (1.1)	40.1 (1.1)	40.4 (1.4)	40.6 (1.1)
MUFA				
16:1 n-7	0.5 (0.2)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)
18:1 n-9t	0.4 (0.2)	0.5 (0.8)	0.4 (0.8)	0.3 (0.1)
18:1 n-9c	8.6 (1.0)	8.7 (1.7)	8.5 (1.4)	8.7 (1.1)
18:1 n-7c	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)
Total MUFA[b]	11.4 (1.3)	11.7 (1.8)	11.5 (1.5)	11.5 (1.3)
n-6 PUFA				
18:2 n-6	24.3 (3.7)	24.3 (3.0)	23.6 (2.9)	23.4 (3.0)
18:3 n-6	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)
20:2 n-6	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)
20:3 n-6	3.1 (0.8)	3.1 (0.8)	3.2 (0.9)	3.2 (0.8)
20:4 n-6	13.1 (2.3)	12.8 (2.3)	12.7 (2.0)	12.7 (2.1)
22:4 n-6	0.5 (0.2)	0.5 (0.4)	0.4 (0.2)	0.4 (0.2)
22:5 n-6	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)
Total n-6[c]	41.4 (2.6)	41.1 (2.3)	40.4 (2.3)	40.2 (2.7)
n-3 PUFA				
18:3 n-3	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
20:5 n-3	0.9 (0.6)	0.9 (0.7)	1.1 (0.6)	1.1 (0.8)
22:5 n-3	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)
22:6 n-3	4.8 (1.8)	4.7 (1.6)	5.1 (1.6)	5.1 (1.7)
Total n-3[d]	6.8 (2.2)	6.7 (2.1)	7.4 (2.1)	7.4 (2.4)

[a] Included 14:0 + 15:0 + 16:0 + 17:0 + 18:0 + 20:0.
[b] Included 16:1 n-7c + 18:1 n-9c + 18:1 n-9t + 18:1 n-7c + 20:1 n-9.
[c] Included 18:2 n-6 + 18:3 n-6 + 20:2 n-6 + 20:3 n-6 + 20:4 n-6 + 22:4 n-6 + 22:5 n-6.
[d] Included 18:3 n-3 + 20:5 n-3 + 22:5 n-3 + 22:6 n-3.

The final temperature was then kept constant for 10 min. Helium was used as carrier gas at a flow rate of 1 ml/min, with N_2 as a make-up gas for the flame ionization detector.

FAMEs were identified by their equivalent chain length in comparison with standards (Sigma, St. Louis, MO). The relative amount for each fatty acid was expressed as the percentage of total area.

The between-day coefficients of variation were based on the analysis of two samples from a standard serum pool for each batch (55 batches). Coefficients of variation ($n = 55$) were 4.3% for 16:0, 3.0% for 18:0, 2.8% for 18:1 n-9c, 2.2% for 18:2 n-6, 4.7% for 20:5 n-3, and 4.9% for 22:6 n-3.

Statistical Analyses. The paired *t* test was used to compare anthropometric values (weight, height, body mass index), age at menarche, age at first full-term birth, and age at menopause of cases and controls.

Age at menarche was categorized in four levels (1 = younger than 12; 2 = 12; 3 = 13; and 4 = older than 13). Age at menopause was categorized in four levels (1 = younger than 48; 2 = 48–51; 3 = older than 51; and 4 = premenopausal women). Age at full-term birth was categorized in four levels (1 = younger than 23; 2 = 23–26; 3 = older than 26; and 4 = nulliparous women).

RRs and associated 95% CIs of exposure variables were estimated by ORs calculated by conditional logistic regression. Fatty acid values were first categorized into quartiles, which were computed according to the entire sample of women and modeled by dummy variables. The effect of known potential confounders was examined in conditional logistic regression models. RR estimates (OR) were adjusted by family history, age at first full-term birth, cholesterol, and history of treatment for benign breast conditions. These variables were systematically included in the model because they were consistently associated with breast cancer risk. Age at menarche and body mass index [body weight(kg)/height(m)^2] were not significantly associated with breast cancer and their inclusion in the model did not substantially change the effect of fatty acids on breast cancer risk. The statistical significance of these variables was assessed by the likelihood ratio test. The test for trend of main exposure was performed using variables on categorized scale (coded as 1, 2, 3, 4). Separate models were used for pre- and postmenopausal women to investigate possible different exposure/disease associations, in strength and direction, between the two groups.

Results

The study included 197 cases (91 pre- and 106 postmenopausal women) and 197 controls (91 pre- and 106 postmenopausal women). Table 1 shows the characteristics of subjects participating in the study: there were no significant differences between cases and controls in age at menarche, age at first full-term birth, age at menopause, and body mass index. The proportion of parous women was higher among controls (72%) than cases (65.5%). The adjusted RR for parous women compared with nulliparous women was 0.52 (95% CI: 0.28–0.97; $P = 0.04$). Family history of breast cancer as well as history of treatment for benign breast diseases were more frequent among cases (28 and 31%, respectively) than controls (20 and 16%, respectively). Family history was weakly related to breast cancer risk (RR = 1.57, 95% CI: 0.95–2.61; $P = 0.08$). Women who had previously undergone a biopsy for benign breast

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Table 3 Estimated RR (OR) of breast cancer and 95% CIs for quartiles of percentages of serum phospholipids fatty acid[a]

Fatty acids	Menopausal status	OR (95% CI)				
		Quartile			P for the overall categorical variable	P for trend with the score variable
		2nd	3rd	4th		
Saturates						
14:0	Pre[b]	0.48 (0.20–1.14)	1.27 (0.52–3.08)	2.22 (0.78–6.31)	0.07	0.14
	Post	0.59 (0.24–1.44)	0.72 (0.28–1.88)	0.57 (0.23–1.41)	0.62	0.37
	Total	0.59 (0.33–1.07)	0.97 (0.52–1.81)	0.91 (0.49–1.67)	0.27	0.86
16:0	Pre	1.36 (0.49–3.71)	0.53 (0.19–1.43)	1.20 (0.45–3.21)	0.21	0.87
	Post	1.85 (0.80–4.26)	2.07 (0.75–5.75)	2.57 (0.99–6.61)	0.26	0.07
	Total	1.57 (0.85–2.92)	1.01 (0.52–1.99)	1.64 (0.86–3.14)	0.20	0.27
18:0	Pre	1.01 (0.39–2.61)	1.27 (0.51–3.28)	2.31 (0.69–7.78)	0.53	0.19
	Post	1.62 (0.64–4.11)	0.88 (0.34–2.29)	1.01 (0.42–2.47)	0.59	0.65
	Total	1.24 (0.66–2.36)	1.04 (0.55–1.97)	1.18 (0.60–2.30)	0.91	0.79
Total SFA[c]	Pre	0.62 (0.24–1.71)	0.85 (0.33–2.14)	1.66 (0.56–4.89)	0.40	0.45
	Post	1.26 (0.49–3.21)	3.91 (1.41–10.87)	1.96 (0.73–5.25)	0.05	0.09
	Total	0.89 (0.46–1.70)	1.75 (0.92–3.34)	1.46 (0.74–2.83)	0.18	0.11
Monounsaturates						
16:1 n-7	Pre	1.31 (0.53–3.24)	1.36 (0.55–3.37)	1.07 (0.41–2.79)	0.91	0.77
	Post	0.96 (0.37–2.36)	1.11 (0.47–2.59)	1.27 (0.54–3.09)	0.92	0.53
	Total	1.09 (0.59–1.99)	1.25 (0.69–2.27)	1.16 (0.62–2.16)	0.90	0.53
18:1 n-9t	Pre	1.40 (0.47–4.18)	0.94 (0.31–2.88)	1.02 (0.36 (2.88)	0.85	0.80
	Post	0.67 (0.27–1.68)	1.07 (0.42–2.73)	0.36 (0.13–1.03)	0.14	0.13
	Total	1.01 (0.52–1.98)	1.08 (0.55–2.11)	0.66 (0.33–1.31)	0.41	0.25
18:1 n-9c	Pre	0.41 (0.16–1.06)	0.52 (0.18–1.52)	0.96 (0.37–2.45)	0.24	0.91
	Post	1.18 (0.49–2.82)	2.06 (0.84–5.05)	1.84 (0.72–4.71)	0.38	0.13
	Total	0.75 (0.41–1.39)	1.25 (0.66–2.37)	1.23 (0.65–2.32)	0.41	0.33
18:1 n-7c	Pre	1.12 (0.43–2.95)	0.55 (0.211.45)	0.63 (0.22–1.79)	0.54	0.31
	Post	0.98 (0.36–2.65)	1.09 (0.45–2.62)	0.72 (0.28–1.84)	0.81	0.57
	Total	1.00 (0.51–1.95)	0.85 (0.46–1.58)	0.74 (0.38–1.46)	0.81	0.36
Total MUFA[d]	Pre	0.44 (0.18–1.08)	0.57 (0.21–1.58)	1.13 (0.42–3.04)	0.18	0.82
	Post	1.01 (0.42–2.44)	1.55 (0.65–3.72)	1.38 (0.55–3.49)	0.71	0.37
	Total	0.71 (0.39–1.29)	1.02 (0.54–1.94)	1.15 (0.60–2.18)	0.43	0.45
PUFA n-6	Pre	1.23 (0.45–3.37)	1.25 (0.41–3.84)	1.11 (0.42–2.94)	0.97	0.93
18:2 n-6	Post	0.91 (0.40–0.36)	0.83 (0.36–1.88)	1.04 (0.40–2.67)	0.96	0.94
	Total	1.03 (0.55–1.92)	0.99 (0.51–1.90)	1.01 (0.52–1.95)	0.99	0.98
18:3 n-6	Pre	1.04 (0.46–2.33)	1.07 (0.39–2.97)	1.65 (0.57–4.78)	0.80	0.39
	Post	1.42 (0.54–3.72)	0.75 (0.29–1.92)	1.46 (0.54–3.96)	0.40	0.79
	Total	1.18 (0.65–2.15)	0.86 (0.44–1.66)	1.45 (0.73–2.89)	0.45	0.50
20:2n-6	Pre	1.71 (0.66–4.41)	0.76 (0.27–2.17)	0.94 (0.38–2.35)	0.39	0.51
	Post	0.74 (0.28–1.98)	1.15 (0.53–2.46)	0.71 (0.27–1.87)	0.69	0.83
	Total	1.24 (0.65–2.38)	1.02 (0.56–1.84)	0.82 (0.43–1.56)	0.68	0.47
20:3 n-6	Pre	2.17 (0.91–5.19)	1.01 (0.41–2.49)	1.90 (0.77–4.72)	0.18	0.40
	Post	0.87 (0.36–2.12)	1.69 (0.67–4.28)	1.21 (0.48–3.03)	0.45	0.34
	Total	1.25 (0.69–2.24)	1.29 (0.70–2.38)	1.44 (0.77–2.66)	0.71	0.27
20:4 n-6	Pre	0.69 (0.25–1.91)	1.68 (0.59–4.73)	0.62 (0.23–1.69)	0.18	0.68
	Post	0.78 (0.34–1.80)	0.61 (0.27–1.38)	0.89 (0.40–1.94)	0.67	0.64
	Total	0.79 (0.43–1.46)	0.99 (0.55–1.81)	0.81 (0.45–1.47)	0.80	0.66
22:4 n-6	Pre	1.66 (0.57–4.86)	1.95 (0.65–5.85)	1.86 (0.57–6.01)	0.69	0.38
	Post	1.76 (0.75–4.13)	1.02 (0.43–2.47)	0.87 (0.35–2.17)	0.46	0.63
	Total	1.53 (0.81–2.88)	1.32 (0.69–2.53)	1.17 (0.59–2.30)	0.59	0.81
22:5 n-6	Pre	1.17 (0.39–3.56)	1.45 (0.51–4.10)	1.52 (0.56–4.12)	0.83	0.37
	Post	1.60 (0.72–3.59)	1.76 (0.74–4.20)	1.28 (0.53–3.13)	0.57	0.49
	Total	1.39 (0.74–2.66)	1.58 (0.83–2.99)	1.43 (0.76–2.69)	0.55	0.22
Total n-6[e]	Pre	1.31 (0.46–3.77)	0.73 (0.27–1.98)	0.64 (0.22–1.86)	0.50	0.22
	Post	1.45 (0.65–3.25)	1.09 (0.49–2.41)	0.69 (0.28–1.73)	0.48	0.49
	Total	1.39 (0.75–2.58)	0.97 (0.53–1.78)	0.70 (0.36–1.36)	0.23	0.20
PUFA n-3	Pre	0.86 (0.35–2.10)	1.37 (0.54–3.46)	0.97 (0.41–2.26)	0.76	0.84
18:3 n-3	Post	1.46 (0.64–3.36)	0.86 (0.32–2.28)	0.64 (0.26–1.57)	0.35	0.23
	Total	1.14 (0.63–2.06)	1.14 (0.59–2.15)	0.80 (0.44–1.46)	0.65	0.48
20:5 n-3	Pre	1.09 (0.48–2.46)	0.56 (0.20–1.58)	0.82 (0.32–2.11)	0.67	0.46
	Post	0.86 (0.33–2.22)	1.14 (0.43–3.01)	0.91 (0.32–2.62)	0.90	0.99
	Total	0.95 (0.53–1.69)	0.87 (0.47–1.63)	0.85 (0.44–1.65)	0.96	0.61

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Table 3 Continued

Fatty acids	Menopausal status	OR (95% CI)				
		Quartile			*P* for the overall categorical variable	*P* for trend with the score variable
		2nd	3rd	4th		
22:5 n-3	Pre	1.33 (0.52–3.36)	0.66 (0.26–1.68)	1.20 (0.42–3.47)	0.54	0.70
	Post	0.69 (0.29–1.65)	0.44 (0.17–1.12)	0.82 (0.33–2.04)	0.29	0.65
	Total	0.97 (0.53–1.75)	0.62 (0.33–1.15)	1.05 (0.55–2.02)	0.30	0.73
22:6 n-3	Pre	0.48 (0.19–1.19)	0.40 (0.14–1.13)	0.83 (0.27–2.58)	0.25	0.51
	Post	1.21 (0.49–2.99)	1.23 (0.52–2.94)	0.67 (0.27–1.70)	0.47	0.41
	Total	0.76 (0.41–1.41)	0.79 (0.41–1.49)	0.70 (0.35–1.40)	0.76	0.49
Total n-3[f]	Pre	0.49 (0.20–1.21)	0.51 (0.19–1.39)	0.79 (0.29–2.18)	0.35	0.52
	Post	1.30 (0.52–3.27)	1.14 (0.44–2.95)	0.68 (0.26–1.74)	0.45	0.30
	Total	0.79 (0.43–1.44)	0.80 (0.41–1.56)	0.69 (0.35–1.34)	0.73	0.30
Total n-3and n-6	Pre	0.52 (0.18–1.47)	0.47 (0.17–1.26)	0.60 (0.24–1.54)	0.48	0.39
	Post	0.86 (0.39–1.87)	0.85 (0.34–2.16)	0.42 (0.17–1.08)	0.31	0.09
	Total	0.77 (0.42–1.41)	0.68 (0.36–1.30)	0.59 (0.31–1.09)	0.42	0.09
16:0/16:1 n-7	Pre	0.56 (0.20–1.57)	0.81 (0.31–2.13)	0.68 (0.26–1.79)	0.69	0.73
	Post	0.73 (0.32–1.69)	0.75 (0.34–1.66)	0.96 (0.39–2.33)	0.82	0.89
	Total	0.69 (0.37–1.28)	0.82 (0.45–1.49)	0.83 (0.44–1.55)	0.71	0.74
18:0/18:1 n-9c	Pre	0.55 (0.21–1.46)	1.34 (0.51–3.49)	1.29 (0.50–3.28)	0.38	0.43
	Post	1.49 (0.61–3.62)	1.07 (0.47–2.41)	0.60 (0.24–1.49)	0.32	0.25
	Total	0.98 (0.52–1.84)	1.09 (0.59–2.01)	0.85 (0.46–1.59)	0.88	0.72
PUFA/SFA	Pre	0.43 (0.15–1.25)	0.51 (0.19–1.30)	0.45 (0.17–1.23)	0.37	0.21
	Post	0.98 (0.44–2.21)	0.63 (0.28–1.43)	1.17 (0.49–2.76)	0.52	0.27
	Total	1.11 (0.62–2.00)	0.82 (0.45–1.51)	0.65 (0.34–1.22)	0.34	0.12

[a] OR adjusted for age at first full-term birth, family history of breast cancer, history of benign breast disease, and total cholesterol.
[b] Pre, premenopausal women; Post, postmenopausal women; Total, entire population (pre- + postmenopausal women).
[c] Included 14:0 + 15:0 + 16:0 + 17:0 + 18:0 + 20:0.
[d] Included 16:1 n-7c + 18:1 n-9c + 18:1 n-9t + 18:1 n-7c + 20:1 n-9.
[e] Included 18:2 n-6 + 18:3 n-6 + 20:2 n-6 + 20:3 n-6 + 20:4 n-6 + 22:4 n-6 + 22:5 n-6.
[f] Included 18:3 n-3 + 20:5 n-3 + 22:5 n-3 + 22:6 n-3.

disease presented a 2-fold increase in breast cancer risk (RR = 2.08, 95% CI: 1.3–3.54; *P* = 0.003).

Table 2 gives the fatty acid composition of serum phospholipids. The major fatty acids in serum were represented by palmitic acid (C16:0), linoleic acid (C18:2 n-6), oleic acid (C18:1 n-9c), and arachidonic acid (C20:4 n-6). The total PUFAs (n-3 and n-6 PUFA) represent >48% of serum fatty acids in cases as well as controls. Mean values of fatty acids expressed as a percentage of total fatty acids were not different between cases and controls.

The estimated RRs (OR) for the association between breast cancer and serum levels of different fatty acids are given in Table 3. Among individual SFAs, an increasing risk tendency was observed in the highest quartile for myristic acid (C14:0) in premenopausal women (OR = 2.22, 95% CI: 0.78–6.31; *P* = 0.07 for overall categorical variable and *P* = 0.14 for the score variable) and for palmitic acid (C16:0) in postmenopausal women (OR = 2.57, 95% CI: 0.99–6.61; *P* = 0.26 for overall categorical variable and 0.07 for the score variable). The percentage of total SFAs in serum phospholipids was positively and significantly associated with breast cancer risk after menopause (OR = 1.96, 95% CI: 0.73–5.25; *P* = 0.05 for overall categorical variable and 0.09 for the score variable).

No significant associations were found between individual or total MUFAs and breast cancer risk.

Concerning n-6 PUFAs, neither the essential fatty acid of this group, linoleic acid (C18:2 n-6), nor other long-chain n-6 fatty acids were associated with breast cancer risk.

Individual n-3 fatty acids of marine origin, eicosapentaenoic acid (C20:5 n-3) and docosahexaenoic acid (C22:6 n-3), or other individual or total n-3 fatty acids were not associated with the risk of breast cancer in this study. However, the results were suggestive of a small protective effect for total PUFAs n-6 and n-3 (OR = 0.58, 95% CI: 0.31–1.09).

Discussion

In this prospective study, we examined the fatty acid composition of phospholipids in serum of 394 subjects to determine the role of different types of fatty acids in the incidence of breast cancer.

Overall, we did not find an association between individual or total MUFA or PUFA and breast cancer risk. The only systematic finding was a significant positive association between serum SFA levels and breast cancer risk after menopause.

Our investigation was based on blood samples collected at baseline in a prospective cohort study. The major strength of this approach is that it is very unlikely that the fatty acid profile we measured could be influenced by the presence of undetected cancer. A study on reliability of fatty acid composition in human serum phospholipids in the NYUWHS cohort (38) showed that fatty acid levels in a single blood sample per subject have a good correlation with repeat measurements after a 2–3-year interval. The fatty acid composition of serum phospholipids can therefore be a useful tool in epidemiological studies. Some caution, however, is required for the extrapolation of our results because the metabolism modifies fatty acids absorbed with diet in a complex manner, mainly as elongation

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and desaturation. Thus, biological levels are influenced by dietary intake but are also correlated to endogenous metabolism.

We observed no evidence of a relationship between the levels of serum phospholipids, MUFAs, or PUFAs and the risk of breast cancer. Similar findings were reported by a cohort study (37), which also analyzed the fatty acid composition of serum phospholipids. A case-control study, also based on the analysis of serum phospholipids (39), found no association between MUFAs or n-3 PUFA. On the contrary, a tendency for a lower risk of breast cancer with an increasing proportion of total n-6 PUFA was observed. MUFAs were significantly associated with breast cancer risk in a cohort study (40) but not in a case-control study (41), which analyzed the fatty acid composition of phospholipids in erythrocyte membranes. No consistent patterns of association were observed for MUFA in case-control studies on s.c. adipose tissue (42) or breast adipose tissue (43, 44). PUFAs were inversely associated with breast cancer risk in a cohort study (40) based on the analysis of phospholipids in erythrocyte membranes but not in case-control studies (42–45) on adipose tissues.

The percentage of serum total SFAs was associated with breast cancer risk in postmenopausal women in the current study. Subjects in the third and fourth quartile for total SFAs had an OR of 3.91 and 1.96, respectively, compared with women in the lowest quartile.

The relationship between dietary fat intake and breast cancer risk was investigated by several other biomarker-based studies. Total SFAs were positively but not significantly correlated with incidence of breast cancer in the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer (46), an ecological study that analyzed the fatty acid composition of s.c. adipose tissue. Individual SFAs (palmitic acid, C16:0) were also associated with the risk of breast cancer in a nested case-control study carried out in northern Sweden, which also analyzed the fatty acid composition of serum phospholipids (37), although the results of case-control studies on serum phospholipids fatty acid (39), s.c. adipose tissue fatty acids (42), or adipose breast tissue fatty acids (44) did not support this finding. The lack of association in these studies might be related to selection biases. Indeed, the majority of these case-control studies used hospital-based controls, and the presence of another disease, even benign, may have modified fat metabolism and consequently influenced the results.

A combined analysis of 12 case-control studies (20), several other case-control studies (12, 14, 17–19), as well as two cohort studies (22, 25) have reported that SFA consumption was a risk factor for breast cancer. Our findings on SFAs were similar to those of a case-control study conducted by some of us (P. T., E. R.) in Italy (16). The latter was based on dietary intake questionnaire measurements and showed a 3-fold increase in risk for postmenopausal women in the highest quartile of SFA intake, although the association was not statistically significant for premenopausal subjects. However, a pooled analysis of 7 prospective studies failed to support the association between SFA intake and breast cancer (29).

It is not yet clear how SFA could enhance mammary carcinogenesis. One possibility is that fat may affect steroid hormone levels. High levels of SFA in the peripheral tissue could modulate the peripheral activity of estrogen through esterification with estradiol. Estradiol can be converted to estrogen fatty acid esters in the liver (47), uterus (48), placenta (49), and breast (50). Estradiol fatty acid esters are highly lipophilic and can be stored at relatively high concentration in fatty tissues (51). The mammary gland contains considerable amounts of fat, which can be used as a reservoir for the storage of these esters. The latter have long half-lives and can release the estradiol after the metabolic cleavage of fatty acid esters by esterase (52, 53). The steroid hormone pool obtained from the degradation of these hydrophobic esters could act as a promoter in breast cancer risk. The endogenous and/or exogenous factors, which can influence the synthesis, storage, and hydrolysis of estrogen fatty acid esters, are not known. Additional studies are needed to determine the exact role of these fatty acid esters in the etiology of breast cancer.

SFAs may also influence mammary tumorigenesis by increasing the risk of insulin resistance. The relation between blood fatty acid levels and insulinemia has been examined in few human studies. Serum insulin was positively associated with the percentage of serum SFAs in these studies (54, 55). Increasing the content of SFA within cell membranes in cultured cells has been associated with a decrease in membrane permeability, the number, and the sensitivity of insulin receptors (56, 57), which together may lead to insulin resistance and therefore to hyperinsulinemia. Chronic hyperinsulinemia has been shown to be associated with an increase in free IGF-I and a decrease in IGF-binding protein I. Epidemiological studies have suggested that an increased bioactive level of IGF-I (58) and a decreased serum level of IGF-binding protein I increase the risk of developing breast cancer. This phenomenon may act in synergy with high amounts of estradiol, stored in fatty acid esters, in promoting mammary carcinogenesis.

In summary, our results, in conjunction with some other epidemiological studies suggest that SFAs may be related to the risk of breast cancer after menopause. On the contrary, this study does not lend support to the hypothesis that plasma levels of n-3 fatty acids, either total or long-chain PUFAs of marine origin, are associated with reduced breast cancer risk. Additional epidemiological studies on biomarkers of fat intake are needed to clarify the role of different subtypes of dietary fat in breast cancer development.

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Mitra Saadatian-Elahi, Paolo Toniolo, Pietro Ferrari, et al.

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