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Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer

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Abstract We examined the association between fat intake and breast cancer incidence in the Nurses' Health Study II. We followed 88,804 women aged 26–45 years from 1991 to 2011 and documented incident breast cancers. Dietary fat, assessed by questionnaires in 1991, was examined in relation to total, premenopausal, and postmenopausal breast cancers. Multivariable-adjusted Cox proportional hazards models were used to estimate relative risk (RR) and 95 % confidence intervals (95 % CI). During 20 years of follow-up, 2,830 incident invasive breast cancer cases were diagnosed. Total fat intake was not associated with risk of breast cancer overall. After adjustment for demographic, anthropometric, lifestyle, and dietary factors, a positive association was observed between animal fat intake and breast cancer overall (RR for highest vs lowest quintile, 1.18; 95 % CI 1.04–1.33; $P_{trend} = 0.01$). A positive association with animal fat intake was also seen among premenopausal women, but not among postmenopausal women. Higher intakes of saturated fat and monounsaturated fat were each associated with modestly higher breast cancer risk among all women, and higher cholesterol intake was associated with higher premenopausal breast cancer risk. However, the associations of saturated fat, monounsaturated fat and animal fat, were attenuated and non-significant after adjustment for red meat intake. Intakes of other types of fat including vegetable fat, dairy fat, polyunsaturated fat, and trans fat were not associated with breast cancer risk. Our finding suggests a positive association between early adult intake of animal fat and breast cancer risk.

Keywords Fat intake · Animal fat · Breast cancer

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Introduction

The potential influence of a high fat diet on risk of breast cancer has received considerable attention, but results from prospective cohort studies have generally provided little support for this hypothesis [1–8]. In a recent randomized controlled trial in Canada, 10 years of reduction in dietary fat intake did not alter breast cancer risk in women with extensive mammographic density [9]. A lack of significant effect of a low fat diet was also seen in the Women's Health Initiative trial [10], but the low compliance with the dietary modification intervention makes interpreting the results more difficult [11]. However, most of the evidence has been based on diet during midlife and later. Animal fat intake during early adulthood was associated with an increased risk of breast cancer in premenopausal women in Nurses' Health Study II (NHSII) cohort [12]. The hypothesis that exposures between menarche and first pregnancy can be more important in breast cancer development has been supported by epidemiologic studies of women who survived the atomic bombing of Hiroshima and Nagasaki and women treated for Hodgkin's lymphoma; exposure to radiation in childhood and early adulthood was associated with subsequent risk of breast cancer, but exposure after age 30 was weakly associated with increased risk [13–15].

In a previous analysis of the NHSII with 8 years follow-up and with 714 incident invasive breast cancer cases [12], animal fat intake in early adulthood was associated with higher risk of premenopausal breast cancer. However, it was not clear whether this finding was due to early age at dietary assessment or the relatively young age of women at diagnosis of breast cancer. In this updated analysis with longer follow-up and almost four times the number of cases, we were able to examine dietary fat intake during early adult life in relation to both premenopausal and postmenopausal breast cancer. Furthermore, we investigated the association between fat intake and breast cancer according to hormone receptor status.

Subjects and methods

Study population

The NHSII is a prospective cohort study established in 1989 with a total of 116,430 female registered nurses aged 24–43 years. For this analysis, we started follow-up in 1991, when participants were first asked to complete the food frequency questionnaire (FFQ). The 95,452 women returned the 1991 FFQ. Participants were excluded if they were postmenopausal in 1991, had reported a prior diagnosis of cancer (except non-melanoma skin cancer), diabetes, coronary heart disease, or stroke before returning the 1991 questionnaire, had missing information on age or had an implausible total energy intake (<600 or >3,500 kcal/day). After exclusions, data from 88,804 women were available for the analysis. The follow-up rate was 95 % of total potential person-years of follow-up through 2011. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health (Boston, MA, United States).

Dietary assessment

As part of the ongoing NHSII study, in 1991, 1995, 1999, 2003, and 2007, participants completed a semi-quantitative FFQ with ~130 items about usual dietary intake and alcohol consumption during the previous year (publicly available at http://www.channing.harvard.edu/nhs/?page_id=246). Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food or beverage by the nutrient content of the specified portion size and then summing across all items. The questionnaire included information about specific types of margarine and types of fat used for baking and frying; this information was incorporated in the nutrient calculations. Nutrient values in foods were obtained from the US Department of Agriculture, food manufacturers, independent academic sources, and our own fatty acid analyses of commonly used margarines, cooking oils, and baked foods [16–18]. The food composition database was updated every 4 years, including updated fatty acid analyses, to account for changes in the food supply. The percentage of energy from each type of fat and protein was calculated by dividing energy intake from each fat or protein by total energy intake. Cholesterol intake was expressed as mg/1,000 kcal.

The reproducibility and validity of intakes of fat and individual fat-contributing foods by FFQ have been evaluated elsewhere [19–22]. In 92 participants in Nurse's Health Study cohort, the correlations were examined between nutrients measured by the mean of three FFQ's and mean of diet records obtained 6 years apart, which provides an assessment of long-term intake. The correlations for energy-adjusted intakes, de-attenuated for variation in the diet records, were 0.83 with total fat and 0.95 for saturated fat.

Documentation of breast cancer

Biennial follow-up questionnaires were used to ascertain newly incident breast cancers. Deaths were reported through family members and the postal service in response to the follow-up questionnaires or identified through annual review of the National Death Index. We asked all women who reported breast cancer (or next of kin for those who had died) for confirmation of the diagnosis and for permission to review pathology reports and hospital record. Because of high confirmation rate (99 %) by medical record review, diagnoses confirmed by participants with missing medical record information were included in the analyses. Cases of carcinoma in situ were excluded from the analyses. Estrogen (ER) and progesterone (PR) receptor status of the breast cancer were abstracted from pathology reports.

Assessment of other variables

Data on potential risk factors for breast cancer were obtained from the biennial NHSII questionnaires including age, height, weight, family history of breast cancer, smoking, race, menopausal status, postmenopausal hormone use, and oral contraceptive use. Women were defined as premenopausal if they still had menstrual periods or had hysterectomy with at least one ovary remaining and were younger than 46 years (for smokers) or younger than 48 years (for nonsmokers). Women were defined as postmenopausal if they reported permanent cessation of menstrual periods or had bilateral oophorectomy surgery. Women who had unknown menopausal status or had hysterectomy without bilateral oophorectomy were considered postmenopausal if they were 54 years or older (for smokers) or 56 years or older (for nonsmokers) [23].

Statistical analysis

Person-year was calculated from the date of return of the 1991 questionnaire until the date of breast cancer diagnosis, death, or end of follow-up period (June 1, 2011), whichever came first. The primary analysis used the 1991 baseline diet as this represents diet earliest in adult life. Participants were divided into quintile categories according to their fat or food group intake. Cox proportional hazards models, stratified by age in months and follow-up cycle, were used to estimate relative risk (RR) and 95 % confidence intervals (95 % CI). Multivariable models adjusted for several breast cancer risk factors, including race, family history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, body mass index (BMI), age at menarche, parity and age at first birth, oral contraceptive use, and intakes of alcohol, energy and protein, and, for postmenopausal women, age at menopause and hormone use. For all women, we additionally adjusted for menopausal status. All variables except race, height and age at menarche were updated from follow-up questionnaires. Because fat intake may increase risk of breast cancer over a long period of time, for a sensitivity analysis, we also calculated premenopausal cumulative averaged intakes of fat using the 1991, 1995, 1999, 2003, and 2007 dietary data, stopping updating at menopause. SAS version 9.3 (SAS Institute, Inc., Cary NC, USA) was used for all analyses. The median value for each quintile was used for tests for trend for each category of fat intake as a continuous variable. We examined the interaction between total, animal and vegetable fat intakes and established breast cancer risk factors by including a cross-product interaction term between risk factors and intake of total, animal and vegetable fat in the multivariable model. P values for the tests of interactions were calculated by using likelihood ratio test with one degree of freedom. To examine differential associations of intakes of total fat, animal fat and vegetable fat with breast cancer risk by hormone receptor status, we used Cox proportional cause-specific hazards regression model with a duplication method for competing risk data [24]. This method permits estimation of separate associations of fat intake with both ER and PR receptors positive (ER+/PR+) and receptors negative (ER−/PR−), and tests whether dietary fat intake has statistically different regression coefficients for different tumor subtypes. All P values were two-sided.

Results

During 1,725,439 person-years of follow-up of 88,804 women, a total of 2,830 incident cases of invasive breast cancer (1,511 premenopausal breast cancers, 918 postmenopausal breast cancers, and 401 cases with uncertain menopausal status) were identified. The mean age of participants in 1991 was 36.4 years (range 26-45). Table 1 shows age-standardized distribution of risk factors for breast cancer according to quintiles of animal fat intake in 1991. Women who consumed a higher amount of animal fat were more likely to smoke, to have 3 children or more, to have lower age at first birth, and to have a larger BMI than women with a lower intake. Women who consumed a higher amount of animal fat were also less likely to drink alcohol, and less likely to have a history of benign breast disease, than women with a lower intake.

Among all women, total fat intake was non-significantly associated with breast cancer risk in multivariable analysis (RR 1.07; 95 % CI 0.95–1.21; $P_{\text{trend}} = 0.10$; for highest vs lowest quintile; Table 2). In both the age-adjusted and multivariable analyses, intake of total fat in 1991 was not significantly associated with risk of either premenopausal or postmenopausal breast cancer. In multivariable analysis, higher intake of animal fat was significantly associated with higher risk of breast cancer overall (RR for highest vs lowest quintile, 1.18; 95 % CI 1.04–1.33; $P_{\text{trend}} = 0.01$). Among premenopausal women, we also observed a positive association between animal fat and breast cancer incidence (RR for highest vs lowest quintile, 1.21; 95 % CI 1.02–1.44; $P_{\text{trend}} = 0.03$). Further adjustment for vegetable fat intake did not alter the results (RR for highest vs. lowest quintile, 1.17; 95 % CI 1.03–1.33; $P_{\text{trend}} = 0.01$ for all women and 1.21; 95 % CI 1.02–1.44; $P_{\text{trend}} = 0.03$ for premenopausal women). However, after adjustment for red meat intake, these associations were no longer statistically significant (RR for highest vs. lowest quintile, 1.10; 95 % CI 0.94–1.28, $P_{\text{trend}} = 0.25$ among all women, and RR for highest vs lowest quintile, 1.20; 95 % CI 0.98–1.49; $P_{\text{trend}} = 0.10$ among premenopausal women). In a sensitivity analysis using the cumulative average of premenopausal intake, there was a significant association between animal fat and risk of premenopausal breast cancer (RR, 1[reference], 1.11, 1.13, 1.22, and 1.21; $P_{\text{trend}} = 0.02$).

Table 1 Age-standardized distribution of potential risk factors for breast cancer according to animal fat intake in 1991 in women enrolled in Nurses' Health Study II

	Animal fat intake quintile				
	Q1 ($n = 17{,}760$)	Q2 ($n = 17{,}761$)	Q3 ($n = 17{,}761$)	Q4 ($n = 17{,}761$)	Q5 ($n = 17{,}761$)
Mean ± SD					
Age (years)	36.4 ± 4.6	36.4 ± 4.6	36.4 ± 4.6	36.4 ± 4.6	36.4 ± 4.6
Animal fat intake (% energy)	11.3 ± 2.2	15.1 ± 0.7	17.3 ± 0.6	19.6 ± 0.8	24.1 ± 2.8
Body mass index (kg/m^2)	23.3 ± 4.5	24.2 ± 4.9	24.6 ± 5.1	25.0 ± 5.4	25.5 ± 5.9
Total energy intake (kcal)	1,794 ± 564	1,819 ± 542	1,801 ± 538	1,791 ± 543	1,750 ± 550
Alcohol consumption (g/day)	3.7 ± 7.3	3.3 ± 6.3	3.0 ± 5.7	3.0 ± 5.7	2.6 ± 5.2
Age at first birth (years)	26.2 ± 4.3	26.0 ± 4.1	25.9 ± 4.1	25.7 ± 4.1	25.5 ± 4.1
%					
Current smokers	9	10	11	13	16
Current oral contraceptive use	12	11	11	11	11
History of benign breast disease	34	34	33	33	32
Family history of breast cancer in mother or sisters	16	15	15	15	15
Parity ≥3	16	20	22	23	22
Age at menarche <12 years	24	25	24	24	25

Cumulative average of premenopausal intake of animal fat was modestly associated with breast cancer among all women (RR for highest vs lowest quintile, 1.12; 95 % CI 0.99–1.27; $P_{trend} = 0.02$). For vegetable fat and dairy fat neither baseline intakes nor cumulative average of premenopausal intakes was associated with risk of either premenopausal or postmenopausal breast cancer.

Higher intakes of saturated fat and monounsaturated fat were each associated with modestly higher risk of breast cancer among all women (comparing the highest vs lowest quintiles RR 1.11; 95 % CI 0.99–1.25; $P_{trend} = 0.04$ for saturated fat, and RR 1.13; 95 % CI 1.00–1.27; $P_{trend} = 0.03$ for monounsaturated fat) (Table 3). However, after adjustment for red meat intake, these associations were no longer statistically significant (comparing the highest vs lowest quintiles RR 1.05; 95 % CI 0.92–1.20; $P_{trend} = 0.39$ for saturated fat, and RR 1.06; 95 % CI 0.92–1.21, $P_{trend} = 0.40$ for monounsaturated fat). Intake of cholesterol was associated with higher risk of premenopausal breast cancer (comparing the highest vs lowest quintiles RR 1.32; 95 % CI 1.03–1.70; $P_{trend} = 0.03$), but this association was attenuated after accounting for intake of red meat (comparing the highest vs lowest quintiles RR 1.28; 95 % CI 0.99–1.66; $P_{trend} = 0.048$). Intakes of polyunsaturated fat, trans-unsaturated fat, and long-chain omega-3 fatty acids were not significant predictors of either premenopausal or postmenopausal breast cancer.

We also evaluated the associations using multivariable nutrient density model approach [25]. We included simultaneously total energy intake, and percent of energy intake from animal fat and vegetable fat (or saturated fat, monounsaturated fat and polyunsaturated fat), alcohol and protein in the multivariable model. We found that substitution of 5 % energy intake from animal fat for an equivalent energy intake from carbohydrate was associated with higher risk of breast cancer among all women (RR 1.06 for an increment of 5 % energy; 95 % CI 1.01–1.10). Substituting animal fat intake for an equivalent energy from protein or vegetable fat and also substituting saturated fat for monounsaturated or polyunsaturated fat were not associated with increasing risk of breast cancer before or after menopause (data not shown).

Information on ER receptor status was available for 81 % ($n = 2{,}306$) and PR receptor status for 80 % ($n = 2{,}275$) of the breast cancer cases. Table 4 presents the associations between total, animal and vegetable fat and breast cancer according to hormone receptor status; data are presented for tumors with both ER and PR positive receptors (ER+/PR+) and for both negative receptors (ER−/PR−) as those with discordant receptor status were too few for analysis. We did not find any significant heterogeneity between tumors characterized by receptor status for total fat, animal fat or vegetable fat intakes in either premenopausal or postmenopausal breast cancer (Table 4).

We also examined whether the association between intakes of total, animal and vegetable fats and breast cancer risk differed by levels of breast cancer risk factors including family history of breast cancer (yes/no), BMI (<25/≥25 kg/m^2), oral contraceptive use (never/past/current), history of benign breast disease (yes/no), alcohol

Table 2 RR and 95 % CI for breast cancer according to quintile of fat intake in 1991 in women

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Total fat						
All women						
Median intake, % energy	24.5	28.7	31.5	34.4	38.6	
No. of cases/person-years	554/344,945	551/345,086	562/345,109	602/345,174	561/345,125	
Age-adjusted RR (95 % CI)	1	1.00 (0.89-1.13)	1.01 (0.90–1.14)	1.07 (0.95–1.20)	1.00 (0.88–1.12)	0.72
Multivariable RR (95 % CI)	1	1.02 (0.91–1.15)	1.04 (0.92–1.17)	1.13 (1.00–1.27)	1.07 (0.95–1.21)	0.10
Premenopausal women						
Median intake, % energy	24.5	28.6	31.4	34.3	38.5	
No. of cases/person-years	291/214,709	312/214,996	301/214,922	315/215,180	292/215,194	
Age-adjusted RR (95 % CI)	1	1.08 (0.92–1.26)	1.03 (0.87–1.21)	1.06 (0.90–1.25)	0.98 (0.84–1.16)	0.81
Multivariable RR (95 % CI)	1	1.12 (0.95–1.31)	1.07 (0.91–1.26)	1.13 (0.96–1.33)	1.07 (0.91–1.26)	0.40
Postmenopausal women						
Median intake, % energy	24.6	28.8	31.8	34.7	39.0	
No. of cases/person-years	198/86,004	153/86,324	186/86,135	194/85,958	187/85,916	
Age-adjusted RR (95 % CI)	1	0.81 (0.65–1.00)	0.96 (0.79–1.18)	1.00 (0.82–1.22)	0.98 (0.80–1.20)	0.61
Multivariable RR (95 % CI)	1	0.82 (0.66–1.01)	0.98 (0.80–1.20)	1.03 (0.84–1.26)	1.02 (0.83–1.26)	0.34
Animal fat						
All women						
Median intake, % energy	11.9	15.1	17.2	19.6	23.3	
No. of cases/person-years	569/344,929	543/345,087	592/345,119	544/345,184	582/345,121	
Age-adjusted RR (95 % CI)	1	0.98 (0.87–1.10)	1.07 (0.96–1.21)	0.98 (0.87–1.10)	1.06 (0.94–1.19)	0.38
Multivariable RR (95 % CI)	1	1.01 (0.90–1.14)	1.14 (1.01–1.29)	1.06 (0.93–1.20)	1.18 (1.04–1.33)	0.01
Premenopausal women						
Median intake, % energy	12.0	15.1	17.2	19.5	23.2	
No. of cases/person-years	299/214,651	295/215,052	313/214,995	292/215,162	312/215,141	
Age-adjusted RR (95 % CI)	1	1.00 (0.85–1.17)	1.08 (0.92–1.26)	1.00 (0.85–1.17)	1.07 (0.92–1.26)	0.42
Multivariable RR (95 % CI)	1	1.06 (0.90–1.25)	1.18 (1.00–1.39)	1.10 (0.93–1.30)	1.21 (1.02–1.44)	0.03
Postmenopausal women						
Median intake, % energy	11.9	15.0	17.3	19.6	23.4	
No. of cases/person-years	196/85,996	176/86,017	193/86,155	178/86,053	175/86,116	
Age-adjusted RR (95 % CI)	1	0.92 (0.75–1.13)	1.01 (0.83–1.23)	0.95 (0.77–1.16)	0.94 (0.77–1.16)	0.67
Multivariable RR (95 % CI)	1	0.95 (0.77–1.17)	1.05 (0.85–1.29)	0.99 (0.80–1.23)	1.03 (0.83–1.29)	0.68
Vegetable fat						
All women						
Median intake, % energy	9.3	11.8	13.8	15.8	19.2	
No. of cases/person-years	544/345,085	543/345,151	583/345,082	596/345,037	564/345,084	
Age-adjusted RR (95 % CI)	1	0.99 (0.88–1.12)	1.05 (0.93–1.18)	1.06 (0.94–1.19)	0.98 (0.87–1.10)	0.94
Multivariable RR (95 % CI)	1	0.99 (0.88–1.11)	1.05 (0.93–1.18)	1.06 (0.94–1.20)	0.97 (0.86–1.10)	0.96
Premenopausal women						
Median intake, % energy	9.3	11.8	13.7	15.7	19.1	
No. of cases/person-years	301/214,986	289/214,934	314/214,957	310/215,058	297/215,066	
Age-adjusted RR (95 % CI)	1	0.95 (0.80–1.11)	1.02 (0.87–1.19)	0.98 (0.84–1.15)	0.92 (0.79–1.08)	0.44
Multivariable RR (95 % CI)	1	0.95 (0.81–1.12)	1.03 (0.88–1.21)	1.00 (0.85–1.18)	0.93 (0.78–1.10)	0.51
Postmenopausal women						
Median intake, % energy	9.4	12.0	14.0	16.1	19.5	
No. of cases/person-years	169/86,144	168/86,176	187/86,073	199/86,071	195/85,874	
Age-adjusted RR (95 % CI)	1	0.99 (0.80–1.23)	1.11 (0.90–1.37)	1.17 (0.95–1.44)	1.12 (0.91–1.38)	0.12

Table 2 continued

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Multivariable RR (95 % CI)	1	0.99 (0.79–1.22)	1.09 (0.88–1.35)	1.15 (0.93–1.42)	1.11 (0.89–1.38)	0.19
Dairy fat						
All women						
Median intake, % energy	3.6	5.3	6.5	8.0	10.6	
No. of cases/person-years	571/344,934	580/345,051	570/345,114	563/345,179	546/345,161	
Age-adjusted RR (95 % CI)	1	1.06 (0.94–1.19)	1.06 (0.94–1.19)	1.07 (0.95–1.21)	1.07 (0.95–1.20)	0.29
Multivariable RR (95 % CI)	1	1.04 (0.93–1.17)	1.05 (0.93–1.18)	1.04 (0.93–1.17)	1.04 (0.92–1.17)	0.59
Premenopausal women						
Median intake, % energy	3.8	5.4	6.6	8.1	10.7	
No. of cases/person-years	332/215,027	294/215,003	306/214,988	291/215,063	288/214,920	
Age-adjusted RR (95 % CI)	1	0.92 (0.79–1.08)	0.98 (0.84–1.14)	0.96 (0.82–1.12)	0.98 (0.84–1.15)	0.99
Multivariable RR (95 % CI)	1	0.93 (0.79–1.08)	0.99 (0.84–1.16)	0.96 (0.82–1.13)	0.96 (0.82–1.13)	0.83
Postmenopausal women						
Median intake, % energy	3.4	5.1	6.3	7.7	10.4	
No. of cases/person-years	172/85,978	190/86,060	198/86,012	187/86,106	171/86,182	
Age-adjusted RR (95 % CI)	1	1.15 (0.94–1.42)	1.19 (0.96–1.46)	1.13 (0.92–1.40)	1.06 (0.86–1.31)	0.80
Multivariable RR (95 % CI)	1	1.15 (0.93–1.41)	1.18 (0.96–1.46)	1.12 (0.91–1.38)	1.06 (0.85–1.31)	0.84

P_{trend} calculated with median intake of each variable in each quintile as a continuous variable

Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white/non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 in.), BMI (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0 kg/m^2), age at menarche (<12, 12, 13, ≥14 yr), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 yr, parity ≤2 and age at first birth 25 to <30 yr, parity ≤2 and age at first birth ≥30 yr, parity 3–4 and age at first birth <25 yr, parity 3–4 and age at first birth 25 to <30 yr, parity 3–4 and age at first birth ≥30 yr, parity ≥5 and age at first birth <25 yr, parity ≥5 and age at first birth ≥25 yr), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy (quintile), and percentage of energy from protein (quintile). Among postmenopausal women, we also adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr). Among all women, we also adjusted for menopausal status (premenopausal, postmenopausal, dubious), hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (premenopause, unknown menopause, <45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr)

intake (never/<5/≥5 g/day), age at first birth (<30/≥30 years), and hormone use (never/past/current). Among all women, the association between animal fat intake and breast cancer risk was modified by BMI (*P* for interaction = 0.02). In normal weight women (BMI <25 kg/m^2), higher intake of animal fat was significantly associated with higher incidence of breast cancer (for each 5 % increase in energy from animal fat: RR 1.10; 95 % CI 1.03–1.17). But among overweight and obese women (BMI ≥25 kg/m^2), there was no significant association (for each 5 % increase in energy from animal fat: RR 1.00; 95 % CI 0.94–1.07). In women with alcohol intake of ≥5 g/day, higher intake of total fat was significantly associated with higher incidence of breast cancer (for each 5 % increase in energy from total fat; RR 1.11; 95 % CI 1.02–1.20; *P* for interaction = 0.02). In addition, higher intake of total fat was significantly associated with higher risk of breast cancer among women with history of benign breast disease (for each 5 % increase in energy from total fat: RR 1.06; 95 % CI 1.01–1.10; *P* for interaction = 0.02). Such association was not observed in women without history of benign breast disease. Moreover, in premenopausal women, the association between vegetable fat and breast cancer was modified by family history of breast cancer (*P* for interaction = 0.002). Higher intake of vegetable fat was associated with lower risk of breast cancer in women without family history of breast cancer (for each 5 % increase in energy from vegetable fat; RR 0.92; 95 % CI 0.85–1.00). Higher intake of animal fat was also associated with higher risk of premenopausal breast cancer in women with age at first birth ≥30 years (for each 5 % increase in energy from animal fat; RR 1.17; 95 % CI 1.03–1.32; *P* for interaction = 0.008).

Discussion

In this prospective cohort study, we assessed the relation of dietary fat intakes and breast cancer diagnosed before and

Table 3 RR and 95 % CI for breast cancer according to quintile of specific types of fat intake in 1991 in women

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Saturated fat						
All women						
Median intake, % energy	8.3	10.0	11.1	12.3	14.2	
No. of cases/person-years	567/344,940	580/345,029	535/345,219	589/345,150	559/345,102	
Age-adjusted RR (95 % CI)	1	1.04 (0.92–1.17)	0.98 (0.87–1.10)	1.08 (0.96–1.22)	1.04 (0.92–1.16)	0.43
Multivariable RR (95 % CI)	1	1.06 (0.94–1.19)	1.01 (0.89–1.14)	1.14 (1.01–1.28)	1.11 (0.99–1.25)	0.04
Premenopausal women						
Median intake, % energy	8.3	10.0	11.2	12.3	14.2	
No. of cases/person-years	308/214,730	334/214,983	269/215,019	307/215,189	293/215,079	
Age-adjusted RR (95 % CI)	1	1.10 (0.94–1.28)	0.90 (0.77–1.07)	1.03 (0.88–1.21)	1.01 (0.86–1.18)	0.84
Multivariable RR (95 % CI)	1	1.15 (0.98–1.34)	0.96 (0.81–1.13)	1.11 (0.94–1.30)	1.10 (0.93–1.29)	0.40
Postmenopausal women						
Median intake, % energy	8.2	9.9	11.1	12.3	14.2	
No. of cases/person-years	186/85,930	173/86,178	188/86,130	199/86,008	172/86,092	
Age-adjusted RR (95 % CI)	1	0.95 (0.77–1.17)	1.04 (0.85–1.28)	1.12 (0.92–1.37)	0.98 (0.79–1.20)	0.69
Multivariable RR (95 % CI)	1	0.95 (0.77–1.18)	1.06 (0.86–1.31)	1.15 (0.94–1.41)	1.03 (0.83–1.27)	0.38
Mono-unsaturated fat						
All women						
Median intake, % energy	8.9	10.7	11.9	13.2	15.0	
No. of cases/person-years	538/344,984	584/345,045	516/345,213	610/345,138	582/345,059	
Age-adjusted RR (95 % CI)	1	1.09 (0.97–1.22)	0.95 (0.84–1.07)	1.11 (0.99–1.25)	1.05 (0.93–1.18)	0.40
Multivariable RR (95 % CI)	1	1.11 (0.98–1.25)	0.98 (0.86–1.10)	1.17 (1.04–1.32)	1.13 (1.00–1.27)	0.03
Premenopausal women						
Median intake, % energy	8.9	10.6	11.9	13.1	15.0	
No. of cases/person-years	286/214,725	322/214,949	272/215,002	336/215,105	295/215,219	
Age-adjusted RR (95 % CI)	1	1.12 (0.96–1.32)	0.94 (0.79–1.10)	1.15 (0.98–1.35)	0.99 (0.84–1.17)	0.98
Multivariable RR (95 % CI)	1	1.16 (0.99–1.36)	0.97 (0.82–1.15)	1.22 (1.04–1.43)	1.08 (0.91–1.27)	0.29
Postmenopausal women						
Median intake, % energy	8.9	10.8	12.1	13.4	15.2	
No. of cases/person-years	187/86,051	164/86,252	178/86,054	194/86,044	195/85,936	
Age-adjusted RR (95 % CI)	1	0.91 (0.74–1.12)	0.97 (0.79–1.19)	1.06 (0.87–1.30)	1.07 (0.87–1.31)	0.25
Multivariable RR (95 % CI)	1	0.92 (0.74–1.13)	0.98 (0.79–1.20)	1.09 (0.89–1.34)	1.12 (0.91–1.37)	0.11
Poly-unsaturated fat						
All women						
Median intake, % energy	4.1	4.9	5.5	6.2	7.3	
No. of cases/person-years	551/344,983	548/345,101	564/345,124	598/345,017	569/345,215	
Age-adjusted RR (95 % CI)	1	0.97 (0.86–1.09)	0.98 (0.87–1.10)	1.02 (0.90–1.14)	0.94 (0.83–1.05)	0.41
Multivariable RR (95 % CI)	1	0.97 (0.86–1.10)	0.99 (0.88–1.11)	1.02 (0.90–1.14)	0.95 (0.84–1.07)	0.54
Premenopausal women						
Median intake, % energy	4.1	4.9	5.5	6.1	7.3	
No. of cases/person-years	297/214,879	284/214,794	302/215,105	314/215,060	314/215,162	
Age-adjusted RR (95 % CI)	1	0.93 (0.79–1.10)	0.97 (0.82–1.14)	0.98 (0.84–1.15)	0.95 (0.81–1.11)	0.73
Multivariable RR (95 % CI)	1	0.94 (0.80–1.11)	0.99 (0.84–1.16)	1.00 (0.85–1.17)	0.98 (0.83–1.15)	0.99
Postmenopausal women						
Median intake, % energy	4.1	5.0	5.6	6.3	7.5	
No. of cases/person-years	168/86,078	181/86,232	194/86,117	206/86,065	169/85,845	
Age-adjusted RR (95 % CI)	1	1.07 (0.87–1.32)	1.14 (0.93–1.40)	1.18 (0.96–1.45)	0.96 (0.78–1.20)	0.90

Table 3 continued

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Multivariable RR (95 % CI)	1	1.06 (0.86–1.31)	1.14 (0.92–1.40)	1.17 (0.95–1.44)	0.96 (0.78–1.19)	0.88
EPA and DHA*, from food and supplement						
All women						
Median intake, % energy	0.03	0.05	0.08	0.12	0.20	
No. of cases/person-years	541/345,073	536/345,076	597/345,085	537/345,151	619/345,056	
Age-adjusted RR (95 % CI)	1	0.98 (0.87–1.11)	1.08 (0.96–1.21)	0.95 (0.84–1.07)	1.06 (0.95–1.19)	0.40
Multivariable RR (95 % CI)	1	0.98 (0.86–1.10)	1.07 (0.95–1.21)	0.92 (0.81–1.05)	1.03 (0.90–1.17)	0.91
Premenopausal women						
Median intake, % energy	0.03	0.05	0.08	0.12	0.20	
No. of cases/person-years	292/214,866	269/215,102	312/215,032	300/215,079	338/214,922	
Age-adjusted RR (95 % CI)	1	0.90 (0.76–1.07)	1.02 (0.87–1.20)	0.97 (0.82–1.14)	1.06 (0.91–1.24)	0.21
Multivariable RR (95 % CI)	1	0.90 (0.76–1.07)	1.02 (0.86–1.21)	0.93 (0.79–1.11)	1.02 (0.85–1.21)	0.64
Postmenopausal women						
Median intake, % energy	0.03	0.05	0.08	0.13	0.21	
No. of cases/person-years	180/86,187	178/86,158	191/86,015	165/86,015	204/85,962	
Age-adjusted RR (95 % CI)	1	0.99 (0.80–1.22)	1.06 (0.86–1.30)	0.90 (0.72–1.11)	1.09 (0.89–1.33)	0.51
Multivariable RR (95 % CI)	1	0.98 (0.80–1.22)	1.08 (0.87–1.33)	0.90 (0.72–1.13)	1.12 (0.89–1.40)	0.42
Trans-unsaturated fat						
All women						
Median intake, % energy	0.95	1.26	1.55	1.88	2.44	
No. of cases/person-years	589/344,966	550/345,111	557/345,117	582/345,126	552/345,120	
Age-adjusted RR (95 % CI)	1	0.94 (0.84–1.06)	0.96 (0.85–1.07)	1.01 (0.90–1.13)	0.95 (0.85–1.07)	0.78
Multivariable RR (95 % CI)	1	0.97 (0.86–1.09)	1.00 (0.89–1.13)	1.06 (0.94–1.20)	1.02 (0.91–1.16)	0.36
Premenopausal women						
Median intake, % energy	0.95	1.26	1.55	1.88	2.43	
No. of cases/person-years	328/214,755	297/214,962	322/215,104	287/215,024	277/215,155	
Age-adjusted RR (95 % CI)	1	0.91 (0.78–1.06)	0.99 (0.85–1.16)	0.90 (0.77–1.05)	0.86 (0.73–1.01)	0.08
Multivariable RR (95 % CI)	1	0.95 (0.81–1.12)	1.05 (0.90–1.23)	0.96 (0.82–1.13)	0.93 (0.79–1.10)	0.42
Postmenopausal women						
Median intake, % energy	0.94	1.26	1.55	1.89	2.45	
No. of cases/person-years	188/85,997	176/86,192	166/86,083	204/86,047	184/86,018	
Age-adjusted RR (95 % CI)	1	0.95 (0.77–1.17)	0.89 (0.72–1.10)	1.11 (0.91–1.36)	1.00 (0.82–1.23)	0.50
Multivariable RR (95 % CI)	1	0.97 (0.79–1.20)	0.92 (0.74–1.14)	1.14 (0.93–1.39)	1.04 (0.84–1.28)	0.37
Cholesterol						
All women						
Median intake, mg/1,000 kcal	80.6	109.0	134.8	167.8	234.8	
No. of cases/person-years	548/345,059	540/345,104	577/345,167	594/345,110	571/344,999	
Age-adjusted RR (95 % CI)	1	0.98 (0.87–1.10)	1.03 (0.92–1.16)	1.04 (0.92–1.17)	0.97 (0.87–1.10)	0.84
Multivariable RR (95 % CI)	1	0.97 (0.85–1.10)	1.03 (0.89–1.18)	1.06 (0.91–1.24)	1.05 (0.87–1.26)	0.48
Premenopausal women						
Median intake, mg/1,000 kcal	80.0	107.8	133.0	164.9	229.6	
No. of cases/person-years	289/215,013	296/214,985	294/214,966	304/215,077	328/214,960	
Age-adjusted RR (95 % CI)	1	1.01 (0.86–1.19)	0.98 (0.84–1.16)	0.99 (0.84–1.16)	1.06 (0.90–1.24)	0.50
Multivariable RR (95 % CI)	1	1.08 (0.90–1.29)	1.09 (0.89–1.32)	1.15 (0.92–1.43)	1.32 (1.03–1.70)	0.03
Postmenopausal women						
Median intake, mg/1,000 kcal	82.2	112.1	138.9	172.8	242.5	
No. of cases/person-years	184/86,131	177/86,127	194/86,107	182/86,000	181/85,973	

Table 3 continued

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Age-adjusted RR (95 % CI)	1	0.97 (0.78–1.19)	1.06 (0.86–1.30)	0.98 (0.80–1.20)	0.96 (0.78–1.18)	0.70
Multivariable RR (95 % CI)	1	0.94 (0.75–1.17)	1.04 (0.82–1.33)	1.00 (0.76–1.31)	1.03 (0.75–1.42)	0.76

P_{trend} calculated with median intake of each variable in each quintile as a continuous variable

Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white/non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 in.), BMI (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0 kg/m^2), age at menarche (<12, 12, 13, ≥14 yr), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 yr, parity ≤2 and age at first birth 25 to <30 yr, parity ≤2 and age at first birth ≥30 yr, parity 3–4 and age at first birth <25 yr, parity 3–4 and age at first birth 25 to <30 yr, parity 3–4 and age at first birth ≥30 yr, parity ≥5 and age at first birth <25 yr, parity ≥5 and age at first birth ≥25 yr), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy (quintile), and percentage of energy from protein (quintile). Among postmenopausal women, we also adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr). Among all women, we also adjusted for menopausa status (premenopausal, postmenopausal, dubious), hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (premenopause, unknown menopause, <45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr)

* *EPA* Eicosapentaenoic acid, *DHA* Docosahexaenoic acid

Table 4 Multivariable RR and 95 % CI of subtypes of breast cancer according to fat intake in 1991, expressed as a continuous variable

Breast cancer subtype	All women		Premenopausal women		Postmenopausal women	
	No. of cases	RR (95 % CI)	No. of cases	RR (95 % CI)	No. of cases	RR (95 % CI)
Total fat, per 5 % increase in energy						
Breast cancer	2,830	1.03 (0.99–1.06)	1,511	1.02 (0.97–1.06)	918	1.03 (0.97–1.09)
ER and PR receptor positive	1,544	1.06 (1.01–1.11)	815	1.05 (0.99–1.12)	513	1.05 (0.97–1.13)
ER and PR receptor negative	423	1.01 (0.93–1.10)	237	1.00 (0.90–1.13)	136	0.98 (0.85–1.14)
P for heterogeneity	0.35		0.51		0.45	
Animal fat, per 5 % increase in energy						
Breast cancer	2,830	1.06 (1.01–1.10)	1,511	1.06 (0.99–1.12)	918	1.02 (0.94–1.10)
ER and PR receptor positive	1,544	1.08 (1.02–1.15)	815	1.09 (1.00–1.18)	513	1.06 (0.96–1.17)
ER and PR receptor negative	423	1.05 (0.95–1.17)	237	1.04 (0.91–1.20)	136	0.95 (0.79–1.15)
P for heterogeneity	0.62		0.62		0.30	
Vegetable fat, per 5 % increase in energy						
Breast cancer	2,830	0.99 (0.94–1.04)	1,511	0.97 (0.90–1.04)	918	1.04 (0.96–1.13)
ER and PR receptor positive	1,544	1.01 (0.95–1.08)	815	0.99 (0.91–1.09)	513	1.02 (0.92–1.14)
ER and PR receptor negative	423	0.96 (0.85–1.09)	237	0.96 (0.82–1.13)	136	1.03 (0.84–1.27)
P for heterogeneity	0.45		0.73		0.93	

Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white/non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 in.), BMI (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0 kg/m^2), age at menarche (<12, 12, 13, ≥14 yr), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 yr, parity ≤2 and age at first birth 25 to <30 yr, parity ≤2 and age at first birth ≥30 yr, parity 3–4 and age at first birth <25 yr, parity 3–4 and age at first birth 25 to <30 yr, parity 3–4 and age at first birth ≥30 yr, parity ≥5 and age at first birth <25 yr, parity ≥5 and age at first birth ≥25 yr), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy (quintile), and percentage of energy from protein (quintile). Among postmenopausal women, we also adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr). Among all women, we also adjusted for menopausal status (premenopausal, postmenopausal, dubious), hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (premenopause, unknown menopause, <45 yr, 45–46 yr, 47–48 yr, 49–50 yr, 51–52 yr, ≥53 yr) after menopause. Our findings suggest that higher intake of animal fat was associated with modestly higher risk of breast cancer. Intakes of saturated fat and mono-unsaturated fat, found in most animal fat, were also related to increased risk of breast cancer among all participants, but these associations were weaker and not significant after accounting for intake of red meat. Cholesterol intake was associated with higher risk of premenopausal breast cancer, but this association was attenuated after accounting for intake of red meat. Higher animal fat intake, relative to an equivalent reduction in the amount of energy from carbohydrates, was significantly associated with greater breast cancer risk. Premenopausal intakes of total fat or types of fat were not associated with postmenopausal breast cancer risk.

Smith-Warner et al. [1] examined the relation between fatty acids and breast cancer incidence using a pooled data of 8 cohorts with 7,329 incident invasive breast cancer cases among over 350,000 women. They found no increase in risk with increasing animal fat intake. Similarly, in an analysis of diet during midlife and later, Kim et al. [4], did not find any association between fat intake and postmenopausal breast cancer in a 20-year follow-up of women in the Nurses' Health Study cohort. No significant association between animal fat intake and breast cancer was observed in a recently published meta-analysis of animal fat consumption and breast cancer that combined these two studies with data from other cohort studies [26]. However, none of these studies were able to focus on fat intake in early adult life.

In an early analysis from NHSII, Cho et al. [12] reported a positive association between animal fat intake and premenopausal breast cancer, and this association was more pronounced among women with ER+/PR+ breast cancers. The extended follow-up of NHSII provided an opportunity to address the issue of early adulthood diet in relation to both premenopausal and postmenopausal breast cancer with higher number of cases. On the basis of the findings from our study and evidence available from generally null findings described above [1, 4, 26], intake of animal fat in early adult life may be associated more with risk of premenopausal breast cancer than with breast cancer after menopause.

In addition, caution is appropriate when interpreting the association between animal fat and breast cancer because this association could be due to specific foods contributing to animal fat. Red meat has been associated with risk of breast cancer, including a previous report from this cohort [27–29]. Adjustment for red meat attenuated the risk associated with high consumption of animal fat, and thus animal fat may be a surrogate for other constituents of red meat. Notably, dairy fat was not associated with risk of breast cancer.

Potential limitations also need to be considered. Because the participants were predominantly white, educated US adults, we cannot determine whether our findings are generalizable to other race or ethnic groups; however, it is unlikely that the biology underlying this association differs by race.

Major strengths of this study include the large number of cases, long length of follow-up, and the ability to examine subtypes of breast cancers. The detailed prospective and updated assessments of diet and lifestyle factors allowed adjustment for many potential confounders. Furthermore, information on diet was obtained before breast cancer was reported, which minimizes recall bias.

In summary, focusing on early adult diet and considering breast cancer incidence before and after menopause, our findings suggest that high intake of animal fat and cholesterol may be associated with risk of premenopausal breast cancer but not postmenopausal breast cancer. However, these associations may be due to other constituents of red meat.

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Conflict of interest No potential conflicts of interest were disclosed.

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