Premenopausal Fat Intake and Risk of Breast Cancer

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Background: **International comparisons and case–control studies have suggested a positive relation between dietary fat intake and breast cancer risk, but prospective studies, most of them involving postmenopausal women, have not supported this association. We conducted a prospective analysis of the relation between dietary fat intake and breast cancer risk among premenopausal women enrolled in the Nurses' Health Study II.** ***Methods:*** **Dietary fat intake and breast cancer risk were assessed among 90 655 premenopausal women aged 26 to 46 years in 1991. Fat intake was assessed with a food-frequency questionnaire at baseline in 1991 and again in 1995. Breast cancers were self-reported and confirmed by review of pathology reports. Multivariable relative risks (RRs) and 95% confidence intervals (CIs) were calculated. All statistical tests were two-sided.** ***Results:*** **During 8 years of follow-up, 714 women developed incident invasive breast cancer. Relative to women in the lowest quintile of fat intake, women in the highest quintile of intake had a slight increased risk of breast cancer (RR = 1.25, 95% CI = 0.98 to 1.59; P_{trend} = .06). The increase was associated with intake of animal fat but not vegetable fat; RRs for the increasing quintiles of animal fat intake were 1.00 (referent), 1.28, 1.37, 1.54, and 1.33 (95% CI = 1.02 to 1.73; P_{trend} = .002). Intakes of both saturated and monounsaturated fat were related to modestly elevated breast cancer risk. Among food groups contributing to animal fat, red meat and high-fat dairy foods were each associated with an increased risk of breast cancer.** ***Conclusions:*** **Intake of animal fat, mainly from red meat and high-fat dairy foods, during premenopausal years is associated with an increased risk of breast cancer. [J Natl Cancer Inst 2003;95:1079–85]**

High intake of total fat has been associated with an increased risk of breast cancer in animal studies, international comparisons, and some case–control studies *(1).* However, this association has not been found in prospective studies *(2).* For specific types of fat, the evidence is more complex. Case–control studies have supported a positive association between breast cancer risk and intake of saturated fat *(3),* but animal studies have supported a positive association with n-6 polyunsaturated fats *(4).* A pooled analysis of prospective studies found no association between breast cancer risk and intake of total fat or specific types of fat, with the exception of a weakly positive association with saturated fat *(5).*

Previous prospective studies on fat intake and breast cancer risk have included relatively few premenopausal women with breast cancer *(5–7).* Because some risk factors for breast cancer vary greatly according to age or menopausal status, the association between fat intake and breast cancer risk among premenopausal and postmenopausal women may be different. Moreover, the associations between fat intake during early adulthood and breast cancer risk have not been investigated extensively. In this study, we evaluated the association of fat intake and risk of breast cancer in premenopausal women enrolled in the Nurses' Health Study (NHS) II.

Subjects and Methods

Study Population

The NHS II is a prospective cohort study of 116 671 female registered nurses aged 25 to 42 years and living in one of 14 states within the United States when they responded in 1989 to a questionnaire about their medical histories and lifestyles. Follow-up questionnaires have been sent biennially to update information on risk factors and medical events.

For the current analysis, we started follow-up at 1991, when diet was first measured. From the 97 807 women who returned the 1991 dietary questionnaire, we excluded women (n = 2361) who had an implausible total energy intake (<800 or >4200 kcal/day) or who left more than 70 food items blank in the 1991 food-frequency questionnaire (FFQ). We also excluded women who reported a diagnosis of cancer, except non-melanoma skin cancer, before returning the 1991 questionnaire (n = 1325). Because the number of postmenopausal women at baseline was small (n = 3466), we excluded them from this analysis, leaving a total of 90 655 premenopausal women. Among those who answered the FFQ in 1991, the follow-up rate was 93% by May 31, 1999. The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Dietary Assessment

A semiquantitative FFQ with 133 and 142 food items was sent to women in 1991 and 1995, respectively, to assess usual dietary intake during the past year. Participants were asked how often, on average, they had consumed each type of food or beverage during the past year. The FFQ had nine possible re-

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sponses, ranging from never or less than once per month to six or more times per day. Fat intake per individual was calculated as the sum of the contributions from all foods on the basis of U.S. Department of Agriculture food composition data *(8),* taking into account types of margarine and fats used in cooking and baking. To calculate the percentage of energy contributed by each type of fat, we divided energy intake from each fat by total energy intake. We also examined food groups contributing to intake of animal fat, such as red meat, chicken, fish, and low- and high-fat dairy foods.

Because fat intake has been hypothesized to promote breast carcinogenesis over an extended period of time, we calculated cumulative averaged intakes of fat and food groups using the 1991 and 1995 dietary data to best represent long-term intake for our primary analysis *(9).* Specifically, the 1991 intake was used for the 1991–1995 follow-up period, and the average of the 1991 and 1995 intake was used for 1995–1999 follow-up to maintain a strictly prospective analysis.

The reproducibility and validity of fat intake determined with a similar FFQ have been assessed in cohorts of older women *(10–12).* For specific types of fat, Pearson correlation coefficients between energy-adjusted intakes from the average of two 1-week diet records and from the FFQ ranged from 0.48 to 0.73 (0.57 for total fat and 0.68 for saturated fat), with a correction for attenuation resulting from random error in diet records *(11).* Total fat intake has been validated using changes in blood lipid levels *(12).* Spearman correlation coefficients between the percentage of fat intake calculated from the FFQ and the fatty acid composition of subcutaneous fat aspirates has confirmed that the FFQ measured specific fatty acids from exogenous sources reasonably well ($r = .51$ for *trans*-unsaturated fat; $r = .48$ for long-chain omega-3 fatty acids) *(10).* The reproducibility and validity of individual fat-contributing foods have been evaluated elsewhere *(13).* Most of the correlation coefficients between diet records and FFQ for intake of meat and dairy foods were greater than .50, after a correction for attenuation resulting from random error in diet records.

Documentation of Breast Cancer

Biennial questionnaires mailed between 1993 and 1999 were used to identify newly diagnosed breast cancers. Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonresponders. When a breast cancer was reported, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and for permission to obtain relevant hospital records and pathology reports. Pathology reports confirmed 98% of the self-reported breast cancers. Because the degree of self-reporting accuracy was high, we included the few self-reported breast cancers for whom records could not be obtained. Cases of carcinoma *in situ* were not included in the analyses. Information on estrogen and progesterone receptor status of the breast cancers was obtained from pathology reports.

Statistical Analysis

Participants contributed person-years from the date of return of the 1991 questionnaire until the date of breast cancer diagnosis, death, or June 1999, whichever came first. Participants were divided into quintiles according to their fat or food group intake. Relative risk (RR) of breast cancer was calculated as the incidence rate for women in a given quintile of fat or food group relative to the rate for those in the lowest quintile. We used Cox proportional hazards regression to account for potential effects of other risk factors for breast cancer *(14).* The assumptions of proportionality were satisfied. To control for confounding by age or calendar time, or any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. Multivariable models also simultaneously adjusted for smoking status, body mass index, height, age at menarche, oral contraceptive use, family history of breast cancer, history of benign breast disease, parity and age at first birth, menopausal status, and intakes of calories, protein, and alcohol. All covariates except height, age at menarche, and family history of breast cancer were updated in each questionnaire cycle. SAS PROC PHREG *(15)* with SAS version 8.2 was used for all analyses. The Anderson–Gill data structure *(16)* was used to handle time-varying covariates efficiently, with a new data record created for every questionnaire cycle at which a participant was at risk and covariates set to their values at the time the questionnaire was returned. For all RRs, 95% confidence intervals (CIs) were calculated. Tests for trend were conducted using the median value for each category of fat or food group as a continuous variable. To examine whether the association between animal fat and breast cancer risk was modified by other measures of breast cancer risk factors, a cross-product term of the ordinal score for the level of each factor and intake of animal fat expressed as a continuous variable was included in the multivariable model. *P* values for tests for interactions were obtained from a likelihood ratio test with one degree of freedom. All *P* values were two-sided. Spearman correlation coefficients were calculated to examine correlations between different fat intake variables.

Results

During 695 036 person-years of follow-up of 90 655 women, 714 women were diagnosed with invasive breast carcinoma. The age range of the participants at baseline in 1991 was 26–46 years (mean = 36 years; standard deviation = 4.6 years). The age range of the participants at time of diagnosis of breast cancer was 26–52 years (mean = 43 years; standard deviation = 4.5 years). Table 1 presents the distribution of risk factors for breast cancer by quintiles of animal fat intake. Women with a higher intake of animal fat were more likely to be smokers, to have more than three children, and to have a larger body mass index than women with a lower intake. Women with a higher intake of animal fat were also less likely to use oral contraceptives, to have a history of benign breast disease, and to consume alcohol than women with a lower intake.

In both the age-adjusted and multivariable analyses (Table 2), intake of total fat was not statistically significantly associated with risk of breast cancer (multivariable RRs for the highest quintile compared with the lowest = 1.25, 95% CI = 0.98 to 1.59; $P_{trend} = .06$). Because total energy and protein intakes were included in the multivariable models, these RRs for total fat intake imply substituting calories from fat for the same percentage of calories from carbohydrate. The weak increased risk associated with total fat intake was attributable to intake of animal fat but not vegetable fat. For the increasing quintiles of animal fat intake, the multivariable RRs were 1.00, 1.28, 1.36, 1.53, and 1.32 ($P_{trend} = .002$). The RRs were unchanged when

Table 1. Age-standardized distribution of potential risk factors for breast cancer according to animal fat intake in 1991 in women aged 26–46 years at baseline enrolled in the Nurses' Health Study II*

	Animal fat intake quintile				
	1	2	3	4	5
No. of women	17 994	18 150	18 188	18 216	18 106
Range of animal fat intake, % of energy†	⩽14	14–16	16–18	18–21	⩾21–46
% of group					
Current smokers	9	10	11	13	16
Current oral contraceptive use	12	11	11	11	10
History of benign breast disease	35	34	33	33	32
Family history of breast cancer in mother and sisters	9	9	9	9	9
Parity ⩾3	16	20	21	23	22
Age at menarche <12 y	24	25	24	24	25
Mean					
Age, y	36	36	36	36	36
Alcohol consumption, g/day	3.7	3.3	3.0	3.0	2.6
Body mass index, kg/m^2	23	24	25	25	26
Age at first birth, y	26	26	26	26	26

*Except for the data on mean age, all data shown are standardized to the age distributions of the cohort in 1991.

†Before rounding, the cutpoint for the 1st quintile was 13.77048 and the ranges for quintiles 2, 3, and 4 were 13.77090–16.20252, 16.20262–18.36415, and 18.36424–21.09027, respectively.

vegetable fat intake was included in the model because the correlation between these fats was low (Spearman correlation coefficient between animal and vegetable fats = –0.10), and vegetable fat intake was not associated with breast cancer risk. The results were similar when calorie and protein intakes were excluded as covariates (data not shown). When animal fat intake was divided into deciles, the RR for breast cancer was 1.79 (95% CI = 1.21 to 2.64) for individuals in the 10th decile relative to those in the 1st decile. Intakes of saturated fat and monounsaturated fat, the major components of animal fat, were somewhat positively associated with breast cancer risk (Table 2). However, mutual adjustment for these two fats, and for cholesterol and polyunsaturated fat, attenuated the RRs for both fats, probably due to high correlations (Spearman correlation coefficient between saturated and monounsaturated fats = 0.78). Intakes of polyunsaturated fat, *trans*-unsaturated fat, long-chain omega-3 fatty acids, and cholesterol were not related to the risk of breast cancer.

The association between animal fat intake and breast cancer risk was consistent when we examined both baseline intake and most recent intake (i.e., intake from the 1995 FFQ for women diagnosed after they submitted the FFQ). The RRs for breast cancer for women in the highest quintile of animal fat intake were 1.29 (95% CI = 1.00 to 1.67) with baseline values and 1.35 (95% CI = 1.04 to 1.76) with the more recent values.

Breast tumors differ clinically and biologically by estrogen and/or progesterone receptor status and may have different underlying etiologies. We had information on estrogen receptor status for 80% (n = 570) of breast cancers and progesterone receptor status for 78% (n = 558) of breast cancers. When we divided cancers according to estrogen and progesterone receptor status, the positive association between animal fat intake and breast cancer risk was stronger among women with estrogen receptor-positive or progesterone receptor-positive cancers than among women with hormone receptor-negative cancers (Table 3). However, the χ^2 test for the difference in associations between receptor-positive and -negative cancers was not statistically significant (data not shown).

We examined whether the association between animal fat intake and breast cancer risk was modified by other risk factors for breast cancer, including family history of breast cancer, body mass index, oral contraceptive use, history of benign breast disease, alcohol intake, age at first birth, and parity (Table 4). The association was stronger among women who used oral contraceptives currently or had previously used them for more than 4 years than among women who had never used oral contraceptives or had previously used them for less than 4 years (*P* for interaction = .02). The association between animal fat intake and breast cancer risk was modified by age at first birth (*P* for interaction = .03).

Some of the participants who were premenopausal at baseline became postmenopausal during the follow-up period. Thus, approximately 10% of the women with breast cancer were postmenopausal at the time of diagnosis. Restricting analyses to those who remained premenopausal throughout follow-up resulted in similar, but slightly weaker, associations between animal fat intake and breast cancer risk: the RR for breast cancer for women in the highest quintile of animal fat intake compared with those in the lowest was 1.24 (95% CI = 0.94 to 1.64).

To examine whether the positive association between animal fat intake and breast cancer risk was attributable to animal fat *per se* or to specific foods contributing to animal fat, we examined animal-based food groups (Table 5). Red meat and high-fat dairy foods (i.e., whole milk, cream, ice cream, butter, cream cheese, and cheese, not including cottage or ricotta cheese), the major contributors of animal fat in this cohort, were both positively associated with breast cancer risk. Intake of dairy fat *per se* was not statistically significantly positively associated with breast cancer risk: the RR for women in the highest quintile compared with those in the lowest was 1.14 (95% CI = 0.90 to 1.45).

When we included both animal fat and red meat intake in the same model, the positive association for red meat intake was mostly attributable to animal fat because the multivariable RRs for increasing quintiles of red meat intake decreased from 1.00, 1.22, 1.25, 1.35, and 1.20 to 1.00, 1.12, 1.09, 1.14, and 0.99, but the RRs for animal fat intake remained essentially the same. When both animal fat and high-fat dairy food intakes were in the same model, the multivariable RRs for increasing quintiles of high-fat dairy food intake decreased slightly from 1.00, 1.09, 1.25, 1.37, and 1.36 to 1.00, 1.06, 1.19, 1.29, and 1.28 and the RRs for animal fat intake decreased to 1.00, 1.21, 1.25, 1.36, and

Table 2. Relative risk (RR) and 95% confidence intervals (CIs) for breast cancer according to quintile of cumulative averaged fat intake in women aged 26–46 years at baseline enrolled in the Nurses' Health Study II

Nutrient	Quintile of intake					P_{trend}*
	1	2	3	4	5	
Total fat						
Median intake, % of energy	24	28	31	34	38	
No. of cases	128	147	146	148	145	
Age-adjusted RR (95% CI)	1.00 (referent)	1.18 (0.93 to 1.49)	1.17 (0.92 to 1.49)	1.18 (0.93 to 1.50)	1.18 (0.93 to 1.50)	.14
Multivariable RR (95% CI)†	1.00 (referent)	1.20 (0.95 to 1.52)	1.20 (0.94 to 1.52)	1.22 (0.96 to 1.56)	1.25 (0.98 to 1.59)	.06
Animal fat						
Median intake, % of energy	12	15	17	20	23	
No. of cases	123	145	151	161	134	
Age-adjusted RR (95% CI)	1.00 (referent)	1.22 (0.96 to 1.55)	1.26 (1.00 to 1.60)	1.38 (1.09 to 1.74)	1.15 (0.90 to 1.47)	.04
Multivariable RR 1 (95% CI)†	1.00 (referent)	1.28 (1.00 to 1.63)	1.36 (1.07 to 1.74)	1.53 (1.20 to 1.96)	1.32 (1.01 to 1.71)	.002
Multivariable RR 2 (95% CI)‡	1.00 (referent)	1.28 (1.00 to 1.64)	1.37 (1.07 to 1.75)	1.54 (1.20 to 1.97)	1.33 (1.02 to 1.73)	.002
Vegetable fat						
Median intake, % of energy	9	12	13	15	19	
No. of cases	144	136	122	163	149	
Age-adjusted RR (95% CI)	1.00 (referent)	0.92 (0.73 to 1.16)	0.82 (0.64 to 1.04)	1.09 (0.87 to 1.36)	1.02 (0.81 to 1.29)	.39
Multivariable RR 1 (95% CI)†	1.00 (referent)	0.91 (0.72 to 1.16)	0.81 (0.63 to 1.04)	1.06 (0.84 to 1.33)	1.00 (0.78 to 1.28)	.56
Multivariable RR 2 (95% CI)‡	1.00 (referent)	0.90 (0.71 to 1.13)	0.79 (0.62 to 1.01)	1.02 (0.81 to 1.29)	0.97 (0.76 to 1.24)	.75
Saturated fat						
Median intake, % of energy	8	10	11	12	14	
No. of cases	133	150	145	161	125	
Age-adjusted RR (95% CI)	1.00 (referent)	1.17 (0.92 to 1.47)	1.18 (0.93 to 1.49)	1.35 (1.07 to 1.70)	1.09 (0.85 to 1.39)	.06
Multivariable RR 1 (95% CI)†	1.00 (referent)	1.21 (0.96 to 1.53)	1.23 (0.97 to 1.56)	1.41 (1.12 to 1.78)	1.17 (0.91 to 1.50)	.02
Multivariable RR 2 (95% CI)‡	1.00 (referent)	1.17 (0.90 to 1.52)	1.16 (0.87 to 1.57)	1.31 (0.96 to 1.80)	1.06 (0.74 to 1.53)	.18
Monounsaturated fat						
Median intake, % of energy	9	11	12	13	15	
No. of cases	125	137	151	149	152	
Age-adjusted RR (95% CI)	1.00 (referent)	1.10 (0.87 to 1.41)	1.20 (0.94 to 1.52)	1.17 (0.92 to 1.49)	1.20 (0.95 to 1.52)	.12
Multivariable RR 1 (95% CI)†	1.00 (referent)	1.12 (0.87 to 1.42)	1.21 (0.95 to 1.54)	1.20 (0.94 to 1.52)	1.26 (0.99 to 1.60)	.06
Multivariable RR 2 (95% CI)‡	1.00 (referent)	1.02 (0.77 to 1.35)	1.05 (0.77 to 1.43)	1.02 (0.72 to 1.44)	1.10 (0.75 to 1.62)	.87
Polyunsaturated fat						
Median intake, % of energy	4	5	5	6	7	
No. of cases	133	127	143	164	147	
Age-adjusted RR (95% CI)	1.00 (referent)	0.91 (0.72 to 1.17)	1.01 (0.80 to 1.28)	1.17 (0.93 to 1.48)	1.06 (0.83 to 1.34)	.22
Multivariable RR 1 (95% CI)†	1.00 (referent)	0.92 (0.72 to 1.17)	1.01 (0.79 to 1.28)	1.18 (0.94 to 1.49)	1.06 (0.84 to 1.35)	.20
Multivariable RR 2 (95% CI)‡	1.00 (referent)	0.88 (0.68 to 1.13)	0.94 (0.73 to 1.22)	1.09 (0.85 to 1.41)	0.96 (0.73 to 1.27)	.67
Cholesterol						
Median intake, mg/1000 kcal	93	115	131	148	178	
No. of cases	131	143	147	153	140	
Age-adjusted RR (95% CI)	1.00 (referent)	1.07 (0.84 to 1.36)	1.10 (0.87 to 1.39)	1.11 (0.88 to 1.40)	1.01 (0.79 to 1.28)	.64
Multivariable RR 1 (95% CI)†	1.00 (referent)	1.13 (0.88 to 1.44)	1.18 (0.92 to 1.52)	1.25 (0.96 to 1.61)	1.16 (0.87 to 1.55)	.14
Multivariable RR 2 (95% CI)‡	1.00 (referent)	1.06 (0.82 to 1.36)	1.08 (0.83 to 1.41)	1.13 (0.85 to 1.50)	1.04 (0.75 to 1.43)	.54
Trans-unsaturated fat						
Median intake, % of energy	0.9	1.2	1.5	1.8	2.3	
No. of cases	146	142	152	133	141	
Age-adjusted RR (95% CI)	1.00 (referent)	0.98 (0.77 to 1.23)	1.06 (0.84 to 1.33)	0.96 (0.76 to 1.22)	1.08 (0.86 to 1.36)	.87
Multivariable RR I (95% CI)†	1.00 (referent)	1.00 (0.79 to 1.26)	1.09 (0.87 to 1.38)	1.00 (0.79 to 1.27)	1.15 (0.90 to 1.47)	.54
Multivariable RR 2 (95% CI)‡	1.00 (referent)	0.92 (0.71 to 1.17)	0.96 (0.74 to 1.25)	0.86 (0.64 to 1.14)	0.96 (0.70 to 1.31)	.38
Long-chain omega-3 fatty acids						
Median intake, % of energy	0.03	0.05	0.08	0.12	0.19	
No. of cases	137	132	132	160	153	
Age-adjusted RR (95% CI)	1.00 (referent)	0.94 (0.74 to 1.19)	0.91 (0.72 to 1.15)	1.06 (0.84 to 1.33)	1.01 (0.80 to 1.27)	.43
Multivariable RR 1 (95% CI)†	1.00 (referent)	0.95 (0.74 to 1.21)	0.92 (0.72 to 1.17)	1.05 (0.82 to 1.33)	1.01 (0.78 to 1.31)	.50
Multivariable RR 2 (95% CI)‡	1.00 (referent)	0.94 (0.74 to 1.20)	0.92 (0.72 to 1.18)	1.06 (0.83 to 1.36)	1.05 (0.80 to 1.38)	.35

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

†Multivariable model 1 was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past <25, past ⩾25, current <25, and current ⩾25 cigarettes/day), height (<62, 62–<65, 65–68, ⩾68 inches), parity and age at first birth (nulliparous, parity ⩽2 and age at first birth <25 years, parity ⩽2 and age at first birth 25–<30 years, parity ⩽2 and age at first birth ⩾30 years, parity ⩾3 and age at first birth <25 years, parity ⩾3 and age at first birth ⩾25 years), body mass index (<18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.9, ⩾30.0 kg/m^2), age at menarche (<12, 12, 13, ⩾14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past <4 years, past ⩾4 years, current <8 years, current ⩾8 years), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (nondrinker, <5, 5–<10, 10–<20, ⩾20 g/day), energy (continuous), and protein (continuous).

‡Multivariable model 2 was adjusted for the same covariates as multivariable model 1 and for other fats in quintiles simultaneously. Animal fat and vegetable fat were adjusted for each other. Saturated, polyunsaturated, and monounsaturated fats and cholesterol were adjusted for each other. *Trans*-unsaturated fats and long-chain omega-3 fatty acids were adjusted for each other, as well as adjustment for saturated, polyunsaturated, and monounsaturated fats and for cholesterol.

1.13. When we included red meat and high-fat dairy food intakes simultaneously in multivariable model, the RRs for both food groups remained essentially unchanged.

We further examined the individual food items included in the red meat and high-fat dairy food groups. Although none of the individual foods appeared to be strongly associated with

Table 3. Multivariable relative risk (RR) and 95% confidence intervals (CIs) of subtypes of breast cancer according to cumulative averaged fat intake in women aged 26–46 years at baseline enrolled in the Nurses' Health Study II*

Breast cancer subtype	Animal fat (RR per 5% increase of energy)	Vegetable fat (RR per 5% increase of energy)
Total (n = 714)	1.12 (1.03 to 1.22)	1.01 (0.90 to 1.12)
Estrogen receptor positive (n = 388)	1.20 (1.07 to 1.35)	1.02 (0.88 to 1.18)
Estrogen receptor negative (n = 182)	1.08 (0.90 to 1.28)	0.92 (0.75 to 1.14)
Progesterone receptor positive (n = 364)	1.17 (1.03 to 1.32)	1.08 (0.93 to 1.25)
Progesterone receptor negative (n = 194)	1.11 (0.94 to 1.32)	0.86 (0.70 to 1.06)
Estrogen and progesterone receptor positive (n = 323)	1.18 (1.04 to 1.35)	1.06 (0.90 to 1.24)
Estrogen and progesterone receptor negative (n = 134)	1.04 (0.85 to 1.28)	0.88 (0.69 to 1.14)

*Age-adjusted results were not presented because the results were similar to multivariable results. The models were adjusted for the same covariates as multivariable model 2 in Table 2.

Table 4. Multivariable relative risk (RR) and 95% confidence interval (CI) of breast cancer according to cumulative averaged animal fat intake by different levels of risk factors in women aged 26–46 years at baseline enrolled in the Nurses' Health Study II*

	Animal fat (RR per 5% increase of energy)	*P* for interaction
Total	1.12 (1.03 to 1.22)	
Family history		
No (n = 576)	1.09 (0.98 to 1.20)	
Yes (n = 138)	1.28 (1.04 to 1.58)	.27
Body mass index		
<25 kg/m^2 (n = 422)	1.17 (1.04 to 1.31)	
⩾25 kg/m^2 (n = 291)	1.06 (0.92 to 1.22)	.12
Oral contraceptive use		
Never or past <4 years duration of use (n = 405)	1.04 (0.92 to 1.17)	
Past ⩾4 years of use or current (n = 304)	1.26 (1.10 to 1.44)	.02
Oral contraceptive use		
Never (n = 97)	0.96 (0.76 to 1.23)	
Past (n = 548)	1.12 (1.01 to 1.24)	
Current (n = 64)	1.36 (1.01 to 1.82)	.19
History of benign breast disease		
No (n = 326)	1.08 (0.94 to 1.23)	
Yes (n = 388)	1.17 (1.04 to 1.32)	.46
Alcohol intake		
Nondrinker (n = 247)	1.07 (0.93 to 1.24)	
<5 g/day (n = 309)†	1.11 (0.97 to 1.26)	
⩾5 g/day (n = 158)†	1.24 (1.02 to 1.50)	.42
Age at first birth		
Nulliparous (n = 154)	1.01 (0.84 to 1.21)	
<25 (n = 184)	1.10 (0.93 to 1.31)	
⩾25 (n = 370)	1.17 (1.03 to 1.32)	.03
Parity		
Nulliparous (n = 154)	1.01 (0.84 to 1.22)	
1 or 2 children (n = 375)	1.16 (1.03 to 1.31)	
3 or more children (n = 173)	1.09 (0.90 to 1.31)	.43

*Age-adjusted results were not presented because the results were similar to multivariable results. The models were adjusted for the same covariates as multivariable model 2 in Table 2.

†The model was also adjusted for continuous alcohol intake.

breast cancer risk, the majority of the associations were weakly positive (data not shown).

Discussion

In this prospective study, we did not find any clear association between total fat intake during early adulthood (i.e., the premenopausal period) and breast cancer risk. However, intake of animal fat, mostly contributed by red meat and high-fat dairy foods, was associated with an elevated risk of breast cancer.

National rates of breast cancer are strongly correlated with per capita total fat consumption *(17,18),* but this relationship is primarily associated with intake of animal fat, rather than vegetable fat, and intake of meat and milk *(19).* Results from case–control studies regarding associations between total fat intake and breast cancer risk have been inconsistent, but a pooled analysis has suggested a positive association *(3,17,18).* By contrast, prospective studies have not supported an association with total fat intake *(2).* The fatty acid composition in fat from animal and vegetable sources differs greatly and may therefore have different associations with breast cancer risk. In the United States, animal fat is composed largely of saturated and monounsaturated fatty acids, whereas vegetable fat consists primarily of polyunsaturated, monounsaturated, and *trans*-fatty acids. Although animal studies have most strongly supported an adverse effect of polyunsaturated fats in mammary tumorigenesis *(4,20),* case–control studies have implicated saturated fat rather than polyunsaturated fat *(3).* A pooled analysis of prospective studies reported a weakly positive association between breast cancer risk and saturated fat among both premenopausal and postmenopausal women; there was no statistically significant association for other fats *(5).* Results from the other prospective studies that were not included in the pooled analysis *(5)* reported divergent findings. A Norwegian study of 248 women with breast cancer found a positive association with intake of monounsaturated fat *(6),* and a study among U.S. postmenopausal women that included 996 women with breast cancer found a positive association with intake of unsaturated fat only among women with no history of benign breast disease (n = 255) *(7).*

Because the etiologies of pre- and postmenopausal breast cancer are different in many respects, the relation between dietary fat intake and breast cancer risk in premenopausal women could be different from that in postmenopausal women. For some risk factors, such as adiposity, the direction of the association is reversed *(21).* For several other known risk factors, effects may be predominately associated with younger age. For example, reproductive factors act on breast tissue largely during the early adult years, and the breast becomes minimally sensitive to radiation-induced carcinogenesis after age 35 *(22).* It is also possible that diet in early adult life may have a stronger impact on breast cancer risk than diet later in life because exposures during the years before the first birth of a child appear to be most relevant to future risk of breast cancer *(23).*

Our study provided a unique opportunity to evaluate fat intake relatively early in adult life in relation to breast cancer risk. The mean age of the women with breast cancer was 43 years, substantially lower than in previous prospective studies *(5).* The finding that the association between animal fat intake and breast cancer risk was weaker when we restricted analysis to women

Table 5. Multivariable relative risk (RR) and 95% confidence interval (CI) of breast cancer according to cumulative averaged intake of animal-based food groups in women aged 26–46 years at baseline enrolled in the Nurses' Health Study II*

	Intake quintile†					
	1	2	3	4	5	P_{trend}‡
Red meat						
Median intake (servings/day)	0.2	0.5	0.7	1.0	1.5	
No. of cases	128	144	148	160	134	
RR (95% CI)	1.00 (referent)	1.22 (0.96 to 1.55)	1.25 (0.98 to 1.59)	1.35 (1.05 to 1.73)	1.20 (0.91 to 1.58)	.20
Fish						
Median intake (servings/day)	0.7	0.1	0.2	0.4		
No. of cases	157	161	220	176		
RR (95% CI)	1.00 (referent)	0.92 (0.74 to 1.15)	1.13 (0.92 to 1.39)	0.92 (0.73 to 1.15)		.52
Chicken or turkey						
Median intake (servings/day)	0.1	0.3	0.4	0.6	0.9	
No. of cases	109	157	162	138	148	
RR (95% CI)	1.00 (referent)	1.00 (0.78 to 1.28)	1.01 (0.78 to 1.29)	1.12 (0.87 to 1.45)	1.04 (0.80 to 1.35)	.58
Total dairy foods						
Median intake (servings/day)	0.7	1.4	1.9	2.8	4.0	
No. of cases	135	155	159	139	126	
RR (95% CI)	1.00 (referent)	1.17 (0.93 to 1.48)	1.18 (0.93 to 1.49)	1.03 (0.80 to 1.33)	1.03 (0.79 to 1.36)	.72
Low-fat dairy foods						
Median intake (servings/day)	0.2	0.6	1.1	1.6	2.8	
No. of cases	150	148	138	167	111	
RR (95% CI)	1.00 (referent)	0.97 (0.77 to 1.22)	0.95 (0.75 to 1.20)	1.00 (0.80 to 1.26)	0.82 (0.63 to 1.06)	.17
High-fat dairy foods						
Median intake (servings/day)	0.2	0.5	0.8	1.1	2.2	
No. of cases	124	138	144	151	157	
RR (95% CI)	1.00 (referent)	1.09 (0.85 to 1.39)	1.25 (0.97 to 1.59)	1.37 (1.07 to 1.75)	1.36 (1.06 to 1.75)	.02

*Age-adjusted results were not presented because the results were similar to multivariable results. The model was adjusted for the same covariates except protein intake as multivariable model 1 in Table 2.

†Quintiles were used for all the food groups except fish, for which quartiles were used because of the limited distribution of the intake.

‡P_{trend} calculated with median intake of each category of food group as a continuous variable.

who remained premenopausal during follow-up than when using results from the entire cohort suggests that the timing of dietary assessment may be more important for detecting an association than menopausal status at diagnosis. However, further data with additional cases of both premenopausal and postmenopausal breast cancers are needed to address this issue.

We are not aware of any compelling biologic mechanism relating intake of animal fat (or saturated fat or monounsaturated fat), but not vegetable fat, to breast cancer risk. Fat in general has been postulated to increase breast cancer risk by elevating levels of circulating estrogen. Although, in a meta-analysis of 13 intervention studies, it was reported that reduction of fat intake decreased serum estradiol levels among both premenopausal and postmenopausal women (especially among postmenopausal women) *(24),* some of the studies had no control groups and participants that were not comparable regarding total energy intake *(25).* Furthermore, in one recent cross-sectional study among postmenopausal women, neither total fat nor animal fat intake was positively related to estrogen levels *(26).* Thus, it is not likely that animal fat intake affects breast cancer risk by modulating estrogen levels.

The positive association we observed between animal fat intake and breast cancer risk could be attributable to other components in foods containing animal fat (e.g., red meat and high-fat dairy foods). For example, cooked red meat is a source of carcinogens such as heterocyclic amines, *N*-nitroso compounds, and polycyclic aromatic hydrocarbons that are related to induction of mammary tumors in animals *(27).* We have limited information on the preparation of red meat and are not able to examine these hypotheses further. High-fat dairy foods contain fat-soluble hormones or growth factors, which may be related to breast cancer risk *(28).*

Our results are not in accord with the pooled analysis of eight prospective studies in which no association was found between intake of red meat and breast cancer risk *(29),* but there was little overlap between the pooled analysis and our study in the age range of women with breast cancer. In two other relatively small prospective studies, a positive association was found between consumption of meat or fried meat and breast cancer risk *(30, 31).* Researchers in one case–control study reported a positive association between breast cancer and doneness of red meat *(32),* and the results of another case–control study among relatively young women suggested a positive association between intake of high-fat meat during adolescence and breast cancer *(33).* Our findings on high-fat dairy foods among younger women are also not consistent with the pooled analysis of prospective studies in which little relationship was seen *(29).* The findings of the few other prospective studies that examined dairy foods and breast cancer risk have also not been consistent *(30, 34).*

Breast cancer subtypes defined by hormone receptor status may have different etiologies, and associations between breast cancers and some risk factors, such as body mass index, have differed by hormone receptor status *(35).* In one previous study among postmenopausal women, a positive association between dietary fat intake and breast cancer was suggested only among women with cancers that were positive for estrogen and progesterone receptors *(36).* We also found that the association between animal fat intake and breast cancer was stronger for women with estrogen receptor-positive cancers than for women with estrogen receptor-negative cancers.

Our study had several strengths. First, the prospective nature of the study avoided some of the biases associated with case–control studies, and few participants have been lost to follow-up.

Second, because we had repeated measures of dietary intake, we were able to examine long-term averaged diet, as well as baseline diet and most recent intake. Third, we had information on a wide range of potential confounders and adjusted for them.

Our study also had several limitations. First, although our dietary assessment method has been shown to be informative by a variety of methods for intakes of total and specific types of fat *(10–12),* some error is inevitable and would tend to underestimate the magnitude of associations. However, error is reduced by the use of repeated measures, and this error would not account for the positive association we observed with animal fat. Second, the duration of follow-up time and number of cases were limited, especially in analyses stratified by hormone receptor status and other breast cancer risk factors.

In conclusion, in this population of relatively young women, premenopausal animal fat intake was associated with a higher risk of breast cancer, which was largely related to intake of red meat and high-fat dairy foods. Prevention of coronary heart disease already provides a good reason for choosing a diet low in red meat and dairy fat. Because prevention of heart disease is likely to be a low priority for young women, these findings have substantial potential implications in encouraging women to adopt healthy diets and should be evaluated further.

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