Dietary Fiber Intake in Young Adults and Breast Cancer Risk

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abstract

OBJECTIVE: We evaluated fiber intake during adolescence and early adulthood in relation to breast cancer (BC) risk in the Nurses' Health Study II.

METHODS: Among 90 534 premenopausal women who completed a dietary questionnaire in 1991, we documented 2833 invasive BC cases during 20 years of follow-up. In 1998, 44 263 of these women also completed a questionnaire about their diet during high school; among these women, we documented 1118 cases of BC by end of follow-up. Multivariable-adjusted Cox proportional hazards regression was used to model relative risks (RRs) and 95% confidence intervals (CIs) for BC across categories of dietary fiber.

RESULTS: Among all women, early adulthood total dietary fiber intake was associated with significantly lower BC risk (RR for highest versus lowest quintile 0.81; 95% CI 0.72–0.91; $P_{trend} = .002$). Higher intakes of soluble fiber (RR for highest versus lowest quintile 0.86; 95% CI 0.77–0.97; $P_{trend} = .02$) and insoluble fiber (RR for highest versus lowest quintile 0.80; 95% CI 0.71–0.90; $P_{trend} < .001$) were each associated with lower BC risk. Total dietary fiber intake in adolescence was also associated with lower BC risk (RR for highest versus lowest quintile 0.84; 95% CI 0.70–1.01; $P_{trend} = .04$). For the average of fiber intake during adolescence and early adult life, the RR comparing highest with lowest quintiles was 0.75 (95% CI 0.62–0.91, $P_{trend} = .004$).

CONCLUSIONS: Our findings support the hypothesis that higher fiber intakes reduce BC risk and suggest that intake during adolescence and early adulthood may be particularly important.

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WHAT'S KNOWN ON THIS SUBJECT: Previous studies of fiber intake and breast cancer (BC) have almost all been nonsignificant, but none of them examined diet during adolescence or early adulthood, a period when BC risk factors appear to be particularly important.

WHAT THIS STUDY ADDS: This study adds to the few potentially modifiable risk factors for BC. Higher fiber intake was associated with lower BC risk and suggests that intake during adolescence and early adulthood may be particularly important.

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Sex steroid hormone levels are strongly related to breast cancer (BC) development,[1,2] and a diet high in fiber has been hypothesized to reduce BC incidence by inhibiting reabsorption of estrogen, thus decreasing circulating levels.[3–5] In most prospective studies,[6–22] including the Nurses' Health Study,[23] no significant associations have been seen between fiber intake and BC risk. In a recent meta-analysis of 16 prospective studies, a weak inverse association was found; for an increment of 10 g fiber per day, a 5% lower BC risk was seen.[24] Notably, most previous evidence on fiber intake and BC has been from studies in which women were enrolled during midlife or later; the effects of fiber during adolescence or early adulthood on BC incidence have been minimally studied. The atomic bombing of Hiroshima and Nagasaki and radiation treatment of Hodgkin's lymphoma indicate that breast tissue may be particularly susceptible to carcinogenic exposures during childhood and early adult life.[25–27] Furthermore, in the Nurses' Health Study II (NHSII) cohort, fiber intake during adolescence was inversely associated with proliferative benign breast disease (BBD), which is thought to reflect an early step in breast carcinogenesis. Women in the highest quintile of fiber intake had a 25% lower proliferative BBD risk than women in the lowest quintile,[28] suggesting the importance of investigating dietary factors during this period of life.

In a previous analysis of NHSII,[29,30] fiber intakes during adolescence or early adulthood were not significantly associated with premenopausal BC risk. Updating these analyses with longer follow-up and a substantially larger number of cases, we were able to examine fiber intakes during adolescence and early adulthood in relation to BC diagnosed before and after menopause. In addition, we investigated the associations between fiber intake and BC by hormone receptor status.

METHODS

Study Population

The NHSII is an ongoing prospective cohort study of 116 430 female registered nurses aged 25 to 42 years at enrollment in 1989. For this analysis, follow-up began in 1991 when diet was first measured. From the 97 813 women who returned the 1991 food frequency questionnaire (FFQ), we excluded women who had an implausible total energy intake (<600 or >3500 kcal/day); were postmenopausal in 1991; or had reported a previous diagnosis of cancer (except nonmelanoma skin cancer) before returning the 1991 questionnaire. After exclusions, data from 90 534 women were available for the early adulthood fiber intake analysis.

In 1997, participants were asked about their willingness to complete a supplemental FFQ about diet during high school (HS-FFQ). Of the 64 380 women (55% of the entire cohort) who indicated willingness to do so, 47 355 returned the questionnaire in 1998.They were 33 to 52 years of age at that time (1997-99). There were minimal differences in baseline demographic characteristics and BC rates between participants who completed the HS-FFQ and women who did not provide information on high school diet.[29]

After excluding women who had any cancer except nonmelanoma skin cancer before 1998 or who reported implausible daily caloric intake during adolescence (<600 or ≥5000 kcal), 44 263 women were available for the adolescent fiber intake analysis.

This study was approved by the Human Subjects Committee at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, Massachusetts).

Dietary Assessment

Dietary intake was obtained from NHSII participants via validated semiquantitative FFQ with ~130 items about usual dietary intake and alcohol consumption during the past year (available at http://www.channing.harvard.edu/nhs/?page_id=246) in 1991 and every 4 years thereafter. Validity of the questionnaire to assess long-term intake was assessed by comparison with weighed diet records collected 3 to 4 years earlier; the correlation for dietary fiber intake, adjusted for energy intake, was 0.56.[31] It is modest to good correlation, although it does cause attenuation of an association. The impact of this degree of measurement error is shown by the change in relative risk (RR) when we corrected for measurement error. Also, fiber intake assessed by this questionnaire has robustly predicted lower risks of coronary heart disease,[32] type 2 diabetes,[33] and constipation.[34]

Food intakes during adolescence were evaluated using a semiquantitative 124-item HS-FFQ that included food items typically consumed between 1960 and 1980 when the participants were in high school. Frequency of consumption was classified into 9 categories ranging from "never or less than once per month" to "6 or more per day." The validity of the HS-FFQ was evaluated among 80 young women by comparing their responses to HS-FFQ with three 24-hour recalls 10 years apart; the mean of corrected correlation coefficients for energy-adjusted nutrient intakes was 0.45 (range 0.16–0.68).[35]

Nutrient values in foods were obtained from the US Department of Agriculture, food manufacturers, and independent academic sources.[36–38] The food composition database was updated every 4 years to account for changes in the food supply. Fiber intakes were energy-adjusted by using the residuals from the regression of nutrient intake on total energy intake.[39]

Documentation of BC

Biennial NHSII questionnaires were used to identify newly diagnosed invasive BC. Deaths in this cohort 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. When a case of BC was identified, we asked the participant (or next of kin for those who had died) for diagnosis confirmation and for permission to obtain relevant hospital records and pathology reports. Pathology reports confirmed 99% of the self-reported diagnoses of BC. Because the degree of self-reporting accuracy was high, diagnoses confirmed by participants with missing medical record information (n = 344) were included in the analysis. Information on estrogen and progesterone receptor (ER and PR) status of the BC was obtained from pathology reports.

Assessment of Other Variables

Data on potential risk factors for BC were obtained from the biennial NHSII questionnaires and updated to the most recent information before date of diagnosis, if available. Data on BMI at age 18 and alcohol consumption during adolescence were obtained from the 1989 questionnaire. Weight change from age 18 was calculated by taking the difference between current weight and recalled weight at age 18. Women missing menopausal status were considered premenopausal if they were <46 (smokers) or <48 (nonsmokers) years old and postmenopausal after a hysterectomy/bilateral oophorectomy or if they were <54 (smokers) or <56 (nonsmokers) years old.[40]

Statistical Analysis

The primary analysis used the 1991 baseline diet, as this represents diet earliest in adult life. For early adulthood fiber intake, participants contributed person-years from the date of return of the 1991 questionnaire until the date of any cancer diagnosis, death, or end of follow-up period (June 1, 2011), whichever came first. For adolescent fiber intake, follow-up time began with return of the baseline questionnaire in 1998 with the same follow-up period. Participants were divided into quintiles according to their dietary intake. Cox proportional hazards regression was used to estimate RR and 95% confidence intervals (CIs) for each category, by using the lowest quintile of intake as the reference category. We replaced missing covariate data with carried-forward method for continuous variables and missing indicator method for categorical variables. To control for confounding by age or calendar time, or any possible 2-way interactions between these 2 time scales, the regression models included age in months as the time scale, stratified by calendar year of the current questionnaire cycle. Multivariable models also simultaneously adjusted for race, family history of BC in mother or sisters, history of BBD, smoking, height, BMI at age 18, weight change since age 18, age at menarche, parity and age at first birth, oral contraceptive use, menopausal status, postmenopausal hormone use, age at menopause, and early adulthood intakes of alcohol and energy. For adolescent fiber intake and BC risk, multivariable models additionally adjusted for adolescent alcohol intake and adolescent energy intake (instead of early adulthood energy intake). The median value for each quintile was used for tests for trend, modeled as a continuous variable.

We further examined whether the associations of fiber intake with BC risk depended on the other dietary factors and healthy eating. We therefore evaluated the influence of adjustment for alternate healthy eating index score[41] as well as red meat, animal fat, or β-carotene. Because longer menstrual cycles have been associated with lower BC risk[42] and higher dietary fiber intake may affect BC risk by increasing menstrual cycle length,[43] we examined the association between dietary fiber intake and BC risk after further adjustment for menstrual cycle length. Because dietary intake has been hypothesized to affect breast carcinogenesis over an extended period of time, for a sensitivity analyses, we calculated premenopausal cumulative average fiber intake (by using the 1991, 1995, 1999, 2003, and 2007 dietary data), stopping updating when a woman reached menopause. We also calculated average of adolescent and adult (1991) fiber intake. Because associations are affected by imperfect assessment of diet, the association between early adulthood fiber intake and BC was also corrected for measurement error using the regression calibration method.[44–46] For the calibration of our dietary questionnaire, we used multiple weighted diet records as the true intake based on an earlier validation study in the Nurses' Health Study.[31] To examine whether the associations between fiber intake and BC risk were modified by BMI at age 18, a cross-product term of the ordinal score for BMI at age 18 and fiber intake expressed as a continuous variable was included in the multivariable model. P values for tests for interactions were obtained from a likelihood ratio test. To examine differential associations of dietary fiber intake with BC risk by hormone receptor status, we used Cox proportional cause-specific hazards regression model with a duplication method for competing

TABLE 1 Age-Standardized Characteristics According to Intake of Energy-Adjusted Dietary Fiber in Adolescence and Early Adulthood Among Women Enrolled in the NHSII

Characteristic	Early Adulthood Dietary Fiber, Quintile					Adolescent Dietary Fiber, Quintile[a]				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
n	18 364	18 110	17 698	18 195	18 167	8865	8870	8863	8828	8837
Age, y	35.8 ± 4.8	36.2 ± 4.6	36.5 ± 4.6	36.7 ± 4.6	37.1 ± 4.5	43.3 ± 4.4	42.8 ± 4.6	42.6 ± 4.7	42.5 ± 4.7	42.1 ± 4.9
Energy-adjusted adulthood total fiber intake, g/d	12.0 ± 1.7	15.3 ± 0.7	17.6 ± 0.7	20.2 ± 0.9	26.4 ± 5.1	16.3 ± 5.2	17.5 ± 5.0	18.3 ± 5.1	19.5 ± 5.5	21.5 ± 6.0
Energy-adjusted adolescent total fiber intake, g/d	18.4 ± 4.2	19.7 ± 4.4	20.7 ± 4.6	21.8 ± 5.1	23.7 ± 6.4	14.7 ± 1.7	18.0 ± 0.7	20.3 ± 0.7	22.9 ± 0.9	28.9 ± 4.8
Adulthood total energy intake, kcal/d	1767 ± 570	1797 ± 551	1813 ± 542	1803 ± 534	1774 ± 543	1741 ± 545	1806 ± 546	1832 ± 555	1840 ± 552	1844 ± 567
Adulthood alcohol consumption, g/d	3.8 ± 8.3	3.2 ± 6.1	3.1 ± 5.6	2.9 ± 5.0	2.7 ± 4.8	3.4 ± 6.2	3.4 ± 6.0	3.4 ± 5.8	3.4 ± 5.8	3.3 ± 5.7
BMI	25.0 ± 5.9	24.8 ± 5.5	24.6 ± 5.2	24.5 ± 5.1	24.0 ± 4.7	25.9 ± 5.9	25.9 ± 6.0	25.9 ± 6.0	25.8 ± 5.8	25.6 ± 5.9
BMI at age 18	21.1 ± 3.5	21.2 ± 3.3	21.2 ± 3.2	21.3 ± 3.3	21.4 ± 3.3	21.1 ± 3.2	21.1 ± 3.2	21.2 ± 3.2	21.2 ± 3.2	21.2 ± 3.2
Age at first birth, y	25.6 ± 4.2	25.8 ± 4.1	25.9 ± 4.1	26.0 ± 4.1	26.1 ± 4.3	26.0 ± 4.4	26.3 ± 4.5	26.4 ± 4.6	26.6 ± 4.7	27.0 ± 4.9
Current smoker	19	13	11	9	8	11	10	10	9	7
Current oral contraceptive use	11	11	11	11	11	9	8	8	9	8
History of BBD	10	9	10	9	9	16	16	16	16	16
Family history of BC in mother or sisters	15	15	15	15	16	15	16	16	17	16
Nulliparous	28	24	24	26	32	20	19	19	20	23
Age at menarche <12 y	23	23	24	25	26	23	24	24	24	26
Mammogram or clinical breast exam	46	48	49	49	50	82	83	83	83	82

Data are expressed as mean ± SD or %.
[a] Participants recalled their dietary intake during adolescence in 1998.

risk data.[47] All *P* values were 2-sided. SAS version 9.3 (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

During 1 725 295 person-years of follow-up of 90 534 women, 2833 women were diagnosed with invasive breast carcinoma. The age range of the participants at baseline in 1991 was 27 to 44 years (mean 36.4 ± 4.6 years). Among 44 263 women with data on adolescent fiber intake, 1118 women were diagnosed with invasive BC from 1998 to 2011. Table 1 presents the distribution of risk factors for BC by quintiles of dietary fiber intake in 1991 and adolescence. Women with a higher fiber intake during either early adulthood or adolescence were less likely to be smokers and more likely to have earlier age at menarche, to be nulliparous, and to be older at first birth. Higher fiber intake during early adulthood was also associated with lower alcohol consumption and lower adulthood BMI as well as slightly higher rates of mammography screening (50% in quintile 5 of fiber intake and 46% in quintile 1) (Table 1).

Among all women, early adulthood total fiber intake was associated with significantly lower BC risk. In multivariable model, compared with the lowest quintile, RRs of BC across increasing quintiles of fiber intake were significantly lower by 17%, 12%, 18%, and 19% (P_{trend} = .002) (Table 2). This association was materially unchanged with adjustment for red meat intake, animal fat, or alternate healthy eating index (data not shown). Additional adjustment for β-carotene intake or menstrual cycle length did not change the association between fiber intake and BC (data not shown). We also observed a significant inverse association between fiber intake and premenopausal BC incidence (highest versus lowest quintile; RR 0.77; 95%

TABLE 2 RR and 95% CI for BC According to Quintile of Dietary Fiber Intake in Adolescence and Early Adulthood Among Women in the NHSII

Item	Quintile of Intake					
	1	2	3	4	5	P_{trend}
Energy-adjusted early adulthood total fiber						
All cases						
Median intake, g/day	12.4	15.3	17.6	20.1	24.9	
No. of cases/person-years	613/349 827	534/345 587	560/336 743	559/347 327	567/345 813	
Age-adjusted RR (95% CI)	1	0.85 (0.76–0.96)	0.90 (0.80–1.01)	0.85 (0.75–0.95)	0.85 (0.75–0.95)	.01
Multivariable RR (95% CI)[a]	1	0.83 (0.74–0.94)	0.88 (0.78–0.98)	0.82 (0.73–0.93)	0.81 (0.72–0.91)	.002
Premenopausal cases						
Median intake, g/day	12.3	15.2	17.5	20.1	24.	8
No. of cases/person-years	355/228 607	308/232 003	338/239 237	337/227 825	321/232 349	
Age-adjusted RR (95% CI)	1	0.82 (0.70–0.96)	0.85 (0.73–0.99)	0.87 (0.75–1.01)	0.80 (0.69–0.93)	.02
Multivariable RR (95% CI)[a]	1	0.81 (0.70–0.95)	0.84 (0.72–0.97)	0.86 (0.74–1.00)	0.77 (0.66–0.90)	.008
Postmenopausal cases						
Median intake, g/day	12.5	15.4	17.7	20.4	25.3	
No. of cases/person-years	191/81 768	162/79 549	176/80 959	165/83 037	181/80 980	
Age-adjusted RR (95% CI)	1	0.84 (0.68–1.03)	0.91 (0.74–1.11)	0.82 (0.66–1.01)	0.90 (0.73–1.10)	.38
Multivariable RR (95% CI)[a]	1	0.82 (0.66–1.01)	0.88 (0.71–1.08)	0.81 (0.66–1.00)	0.87 (0.70–1.07)	.29
Energy-adjusted adolescent total fiber						
All cases						
Median intake, g/day	15.1	18.0	20.3	22.8	27.5	
No. of cases/person-years	261/118 382	227/118 811	223/118 666	198/118 493	209/118 483	
Age-adjusted RR (95% CI)	1	0.87 (0.73–1.04)	0.88 (0.73–1.05)	0.79 (0.66–0.95)	0.85 (0.71–1.03)	.07
Multivariable RR (95% CI)[b]	1	0.86 (0.72–1.03)	0.87 (0.73–1.04)	0.78 (0.64–0.93)	0.84 (0.70–1.01)	.04
Premenopausal cases						
Median intake, g/day	15.2	18.2	20.5	23.1	27.8	
No. of cases/person-years	130/67 181	113/67 287	110/67 126	97/67 290	94/67 117	
Age-adjusted RR (95% CI)	1	0.89 (0.69–1.14)	0.87 (0.67–1.12)	0.79 (0.61–1.03)	0.78 (0.60–1.02)	.05
Multivariable RR (95% CI)[b]	1	0.88 (0.68–1.13)	0.86 (0.66–1.11)	0.78 (0.60–1.02)	0.76 (0.58–1.00)	.04
Postmenopausal cases						
Median intake, g/day	14.9	17.8	20.0	22.5	27.1	
No. of cases/person-years	106/41 588	98/41 247	88/41 386	84/41 423	90/41 322	
Age-adjusted RR (95% CI)	1	0.93 (0.70–1.22)	0.84 (0.63–1.11)	0.80 (0.60–1.06)	0.86 (0.65–1.14)	.20
Multivariable RR (95% CI)[b]	1	0.93 (0.70–1.23)	0.84 (0.63–1.12)	0.78 (0.58–1.04)	0.85 (0.64–1.13)	.16

P_{trend} calculated with median intake of each variable in each quintile as a continuous variable.
[a] 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, nonwhite), family history of BC in mother or sisters (yes, no), history of BBD (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 inches), BMI at age 18 y (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0), weight change since age 18 (continuous), age at menarche (<12, 12, 13, ≥14 y), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 y, parity ≤2 and age at first birth 25 to <30 y, parity ≤2 and age at first birth ≥30 y, parity 3 to 4 and age at first birth <25 y, parity 3 to 4 and age at first birth 25 to <30 y, parity 3 to 4 and age at first birth ≥30 y, parity ≥5 and age at first birth <25 y, parity ≥5 and age at first birth ≥25 y), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), and energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45, 45–46, 47–48, 49–50, 51–52, ≥53 y). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, ≥53 y). [b] For adolescent fiber, we additionally adjusted for adolescent alcohol intake (nondrinker, <1.5, 1.5 to <5, 5 to <10, ≥10 g/day) and adolescent energy intake (quintile; instead of adult energy intake).

CI 0.66–0.90; P_{trend} = .008). A slightly weaker association was observed among postmenopausal women, though this did not reach statistical significance (RR 0.87; 95% CI 0.70–1.07; P_{trend} = .29).

In a sensitivity analysis using the cumulative average of premenopausal fiber intake, similar results were found (among all women: RR 0.84; 95% CI 0.75–0.95, P_{trend} = .004; among premenopausal women: RR 0.83; 95% CI 0.71–0.97; P_{trend} = .008; and among postmenopausal women: RR 0.88; 95% CI 0.71–1.08, P_{trend} = .46; highest versus lowest quintile) (P = .67 for differences in RRs). After correction for measurement error in measuring adulthood fiber intake, treated as a continuous variable, the RR was deattenuated from 0.91 (0.85–0.98) to 0.81 (0.69–0.96) for each 10 g/day of fiber intake in the age-adjusted model.

Adolescent fiber intake was only modestly correlated with early adult (1991) fiber intake (r = 0.34). Higher fiber intake during adolescence was associated with lower BC risk (RR 0.84; 95% CI 0.70–1.01; P_{trend} = .04; highest versus lowest quintile) among all women. This association was minimally changed after additional adjustment for red meat intake (RR 0.86; 95% CI 0.71–1.04; P_{trend} = .08; highest versus lowest quintile) and animal fat intake (RR 0.81; 95% CI 0.66–0.99; P_{trend} = .03; highest versus lowest quintile). Controlling for β-carotene or adult fiber intake minimally affected the RR, but the CI widened slightly so

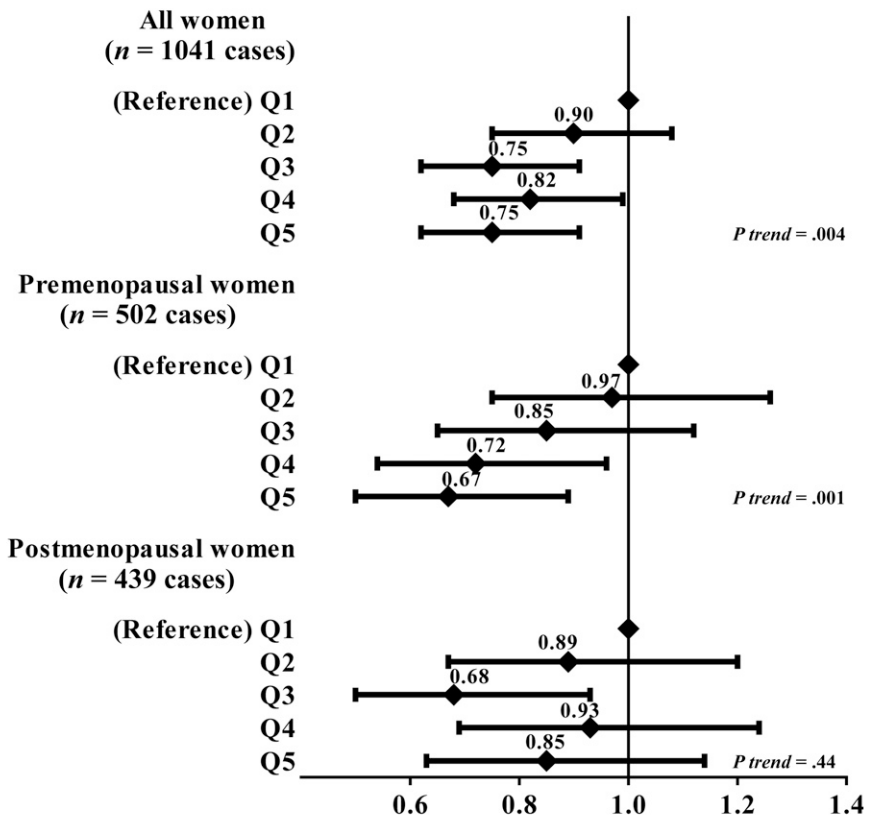

FIGURE 1
Multivariable* RR of BC (and 95% CI) associated with average intake of fiber in adolescence and early adulthood among women in the NHSII. Categories are quintiles of intake. Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white, nonwhite), family history of BC in mother or sisters (yes, no), history of BBD (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 inches), BMI at age 18 years (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0), weight change since age 18 (continuous), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, past, current), adolescent alcohol intake (nondrinker, <1.5, 1.5 to <5, 5 to <10, ≥10 g/day), adult alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), and adolescent energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45, 45–46, 47–48, 49–50, 51–52, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, ≥53 years). Median of fiber intake for each quintile are 14.8, 17.3, 19.2, 21.4, and 25.3 g/day for all women and premenopausal women; 14.7, 17.2, 19.2, 21.4, and 25.3 g/day for postmenopausal women.

the trend was marginally significant (comparing the highest versus lowest quintiles, adjusting for β-carotene: RR 0.84; 95% CI 0.67–1.05; P_{trend} = .11; adjusting for early adulthood fiber: RR 0.88; 95% CI 0.73–1.07; P_{trend} = .17). In this model with both adolescent and early adulthood fiber intake, the RR for adult fiber was 0.81 (95% CI 0.66–1.00, P_{trend} = .07). Similar associations with adolescent fiber intake were observed among premenopausal and postmenopausal women, though they did not reach statistical significance for postmenopausal BC (Table 2).

Among women with both early adulthood and adolescent dietary data (n = 41 092), for the average of intakes at both times, the RR of BC overall was 0.75 (95% CI 0.62–0.91, P_{trend} = .004) comparing the highest versus lowest quintile. A somewhat stronger association was seen for premenopausal than for postmenopausal BC (highest versus lowest quintile, among premenopausal women: RR 0.67; 95% CI 0.50–0.89; P_{trend} = .001; among postmenopausal women: RR 0.85; 95% CI 0.63–1.14; P_{trend} = .44). However, this difference was not significant (P = .25 for differences in RRs) (Fig 1).

When evaluating types of fiber, among all women, we observed a lower BC risk with higher early adulthood intake of fruit fiber and vegetable fiber (Table 3). Early adulthood soluble fiber (RR 0.86; 95% CI 0.77–0.97; P_{trend} = .02) and insoluble fiber (RR 0.80; 95% CI 0.71–0.90; P_{trend} < .001) were each associated with lower BC risk among all women.

When total dietary fiber intake was modeled as a continuous variable, each 10 g/day increase in fiber intake during early adulthood was associated with a 13% decrease in BC risk among all women (RR 0.87; 95% CI 0.80–0.95) (Table 4). While high fiber intake during early adulthood was associated with lower risk of premenopausal ER^+/PR^+ BC (RR 0.68; 95% CI 0.58–0.79; for 10 g/day), high fiber intake during adolescence was associated with lower risk of premenopausal ER^-/PR^- BC (RR 0.49; 95% CI 0.29–0.85; for 10 g/day). However, the test for heterogeneity was not significant (for early adulthood fiber: $P_{heterogeneity}$ = .08; for adolescent fiber: $P_{heterogeneity}$ = .07). We also did not observe significant heterogeneity between adolescent and early adulthood fiber intake and tumor receptor status in overall or postmenopausal BC (Table 4).

We also examined whether association between early adult fiber

TABLE 3 RR and 95% CI for BC According to Quintile of Types of Fiber Intake in Early Adulthood Among All Women in the NHSII

Item	Quintile of Intake					
	1	2	3	4	5	P_{trend}
Fiber from cereals						
Median intake, g/day	2.9	4.1	5.1	6.3	8.9	
No. of cases/person-years	573/350 429	551/342 325	598/353 290	566/337 429	545/341 822	
Age-adjusted RR (95% CI)	1	0.98 (0.87–1.11)	1.03 (0.92–1.15)	1.02 (0.91–1.15)	0.95 (0.85–1.07)	.49
Multivariable RR (95% CI)	1	0.96 (0.86–1.08)	1.00 (0.89–1.12)	0.97 (0.86–1.09)	0.90 (0.80–1.02)	.09
Fiber from fruits						
Median intake, g/day	1.1	2.0	2.9	4.1	6.2	
No. of cases/person-years	612/363 391	533/317 120	542/364 555	576/330 105	570/350 124	
Age-adjusted RR (95% CI)	1	0.98 (0.87–1.10)	0.86 (0.76–0.96)	0.99 (0.88–1.11)	0.90 (0.80–1.01)	.15
Multivariable RR (95% CI)	1	0.96 (0.86–1.08)	0.83 (0.74–0.93)	0.96 (0.85–1.08)	0.88 (0.78–0.98)	.06
Fiber from vegetables						
Median intake, g/day	3.3	4.8	6.1	7.7	10.7	
No. of cases/person-years	551/340 101	577/342 452	566/353 923	570/342 094	569/346 726	
Age-adjusted RR (95% CI)	1	1.00 (0.89–1.12)	0.92 (0.82–1.04)	0.94 (0.83–1.05)	0.91 (0.80–1.02)	.06
Multivariable RR (95% CI)	1	0.98 (0.87–1.10)	0.90 (0.80–1.02)	0.92 (0.81–1.03)	0.89 (0.79–1.00)	.04
Fiber from legumes						
Median intake, g/day	0	0.4	0.7	1.0	2.0	
No. of cases/person-years	523/322 859	582/356 518	553/327 916	581/355 135	594/362 867	
Age-adjusted RR (95% CI)	1	1.02 (0.90–1.14)	1.02 (0.90–1.15)	0.97 (0.86–1.09)	0.96 (0.85–1.08)	.31
Multivariable RR (95% CI)	1	1.03 (0.91–1.16)	1.00 (0.88–1.13)	0.94 (0.84–1.06)	0.94 (0.83–1.05)	.12
Soluble fiber						
Median intake, g/day	3.7	4.6	5.3	6.0	7.	4
No. of cases/person-years	566/336 375	530/335 976	600/366 156	567/345 936	570/340 853	
Age-adjusted RR (95% CI)	1	0.91 (0.80–1.02)	0.91 (0.81–1.02)	0.88 (0.79–0.99)	0.88 (0.78–0.99)	.04
Multivariable RR (95% CI)	1	0.90 (0.80–1.01)	0.89 (0.79–1.00)	0.86 (0.77–0.97)	0.86 (0.77–0.97)	.02
Insoluble fiber						
Median intake, g/day	9.2	11.5	13.2	15.2	19.0	
No. of cases/person-years	593/352 915	543/333 420	568/345 880	595/344 527	534/348 554	
Age-adjusted RR (95% CI)	1	0.93 (0.83–1.05)	0.92 (0.82–1.03)	0.95 (0.85–1.07)	0.83 (0.74–0.93)	.004
Multivariable RR (95% CI)	1	0.91 (0.81–1.03)	0.90 (0.80–1.01)	0.93 (0.82–1.04)	0.80 (0.71–0.90)	<.001

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, nonwhite), family history of BC in mother or sisters (yes, no), history of BBD (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 inches), BMI at age 18 y (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0), weight change since age 18 (continuous), age at menarche (<12, 12, 13, ≥14 y), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 y, parity ≤2 and age at first birth 25 to <30 y, parity ≤2 and age at first birth ≥30 y, parity 3 to 4 and age at first birth <25 y, parity 3 to 4 and age at first birth 25 to <30 y, parity 3 to 4 and age at first birth ≥30 y, parity ≥5 and age at first birth <25 y, parity ≥5 and age at first birth ≥25 y), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy intake (quintile), hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, ≥53 y).

intake and BC risk differed by BMI at age 18. No significant interactions were noted (data not shown).

DISCUSSION

Our findings suggest that higher fiber intakes during adolescence and early adulthood are associated with reduced BC incidence in women. The associations were apparent for most sources of fiber and were independent of other dietary factors and healthy eating behavior.

Although no significant association was observed in nearly all prospective studies of dietary fiber and BC incidence,[6–11,14,16,19–23] in a recently published meta-analysis of 16 prospective studies[24] a5% lower BC risk was seen for each 10 g/day increment of fiber intake. Our results are consistent, although stronger, with a 13% lower BC risk per 10 g/day fiber increment during early adulthood and 14% lower BC risk per 10 g/day fiber increment during adolescence. Although a stronger association between soluble fiber and BC was observed in the meta-analysis,[24] we noted an inverse association for both soluble and insoluble fibers. In addition, despite no association between specific fiber sources and BC in the meta-analysis, we observed inverse significant associations between fiber from fruits or vegetables and BC overall. In recent studies,[48–50] we observed a positive association between red meat and animal fat intake and BC risk, but we found no appreciable difference in the results when additionally adjusted for them, suggesting that other dietary

TABLE 4 Risk of BC by ER/PR Status and Adolescent and Early Adulthood Total Fiber Intake Among Women in the NHSII

BC Subtype	Energy-Adjusted Total Fiber, per 10 g/day					
	All Cases		Premenopausal Cases		Postmenopausal Cases	
	n	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)
Early adulthood fiber intake						
All BC	2833	0.87 (0.80–0.95)	1659	0.85 (0.76–0.96)	875	0.92 (0.79–1.07)
ER+/PR+	1571	0.78 (0.69–0.88)	922	0.68 (0.58–0.80)	501	0.90 (0.74–1.11)
ER−/PR−	429	0.89 (0.71–1.11)	255	0.91 (0.68–1.22)	131	1.05 (0.71–1.56)
P for heterogeneity		.32		.08		.49
Adolescent fiber intake						
All BC	1118	0.86 (0.75–0.99)	544	0.80 (0.65–0.99)	466	0.85 (0.68–1.07)
ER+/PR+	695	0.87 (0.73–1.05)	350	0.84 (0.66–1.08)	282	0.78 (0.58–1.03)
ER−/PR−	162	0.69 (0.47–1.00)	83	0.49 (0.29–0.85)	65	1.11 (0.62–1.98)
P for heterogeneity		.25		.07		.28

The 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, nonwhite), family history of BC in mother or sisters (yes, no), history of BBD (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 inches), BMI at age 18 y (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0), weight change since age 18 (continuous), age at menarche (<12, 12, 13, ≥14 y), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 y, parity ≤2 and age at first birth 25 to <30 y, parity ≤2 and age at first birth ≥30 y, parity 3 to 4 and age at first birth <25 y, parity 3 to 4 and age at first birth 25 to <30 y, parity 3 to 4 and age at first birth ≥30 y, parity ≥5 and age at first birth <25 y, parity ≥5 and age at first birth ≥25 y), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), and energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45, 45–46, 47–48, 49–50, 51–52, ≥53 y). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status) and age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, ≥53 y). For adolescent fiber, we additionally adjusted for adolescent alcohol intake (nondrinker, <1.5, 1.5 to <5, 5 to <10, ≥10 g/day) and adolescent energy intake (quintile; instead of adult energy intake).

factors are not a plausible explanation of the inverse associations observed with fiber intake.

Several biological mechanisms support the beneficial role of dietary fiber on BC risk. Fiber may reduce BC risk through improving insulin sensitivity[51], and decreasing insulin-like growth factors.[52] Furthermore, dietary fiber may decrease plasma levels of estrogen by inhibiting colonic β-D-glucuronidase activity, resulting in decreased deconjugation and reabsorption of estrogen and thereby increased fecal excretion.[4,53,54]

This study has several limitations. This cohort does not represent random samples of US women, but it is unlikely that biological relations among women in this cohort will differ substantially from women in general. Women reported their adolescent diet when they were at age 33 to 52 years. However, the recalled adolescent diet was largely independent of current adult diet, and further evidence of validity came from the comparison of recalled adolescent diet and our questionnaire administered 10 years later.[35] Residual confounding is always of concern in any observational studies. Although we adjusted for a wide range of potential confounders for BC, we still could not rule out the possibility that other unmeasured or inadequately measured factors have confounded the true association. However, adjustment for confounders made the association stronger. Because foods high in fiber contain many other biologically active constituents, we cannot exclude the possibility that these contribute to lower BC incidence.

Our study has several strengths. To evaluate the importance of timing, we assessed the association between fiber intake during specific life periods (adolescence, early adulthood, and cumulative average of the premenopausal period). The dietary questionnaire used to assess fiber intake has documented validity, and we evaluated the association between fiber intake and BC after correction for measurement error as well as using the cumulative averages of repeated dietary assessments. Dietary information was evaluated before BC diagnosis, minimizing the possibility of recall bias. The large number of cases afforded adequate power to detect modest differences in risk, as well as the ability to examine BCs before and after menopause and by hormone receptor status. Detailed prospective and updated assessments of diet and other lifestyle factors reduced the likelihood of residual confounding.

CONCLUSIONS

The findings in this large prospective study support the hypothesis that consumption of foods high in fiber reduce BC risk. These results also suggest that dietary fiber intake during adolescence and early adulthood may be particularly important. Our findings are in line with the American Cancer Society guidelines[55] to consume foods rich in fiber such as fruits, vegetables, and whole grains, and indicate the importance of adopting these food choices during childhood and early adult life.

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ABBREVIATIONS

BBD: benign breast disease
BC: breast cancer
CI: confidence interval
ER: estrogen receptor
FFQ: food frequency questionnaire
HS-FFQ: high school food frequency questionnaire
NHSII: Nurses' Health Study II
PR: progesterone receptor
RR: relative risk

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Dietary Fiber Intake in Young Adults and Breast Cancer Risk

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