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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adolescent Diet in Relation to Breast Cancer Risk among Premenopausal Women

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Abstract

Background: Although the association between adult diet and breast cancer has been investigated extensively, large prospective studies have generally not shown a direct link between intakes of carbohydrate, fat, fiber, and other nutrients and risk of breast cancer. Adolescence may be a period of increased susceptibility to risk factors that predispose to breast cancer. Dietary risk factors could therefore be more important during early life than later in adulthood.

Methods: This is a prospective observational study of 39,268 premenopausal women in the Nurses' Health Study II who completed a 124-item food frequency questionnaire on their diet during high school (HS-FFQ) in 1998, at which time participants were 34 to 53 years of age. Cox proportional hazards regression was used to estimate relative risks and 95% CIs.

Results: Four hundred fifty-five incident cases of invasive breast cancer were diagnosed between 1998 and 2005. Compared with women in the lowest quintile of intake, the relative risk of breast cancer in the highest quintile of adolescent total fat consumption was 1.35 (95% confidence interval, 1.00-1.81). Adolescent consumption of saturated, monounsaturated, polyunsaturated, and trans fats was not significantly associated with breast cancer risk. Total dairy, milk, carbohydrate intake, glycemic index, glycemic load, and fiber consumed during adolescence were not significantly related to breast cancer incidence.

Conclusion: Dietary fat consumed during adolescence may be associated with an elevated risk of breast cancer. Further studies to assess this relationship among postmenopausal women, and confirm these results in premenopausal women, are needed. *Cancer Epidemiol Biomarkers Prev; 19(3); 689–96. ©2010 AACR.*

Introduction

To explain the large international variation in breast cancer rates and identify modifiable targets for prevention, scientists have searched for links between diet and breast cancer. Despite extensive investigation, there is no conclusive evidence that adult consumption of macronutrients including fat, carbohydrate, or fiber is strongly related to breast cancer incidence (1). This null result could be because breast cancer risk is determined earlier in life, before the period of investigation, and adult dietary exposures have little influence on carcinogenesis.

The hypothesis that exposures that occur between menarche and first pregnancy are especially important in determining subsequent risk of breast cancer is supported by several lines of evidence. Animal studies show increased susceptibility to mammary carcinogens before first pregnancy compared with administration at a later age (2, 3), and epidemiologic investigations of women who survived the atomic bomb in Hiroshima and Nagasaki show no increase in risk among women older than 35 years at the time of the bombing but increased breast cancer risk among women younger than 20 years when exposed (4, 5). Additionally, migration studies suggest that breast cancer risk remains low in first generation immigrants who have spent their early life in a country with lower overall risk of breast cancer, but increases among second generation immigrants, who have spent their childhood in a country with higher risk of breast cancer (6).

We investigated the relation of diet during adolescence in a prospective cohort study of 39,268 premenopausal women within the Nurses Health Study II (NHS II). We focused our analysis on *a priori* hypotheses generated from previous retrospective studies (7) to examine the role of fat, carbohydrate, and fiber intake during this period of life in subsequent risk of breast cancer.

Materials and Methods

Study Population

The NHS II is a prospective cohort of 116,671 female registered nurses ages 25 to 43 y at enrollment in 1989

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who have completed biennial questionnaires on life-style and medical events. Incident cases of breast cancer are ascertained on biennial follow-up questionnaire and by a search of the National Death Index. The study has maintained a response rate of >90% (8). All reported cases of breast cancer are confirmed by next of kin, and permission to access medical records and pathology reports is requested. Pathology reports are available for 98% of the self-reported cancers and were used to extract information on hormone receptor characteristics of the tumor. One hundred ninety-one cases of carcinoma *in situ* were excluded from this analysis. Covariates including age, height, body mass index (BMI) at age 18 y, age at menopause and menarche, family history of breast cancer, and history of benign breast disease (BBD) were obtained from the biennial questionnaires. BMI was calculated as weight divided by height squared (kg/m^2) to estimate total adiposity.

In 1997, participants were asked if they would be willing to complete a supplemental food frequency questionnaire about diet during high school (HS-FFQ). Fifty-six thousand nine hundred twenty-eight women (49% of the entire cohort) indicated willingness, and 47,355 women returned the HS-FFQ in 1998 (83% of those sent the questionnaire). Participants with implausible daily caloric intake (<500 or ≥5,000 Kcal) and participants diagnosed with any cancer, except nonmelanoma skin cancer before 1999, were excluded. We restricted our analysis to women who were premenopausal at baseline. The overall number of women who met the inclusion criteria was 39,268.

The differences between participants who completed the HS-FFQ compared with participants who did not provide information on adolescent diet, in terms of baseline demographic characteristics or rates of breast cancer, were minimal (data not shown).

Adult and Adolescent Dietary Assessment

In 1991 and 1995, participants of the NHS II study completed a semiquantitative FFQ of usual dietary intake during the past year. The average of the 1991 and 1995 FFQ was used to estimate current nutrient intake. The main foods contributing to adult fat intake from this questionnaire were beef, chicken, pork, milk, mayonnaise, deep fried foods, margarine, and potato chips. Adolescent diet was measured using the 124-item HS-FFQ, which includes questions on main dishes, bread and cereals, fruits, vegetables, condiments, snack foods, dairy products, and beverages. This questionnaire was specifically designed to include foods that were commonly consumed during the period from 1960 to 1980 when these women would have been in high school (e.g., milkshakes, peanut butter, french fries). The HS-FFQ also included questions on type of fat usually used for frying and sautéing or baking, as well as questions on the form and brand of margarine and type of dairy products consumed (e.g., whole, low-fat, or skim milk and types of cheese).

Recall of adolescent diet among NHS II participants is reproducible (9, 10). The HS-FFQ was administered 4 y later to a random sample of 333 NHS II participants; the mean correlation for adolescent nutrient intakes reported 4 y apart was 0.65 (range, 0.50-0.77), whereas current adult diet was only weakly correlated with recalled adolescent diet (mean nutrient correlation, 0.20; for dietary fat, the correlation was 0.28; refs. 9, 10). The validity of the HS-FFQ was further assessed by administering it to 80 young adults who had provided dietary information 10 y earlier while in high school (11). The mean of correlations for nutrients between the two FFQs administered 10 y apart was 0.58 (range, 0.40-0.88). Furthermore, data on the diet of the nurses during teenage years were also collected from the nurses' mothers; the mean nutrient correlation of the mothers' compared with the nurses' own report was 0.40 (range, 0.13-0.59; ref. 10).

Nutrient intakes on the HS-FFQ were computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions, and then summing the contributions from all foods. Nutrient values in foods were obtained from the U.S. Department of Agriculture (12), food manufacturers, and independent academic sources (13, 14). Secular trends in food formulation and fortification were taken into account by using NHS II participants' year of birth to assign different nutrient profiles for specific foods. All nutrients were energy adjusted by using the residuals from the regression of nutrient intake on total caloric intake (15, 16). Energy-adjusted food and nutrient values were then divided into quintiles according to the distribution of all women who completed the HS-FFQ.

Statistical Analysis

Follow-up time in person-months extended from the time the participant completed the HS-FFQ until either June 2005, the date of breast cancer diagnosis, or death, whichever came first. Participants were divided into quintile categories, according to their adolescent intake of the nutrients studied. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (95% CI) for each category, using the lowest quintile of intake as the reference category, while controlling for potential confounding variables (17). Linear trends were examined by modeling fat and carbohydrate intake as a continuous variable in 100-calorie increments. The median value for each quintile was used for tests for trend for each food or food group. Missing value indicators were created for covariates with missing values (18).

Multivariate models were adjusted for age, total adolescent energy intake, age in 1989, age at onset of menarche, BMI at age 18 y, menopausal status, family history of breast cancer, current oral contraceptive use, age at first birth, parity, history of BBD, adult alcohol intake, and weight gain since age 18 y. Menopausal status, family history of breast cancer, oral contraceptive use, age at first birth and parity, history of BBD, alcohol intake,

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and weight were updated from the biennial questionnaires to the most recent information before date of diagnosis. All *P* values and 95% CIs are two sided.

Results

Table 1 shows the baseline characteristics of participants according to quintiles of adolescent total fat intake in adolescence. The mean age of participants in 1998 was 44 years (range, 34-53). The reported intake of total dietary fat ranged from 28 to 188 g/d (mean, 124 g/d, representing ~40% of total calories from fat. Compared with women in the lowest quintile of adolescent dietary fat intake, those in the highest quintile were more likely to be smokers and drink alcohol in adulthood.

During the average 7.8 years of follow-up, ranging from the return of the HS-FFQ in 1998 to June 2005, 455 premenopausal women were diagnosed with invasive breast cancer. The risk of breast cancer was higher among women who consumed more fat during adolescence. The multivariate RR was 1.35 (95% CI, 1.00-1.81; P_{trend} = 0.05) comparing the highest quintile to the lowest; however, no clear dose-response relationship was noted across quintiles of total fat (Table 2). Of note, total fat intake in adulthood was inversely related to breast cancer in this subgroup of women. Adjustment for adult fat intake did not appreciably change the fat-breast cancer association, which remained statistically significant (RR, 1.47; 95% CI, 1.08-2.01; P_{trend} = 0.02). Our results did not change appreciably when using different models for energy adjustment including the standard model, nutrient density model, or residual models (data not shown; ref. 19). Concurrent adjustment for adolescent red meat intake attenuated this association to RR (1.24; 95% CI, 0.89-1.72; P_{trend} = 0.25).

Table 1. Characteristics of participants at baseline in adulthood by 1998 and in adolescence by quintiles of energy-adjusted adolescent total fat intake

	Total fat quintiles				
	1 (*n* = 8,095)	2 (*n* = 7,984)	3 (*n* = 7,922)	4 (*n* = 7,666)	5 (*n* = 7,601)
Adolescence					
Mean					
Total calories per day	2,690	2,816	2,807	2,764	2,629
Total fat (g/ d)	105	118	125	131	142
Total animal fat (g/d)	62	73	78	84	94
Total vegetable fat (g/d)	43	45	46	47	48
Total carbohydrate (g/d)	360	327	310	293	264
Total red meat (servings per day)	1.07	1.38	1.53	1.67	1.88
Glycemic load	201	181	171	160	143
Glycemic index	56	55	55	55	54
BMI at age 18 y (kg/m^2)	20.9	21.0	21.1	21.3	21.5
Adulthood					
Mean					
BMI (kg/m^2)	25.2	25.5	25.7	25.9	26.3
Height (m)	1.65	1.65	1.65	1.65	1.65
Alcohol (g/d)	3.3	3.6	3.8	3.9	4.3
Age at first birth in parous women	27.1	26.9	26.8	26.6	26.5
Weight gain from age 18 y to 1997 (kg)	12	12	13	13	13
Current smokers (%)	7	7	8	9	10
Current oral contraceptive users (%)	9	9	9	8	9
History of biopsy-confirmed BBD (%)	18	18	18	18	19
Family history of breast cancer in mother or sister (%)	11	12	12	11	11
Nulliparity (%)	19	19	17	18	20
Parity of ≥3 children (%)	27	29	29	29	27
Age at menarche <12 y (%)	25	23	23	24	25

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Table 2. Energy and multivariable-adjusted hazard ratios and 95% CIs for invasive breast cancer risk in association with total and type of fat intake during adolescence among 39,268 premenopausal women in the NHS II

	Quintile of dietary fat intake during high school					P_{trend}
	1 (n = 8,095)	2 (n = 7,984)	3 (n = 7,922)	4 (n = 7,666)	5 (n = 7,601)	
Adolescent total fat						
No. of cases	76	84	88	89	118	
Median g/d	105	118	125	131	142	
% of total energy from fat	35	39	41	43	46	
Age and energy-adjusted RR (95% CI)	1.00	1.05 (0.77-1.43)	1.03 (0.76-1.41)	1.03 (0.76-1.41)	1.30 (0.97-1.74)	0.10
Multivariable-adjusted (M*) RR (95% CI)	1.00	1.06 (0.78-1.46)	1.04 (0.76-1.42)	1.06 (0.78-1.45)	1.35 (1.00-1.81)	0.05
M* + adult fat	1.00	1.14 (0.82-1.58)	1.10 (0.77-1.52)	1.14 (0.82-1.57)	1.47 (1.08-2.01)	0.02
M* + adolescent red meat	1.00	1.04 (0.76-1.42)	1.00 (0.73-1.38)	1.00 (0.73-1.39)	1.24 (0.89-1.72)	0.25
Adolescent saturated fat						
No. of cases	66	92	76	120	101	
Median g/d	39.6	45.1	48.9	52.9	58.9	
Age and energy-adjusted RR (95% CI)	1.00	1.29 (0.94-1.78)	0.99 (0.71-1.38)	1.44 (1.06-1.96)	1.15 (0.83-1.78)	0.35
M* RR (95% CI)	1.00	1.31 (0.95-1.80)	1.00 (0.72-1.40)	1.46 (1.07-1.99)	1.17 (0.84-1.62)	0.29
M* + adolescent red meat	1.00	1.26 (0.91-1.74)	0.94 (0.67-1.33)	1.35 (0.98-1.87)	1.05 (0.74-1.49)	0.66
Adolescent monounsaturated fat						
No. of cases	85	88	85	95	102	
Median g/d	37.7	41.8	44.5	47.2	51.2	
Age and energy-adjusted RR (95% CI)	1.00	1.00 (0.74-1.35)	0.95 (0.70-1.28)	1.07 (0.80-1.44)	1.10 (0.82-1.47)	0.45
M* RR (95% CI)	1.00	1.00 (0.75-1.31)	0.96 (0.71-1.31)	1.09 (0.81-1.46)	1.16 (0.86-1.55)	0.26
Adolescent polyunsaturated fat						
No. of cases	88	92	79	97	99	
Median g/d	15.4	18.0	20.0	22.0	25.5	
Age and energy-adjusted RR (95% CI)	1.00	1.08 (0.80-1.45)	0.94 (0.69-1.28)	1.18 (0.89-1.57)	1.26 (0.94-1.69)	0.09
M* RR (95% CI)	1.00	1.07 (0.80-1.43)	0.94 (0.69-1.28)	1.17 (0.88-1.57)	1.29 (0.96-1.73)	0.07
Adolescent trans fat						
Number of cases	105	98	86	84	82	
Median g/d	4.57	5.87	6.95	8.13	9.99	
Age and energy-adjusted RR (95% CI)	1.00	1.02 (0.77-1.35)	0.94 (0.70-1.25)	0.94 (0.70-1.26)	0.87 (0.65-1.17)	0.29
M* RR (95% CI)	1.00	1.02 (0.78-1.35)	0.95 (0.71-1.27)	0.95 (0.71-1.28)	0.89 (0.66-1.19)	0.35
Adolescent animal fat						
No. of cases	72	77	90	111	105	
Median g/d	57.5	69.7	78.6	87.7	101.1	
Age and energy-adjusted RR (95% CI)	1.00	0.94 (0.68-1.30)	1.01 (0.74-1.40)	1.14 (0.83-1.56)	1.03 (0.74-1.41)	0.56
M* RR (95% CI)	1.00	0.94 (0.68-1.30)	1.02 (0.74-1.41)	1.15 (0.84-1.57)	1.04 (0.75-1.43)	0.47
M* also adjusted for red meat	1.00	0.88 (0.63-1.23)	0.93 (0.66-1.29)	1.00 (0.71-1.41)	0.85 (0.58-1.25)	0.77
Adolescent vegetable fat						
No. of cases	110	84	90	85	86	
Median g/d	30.1	38.3	44.4	50.9	60.9	
Age and energy-adjusted RR (95% CI)	1.00	0.78 (0.60-1.01)	0.92 (0.71-1.19)	0.86 (0.66-1.13)	1.06 (0.81-1.40)	0.50
M* RR (95% CI)	1.00	0.76 (0.59-1.00)	0.90 (0.69-1.17)	0.83 (0.63-1.10)	1.05 (0.79-1.39)	0.44

NOTE: Multivariable-adjusted RR (M*) were adjusted for age, total energy intake, family history of breast cancer, history of BBD, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use.

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Red meat intake during adolescence was associated with breast cancer in this group of women (RR, 1.34; 95% CI, 0.94-1.89 comparing highest to lowest quintile; ref. 20). The main food item contributing to total fat intake in this population was milk (8%) followed by main dishes of beef (7%), pork (5%), chicken or turkey (4%), and processed meat (4%).

Polyunsaturated fat showed a borderline significant trend toward a positive association with breast cancer (RR, 1.29; 95% CI, 0.96-1.73; P_{trend} = 0.07). Individual types of fat including saturated, monounsaturated, and trans fat were not significant predictors of premenopausal breast cancer in this study. Similarly, subdividing fat intake according to animal or vegetable origin did not show a significant association between either of these groups and breast cancer.

The associations between total carbohydrate and quality of carbohydrate are shown in Table 3. Comparing the highest quintile of intake to the lowest, there was an inverse association between breast cancer and total carbohydrate (RR, 0.85; 95% CI, 0.63-1.14) and glycemic load (RR, 0.89; 95% CI, 0.66-1.20), although these trends did not reach statistical significance. Total carbohydrate was highly inversely correlated with dietary fat in this group of women (R = −0.89). Fiber was not significantly associated with breast cancer risk (RR, 0.96; 95% CI, 0.80-1.14).

Of the breast cancer cases with available pathology reports, 268 were estrogen receptor (ER) and progesterone receptor (PR) positive, and 72 were ER/PR negative. Table 4 presents the association between the total and the subtypes of fat and breast cancer according to hormone receptor status. When total fat intake was modeled as a continuous variable, the RR of breast cancer was 1.07 (95% CI, 0.99-1.15) for each additional 100 calories from fat. When we subdivided breast cancers according hormone receptor status, associations between total dietary fat were stronger among ER/PR-negative tumors (RR, 1.27; 95% CI, 1.04-1.56; P = 0.02) than for ER/PR-positive tumors (RR, 1.04; 95% CI, 0.94-1.15; P = 0.43) per 100 calories. Saturated fat was significantly related to ER/PR-negative tumors (RR, 1.57; 95% CI, 1.11-2.23; P = 0.01) but not to ER/PR-positive tumors (RR, 0.95; 95% CI, 0.79-1.13; P = 0.55). No overall association between total milk or total dairy intake were observed, although a nonsignificant inverse trend between breast cancer and low-fat milk and low-fat dairy was noted (Table 5).

Table 3. Energy and multivariable-adjusted hazard ratios and 95% CIs for invasive breast cancer risk in association with total carbohydrate and carbohydrate quality among 39,268 premenopausal women in the NHS II

	Quintile of carbohydrate intake during high school					P_{trend}
	1 (*n* =7,652)	2 (*n* = 7,734)	3 (*n* = 7,867)	4 (*n* = 8,017)	5 (*n* = 7,998)	
Total carbohydrate						
No. of cases	105	103	85	81	81	
Median g/d	258	291	310	330	366	
Energy-adjusted RR (95% CI)	1.00	1.03 (0.78-1.36)	0.87 (0.65-1.16)	0.83 (0.62-1.11)	0.88 (0.65-1.18)	0.17
M* RR (95% CI)	1.00	1.00 (0.76-1.32)	0.84 (0.63-1.13)	0.80 (0.59-1.07)	0.85 (0.63-1.14)	0.10
Glycemic ondex						
No. of cases	93	98	79	90	95	
Median value per day	51.6	53.6	55.0	56.3	58.4	
Energy-adjusted RR (95% CI)	1.00	1.10 (0.83-1.47)	0.89 (0.66-1.21)	1.04 (0.78-1.40)	1.17 (0.88-1.56)	0.40
M* RR (95% CI)	1.00	1.10 (0.82-1.46)	0.89 (0.66-1.21)	1.04 (0.78-1.40)	1.18 (0.88-1.58)	0.37
Glycemic load						
No. of cases	103	107	68	99	78	
Median value per day	142	158	170	182	203	
Energy-adjusted RR (95% CI)	1.00	1.13 (0.86-1.48)	0.76 (0.56-1.04)	1.04 (0.78-1.37)	0.92 (0.68-1.24)	0.46
M* RR (95% CI)	1.00	1.11 (0.84-1.46)	0.74 (0.54-1.01)	1.01 (0.76-1.33)	0.89 (0.66-1.20)	0.33
Fiber						
No. of cases	120	97	103	95	102	
Median g/d	15.1	18.0	20.3	22.8	27.5	
Energy-adjusted RR (95% CI)	1.00	0.92 (0.69-1.22)	0.90 (0.68-1.20)	0.83 (0.62-1.11)	0.93 (0.70-1.24)	0.52
M* RR (95% CI)	1.00	0.91 (0.68-1.20)	0.88 (0.66-1.17)	0.81 (0.61-1.09)	0.90 (0.67-1.20)	0.38

NOTE: Multivariable-adjusted RR (M*) were adjusted for age, total energy intake, family history of breast cancer, history of BBD, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use.

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Table 4. Multivariable-adjusted hazard ratios and 95% CIs for invasive breast cancer risk in association with fat and carbohydrate intake according to ER and PR status of tumors

	Multivariate adjusted RR (95% CI) 100 calorie increment/d	*P*
Total fat		
All breast cancer (*n* = 455)	1.07 (0.99-1.15)	0.11
ER/PR positive (*n* = 268)	1.04 (0.94-1.15)	0.43
ER/PR negative (*n* = 72)	1.27 (1.04-1.56)	0.02
Saturated fat		
All breast cancer (*n* = 455)	1.05 (0.91-1.20)	0.51
ER/PR receptor positive (*n* = 268)	0.95 (0.79-1.13)	0.55
ER/PR receptor negative (*n* = 72)	1.57 (1.11-2.23)	0.01
Monounsaturated fat		
All breast cancer (*n* = 455)	1.12 (0.93-1.36)	0.24
ER/PR receptor positive (*n* = 268)	1.18 (0.92-1.50)	0.20
ER/PR receptor negative (*n* = 72)	1.43 (0.89-2.30)	0.14
Polyunsaturated fat		
All breast cancer (*n* = 455)	1.33 (1.04-1.70)	0.02
ER/PR receptor positive (*n* = 268)	1.30 (0.94-1.78)	0.11
ER/PR receptor negative (*n* = 72)	1.30 (0.70-2.41)	0.40
Trans fat		
All breast cancer (*n* = 455)	0.97 (0.60-1.56)	0.90
ER/PR receptor positive (*n* = 268)	1.01 (0.55-1.86)	0.97
ER/PR receptor negative (*n* = 72)	1.31 (0.41-4.18)	0.65
Animal fat		
All breast cancer (*n* = 455)	1.02 (0.96-1.09)	0.51
ER/PR receptor positive (*n* = 268)	1.00 (0.92-1.09)	0.98
ER/PR receptor negative (*n* = 72)	1.19 (1.01-1.40)	0.04
Vegetable fat		
All breast cancer (*n* = 455)	1.05 (0.96-1.15)	0.32
ER/PR receptor positive (*n* = 268)	1.06 (0.94-1.20)	0.32
ER/PR receptor negative (*n* = 72)	0.98 (0.78-1.24)	0.88
Carbohydrate		
All breast cancer (*n* = 455)	0.95 (0.90-1.01)	0.13
ER/PR receptor positive (*n* = 268)	0.96 (0.89-1.04)	0.31
ER/PR receptor negative (*n* = 72)	0.86 (0.74-1.01)	0.06
Fiber (10-g increment)		
All breast cancer (*n* = 455)	0.96 (0.80-1.14)	0.63
ER/PR receptor positive (*n* = 268)	0.97 (0.77-1.21)	0.76
ER/PR receptor negative (*n* = 72)	0.90 (0.57-1.42)	0.64

NOTE: Multivariable-adjusted RR (M*) were adjusted for age, total energy intake, family history of breast cancer, history of BBD, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use.

Discussion

In this prospective study of 39,268 premenopausal women, we observed a modest direct association between adolescent intake of fat and breast cancer. This association persisted after adjusting for adult fat intake. Subtypes of fat were not significantly related to invasive breast cancer overall. Milk, dairy, and total carbohydrate intake in adolescence as well as the quality of carbohydrate as assessed by glycemic load, glycemic index and dietary fiber were not associated with breast cancer. Frequent consumption of fat and especially saturated fat during adolescence was positively related to incidence of hormone receptor–negative breast tumors. However, dietary fat was not related to hormone receptor–positive tumors in this study.

The task of accurately evaluating diet many years prior in a woman's life is inevitably a difficult one and, since exposure was assessed retrospectively, is limited by our study participants' memory. Yet in the absence of data

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collected during adolescence itself, with many decades of follow-up, the use of a validated and reproducible (10, 11) questionnaire is the best available tool to examine this potentially important hypothesis.

Although detailed case ascertainment including pathology reports provides important information on hormone receptor status, the sample size is too small to examine effect modification in detail in this analysis. Including only those breast cancer cases occurring after the return of the HS-FFQ ensures that a recall is not influenced by a diagnosis of cancer. Furthermore, the younger, premenopausal women included here have a shorter time interval between adolescence and the reporting of their diet, which should aid recall. The repeated measures of other risk factors allow for updated and detailed control for confounding, including confounding by adult diet.

To our knowledge, these are the first prospective data on adolescent dietary fat and carbohydrate intake in relation to breast cancer risk. Several retrospective case-control studies to date have examined the relationship between dietary fat, carbohydrate, milk, meat, fiber, and other nutrients during early life and breast cancer. Results of previous studies on childhood fat intake are mixed: some studies find inverse associations with total fat (21) and vegetable fat (7), whereas others note positive associations with high-fat meat and breast cancer (22). In our study, total fat intake as well as saturated fat intake were both significantly related to incidence of hormone receptor–negative tumors. This was contrary to our *a priori* hypothesis that hormone receptor–positive tumors would be more sensitive to the effect of dietary fat because of the theoretical influence of fat-soluble hormones in food. Whether this finding is a real effect or a chance finding due to small numbers of cases of hormone receptor–negative tumors remains unclear. Finally, the detrimental effect of total fat disappeared when we controlled for adolescent red meat consumption, suggesting that the causative agent may be red meat, and not dietary fat itself. Red meat intake during adolescence was also related to premenopausal breast cancer in a prior analysis (20). Interestingly, this association was clearest for ER/PR-positive tumors, raising the possibility of a distinct mechanistic pathway of red meat compared with dietary fat on breast cancer subtypes.

Our results are consistent with previous retrospective studies on adolescent fiber intake showing no significant associations with breast cancer (7, 21). Glycemic index was directly associated with breast cancer in the earlier retrospective analysis of the NHS II (RR, 1.47; 95% CI, 1.04-2.08; ref. 7); however, the present prospective analysis did not

Table 5. Milk and dairy intake in adolescence and risk of breast cancer

	Quintile of milk intake during high school					P_{trend}
	1	2	3	4	5	
Total milk						
Energy-adjusted RR (95% CI)	1.00	1.06 (0.79-1.41)	0.99 (0.72-1.37)	0.93 (0.69-1.25)	1.01 (0.74-1.38)	0.66
M* RR (95% CI)	1.00	1.05 (0.79-1.40)	0.99 (0.71-1.36)	0.91 (0.68-1.23)	0.98 (0.71-1.34)	0.51
Full-fat milk						
Energy-adjusted RR (95% CI)	1.00	1.43 (1.01-2.02)	1.00 (0.66-1.50)	1.03 (0.73-1.04)	1.12 (0.75-1.66)	0.65
M* RR (95% CI)	1.00	1.42 (1.00-2.01)	1.01 (0.67-1.51)	1.00 (0.71-1.41)	1.09 (0.73-1.63)	0.49
Low-fat milk						
Energy-adjusted RR (95% CI)	1.00	0.85 (0.45-1.63)	0.92 (0.43-1.99)	0.96 (0.52-1.78)	0.84 (0.45-1.56)	0.62
M* RR (95% CI)	1.00	0.88 (0.46-1.69)	0.94 (0.43-2.02)	0.95 (0.51-1.77)	0.83 (0.45-1.55)	0.47
Total dairy						
Energy-adjusted RR (95% CI)	1.00	0.99 (0.74-1.33)	0.92 (0.68-1.25)	1.02 (0.76-1.38)	0.94 (0.67-1.33)	0.84
M* RR (95% CI)	1.00	0.99 (0.73-1.32)	0.91 (0.67-1.23)	1.00 (0.74-1.36)	0.90 (0.64-1.27)	0.64
High-fat dairy						
Energy-adjusted RR (95% CI)	1.00	1.17 (0.87-1.58)	1.19 (0.87-1.61)	1.26 (0.93-1.70)	1.00 (0.71-1.41)	0.82
M* RR (95% CI)	1.00	1.16 (0.85-1.58)	1.17 (0.86-1.59)	1.22 (0.90-1.66)	0.95 (0.68-1.35)	0.61
Low-fat dairy						
Energy-adjusted RR (95% CI)	1.00	0.85 (0.64-1.13)	0.88 (0.64-1.21)	0.91 (0.66-1.24)	0.75 (0.54-1.06)	0.22
M* RR (95% CI)	1.00	0.85 (0.64-1.13)	0.88 (0.64-1.21)	0.91 (0.66-1.25)	0.76 (0.54-1.07)	0.25

NOTE: Multivariable-adjusted RR (M*) were adjusted for age, total energy intake, family history of breast cancer, history of BBD, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use. Full-fat milk: reported whole milk; low-fat milk: skim or low-fat milk; high-fat dairy: whole milk, whole chocolate milk, ice cream, frappe, cheese (except for ricotta or cottage), and butter; low-fat dairy: low-fat milk, low-fat chocolate milk, ricotta or cottage cheese, sherbert, yogurt, and instant breakfast cereal.

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show an association with this marker of carbohydrate quality. The positive association of dietary fat with premenopausal breast cancer and strong inverse correlation between carbohydrate and fat intake makes the interpretation of effect measures of carbohydrate intake difficult. Milk consumption in childhood has been inversely associated with breast cancer in most studies (7, 21, 23-29); however, only two showed statistically significant decreased risk of breast cancer (21, 29). Although not statistically significant, our findings of inverse trends with low-fat dairy and low-fat milk products are similar to those of earlier studies.

In addressing our original hypothesis that diet in early life may predict future breast cancer risk, we found some evidence that adolescent dietary fat may influence the risk of breast cancer among premenopausal women. The absence of strong effects with other nutrients may be due to attenuated effects from distant recall and measurement error in the HS-FFQ. Alternatively, it is possible that dietary factors play a role even earlier in childhood, for example, by influencing the timing of menarche (30) or affecting rate of physical growth (31). Future studies are needed to confirm these results in premenopausal women and to assess the relation of adolescent diet to risk of breast cancer among postmenopausal women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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