Dietary fiber intake and risk of breast cancer in postmenopausal women: the National Institutes of Health–AARP Diet and Health Study[1–4]

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ABSTRACT

Background: Although dietary fiber has been hypothesized to lower risk of breast cancer by modulating estrogen metabolism, the association between dietary fiber intake and risk of breast cancer by hormone receptor status is unclear.

Objective: The objective was to examine the relation of dietary fiber intake to breast cancer by hormone receptor status and histologic type among postmenopausal women in the National Institutes of Health–AARP Diet and Health Study (n = 185,598; mean age: 62 y).

Design: Dietary intakes were assessed with a food-frequency questionnaire. Incident breast cancer cases were identified through linkage with state cancer registries. Cox proportional hazard models were used to estimate relative risks (RRs) and 2-sided 95% CIs.

Results: During an average of 7 y of follow-up, 5461 breast cancer cases were identified, of which 3341 cases had estrogen receptor (ER) and progesterone receptor (PR) status. Dietary fiber intake was inversely associated with breast cancer risk [RR for the highest quintile (Q5) compared with the lowest quintile (Q1): 0.87; 95% CI: 0.77, 0.98; P for trend: 0.02]. The inverse association appeared to be stronger for ER^-/PR^- tumors (RR_{Q5vsQ1}: 0.56; 95% CI: 0.35, 0.90; P for trend: 0.008; 366 cases) than for ER^+/PR^+ tumors (RR_{Q5vsQ1}: 0.95; 95% CI: 0.76, 1.20; P for trend: 0.47; 1641 cases). The RR_{Q5vsQ1} of lobular tumors was 0.66 (95% CI: 0.44, 0.97; P for trend: 0.04), and the RR_{Q5vsQ1} of ductal tumors was 0.90 (95% CI: 0.77, 1.04; P for trend: 0.10). Fiber from grains, fruit, vegetables, and beans was not related to breast cancer.

Conclusion: Our findings suggest that dietary fiber can play a role in preventing breast cancer through nonestrogen pathways among postmenopausal women. *Am J Clin Nutr* 2009;90:664–71.

INTRODUCTION

Breast cancer, the most common cancer in women worldwide, is a hormone-related malignancy. Reproductive factors and body fatness, which affect estrogen, progesterone, and insulin status, have been identified as risk factors for breast cancer (1). In addition, intakes of dietary fat and alcohol, which have been implicated in estrogen metabolism, have been related to an increased risk of breast cancer (1).

More than 2 decades ago, dietary fiber was hypothesized to lower the risk of breast cancer, based on findings suggesting that vegetarian women had increased fecal excretion of estrogens and decreased plasma concentration of estrogen compared with omnivorous women (2). Dietary fiber could protect against breast cancer through inhibition of the intestinal reabsorption of estrogens excreted by the biliary system and an increase in fecal excretion of estrogens; both mechanisms could lower circulating estrogen concentrations (2–4). In addition, dietary fiber could play a role in modulating insulin resistance and insulin-like growth factors, which have been associated with breast cancer risk (5–7).

Observational epidemiologic studies, however, have reported inconsistent findings. A meta-analysis of 12 case-control studies (8) found that dietary fiber intake was significantly inversely associated with risk of breast cancer in postmenopausal women [relative risk (RR): 0.85 for a 20-g/d increment of dietary fiber intake; P = 0.02]. However, most prospective cohort studies have found no association between dietary fiber and breast cancer risk (9–15). A few cohort studies observed a suggestive inverse association between dietary fiber and breast cancer in premenopausal (14) and postmenopausal (16, 17) women. These inconsistent results may be explained, in part, by breast cancer heterogeneity. If the relation of dietary fiber to breast cancer differed by breast cancer hormone receptor status (eg, both estrogen and progesterone positive, both estrogen and progesterone negative) or by histology type (eg, ductal tumor, lobular tumor), examinations of total breast cancer may have missed breast cancer subtype-specific associations. Moreover, associations with breast cancer may differ by type of dietary fiber (eg, soluble and insoluble fiber) as well as specific food sources of fiber. We therefore examined among postmenopausal women in a large prospective cohort study whether total dietary

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fiber as well as fiber subtypes were associated with risk of breast cancer according to histology and hormone receptor status.

SUBJECTS AND METHODS

Study population

The National Institutes of Health (NIH)–AARP Diet and Health Study was initiated when 567,169 AARP members aged 50–71 y from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) responded to a mailed questionnaire in 1995–1996. The NIH-AARP Study has been described previously (18). Among women who returned questionnaires with satisfactory dietary data, we excluded individuals who indicated they were proxies for the intended respondent (n = 1265), who had any prevalent cancer except nonmelanoma skin cancer at baseline (n = 23,954), who had self-reported end-stage renal disease at baseline (n = 371), or who were premenopausal (n = 3849), or of uncertain menopausal status (n = 10,023). In addition, we excluded individuals who reported extreme intakes (beyond 2 times the interquartile ranges of Box-Cox log transformed intake) of total energy (n = 1609). After exclusions, the analytic cohort consisted of 185,598 postmenopausal women. The NIH-AARP Diet and Health study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Diet and risk factor assessment

At baseline, dietary intakes were assessed with a self-administered 124-item food-frequency questionnaire (FFQ), which was an early version of the Diet History Questionnaire developed at the National Cancer Institute (19). Participants were asked to report their usual frequency of intake and portion size over the past 12 mo, with the use of 10 predefined frequency categories ranging from never to $\geq$6 times/d for beverages and from never to $\geq$2 times/d for solid foods; and 3 categories of portion size. The food items, portion sizes, and nutrient database were constructed with the use of the US Department of Agriculture's 1994–1996 Continuing Survey of Food Intakes by Individuals (20). In addition, food groups and their serving sizes were defined by the Pyramid Servings Database (http://riskfactor.cancer.gov/pyramid/) corresponding to the 1994–1996 Continuing Survey of Food Intakes by Individuals, which uses a recipe file to disaggregate food mixtures into their component ingredients and assigns them to food groups. The nutrient database for dietary fiber was informed by the Association of Official Analytic Chemist method (21). Fiber from grains, fruit, vegetables, and beans were estimated by summing dietary fiber from all grains, all fruit, all vegetables, and all beans on the questionnaire, including mixed dishes, respectively.

The FFQ used in the study was calibrated with the use of 2 nonconsecutive 24-h dietary recalls in 1953 NIH-AARP study participants (22). The energy-adjusted correlation coefficients of dietary fiber intake between a FFQ and 24-h recalls were 0.66 in women. We also collected demographic, anthropometric, and lifestyle information, including smoking, physical activity, reproductive history, family history of cancers, and menopausal hormone therapy use at baseline.

Cancer ascertainment

We identified breast cancer cases through probabilistic linkage with 11 state cancer registry databases that included the 8 original states and 3 additional states (Arizona, Nevada, and Texas) that participants tended to move during follow-up. The state cancer registries are certified by the North American Association of Central Cancer Registries as being 90% complete within 2 years of cancer occurrence. The case ascertainment method used in the study was estimated to identify $\approx$90% of all cancer cases in our cohort (23). Vital status was ascertained through annual linkage of the cohort to the Social Security Administration Death Master File and follow-up searches of the National Death Index Plus.

We defined breast cancer cases as primary incident breast tumors that had invasive behavior and were not a metastatic site from a prevalent cancer. Histology of breast cancer was available from all 11 state cancer registries, and tumor estrogen receptor (ER) and progesterone receptor (PR) status was available from 7 state cancer registries. Sixty-one percent of breast cancers were identified from states that reported hormone receptor status. With the use of histology codes from the *International Classification of Diseases for Oncology, Third Edition* (24), we classified breast cancer into ductal (ICD code: 8500), lobular (ICD code: 8520), ductal-lobular (ICD code: 8522), and other tumors (ICD code except 8500, 8520, and 8522).

Statistical analysis

We used the Cox proportional hazards model (25) to estimate RRs and 2-sided 95% CIs using the SAS PROC PHREG procedure (version 9.1; SAS Institute Inc, Cary, NC). Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of cancer diagnosis, death, move-out of the registry areas, or end of follow-up (31 December 2003), whichever occurred first. The proportional hazards assumption was evaluated and confirmed by modeling interaction terms comprising the cross-products of time and dietary fiber intake.

Dietary fiber intake was adjusted for total energy intake with the use of the residual method (26) and was categorized into quintiles. The RRs were estimated according to quintiles of intake and to an increment of specific amount listed in the footnotes of the tables. To test linear trends across quintiles of intake, we created a continuous variable based on the median value in each quintile and regressed breast cancer on this variable.

In multivariate models, we adjusted for age, race-ethnicity, education, family history of breast cancer, history of breast biopsy, history of oophorectomy or hysterectomy, age at first birth and parity, age at menopause, duration of menopausal hormone therapy use, smoking, body mass index (BMI; in kg/m^2), physical activity, and intakes of alcohol, total fat, fruit, and vegetables and total energy. For each covariate except BMI, we checked whether breast cancer risk in women with a missing value was significantly different from that of women in the reference category. If no significant difference was observed, we reassigned women with a missing value to the reference category. For BMI, we assigned missing values to the mean value in the study population. The proportion of missing values for each covariate was $<$4%.

We tested whether the association between dietary fiber and breast cancer was modified by total fat intake, alcohol intake,

BMI, and use of menopausal hormone therapy. The test for interaction was performed by entering a cross-product term of dietary fiber intake and total fat intake, BMI, and use of menopausal hormone therapy, both as continuous variables. We also tested whether associations differ by histologic types and hormone receptor status with the use of a contrast test (27). We also estimated measurement error-corrected RRs in age-adjusted models with the use of a linear regression calibration method (28).

RESULTS

During an average of 7 y of follow-up, we identified 5461 breast cancer cases, of which 3531 were ductal tumors, 550 lobular tumors, 424 ductal and lobular tumors, and 956 other tumors. Of the 3341 breast cancers that were identified from state cancer registries that reported hormone receptor status, there were 1641 ER^+/PR^+ tumors, 336 ER^+/PR^- tumors, 48 ER^-/PR^+ tumors, 366 ER^-/PR^- tumors, and 950 tumors with unknown ER or PR status. We do not present results of ER^-/PR^+ tumors because of small number of cases. Dietary fiber intake ranged from 11 g/d (10th percentile) to 26 g/d (90th percentile). Compared with women in the lowest quintile of dietary fiber intake (Q1), women in the highest quintile (Q5) were more likely to be physically active, have never smoked, have used menopausal hormone therapy, and consume less alcohol and fat and more fruit and vegetables (**Table 1**).

We found that dietary fiber intake was significantly inversely associated with breast cancer (**Table 2**). In analysis of fiber as a continuous variable, for an increment of 10 g/d of dietary fiber intake, the age-adjusted RR was 0.94 (95% CI: 0.90, 0.98), and the multivariate RR was 0.95 (95% CI: 0.89, 1.01). After correction for measurement error in dietary fiber intake, the age-adjusted RR became 0.89 (95% CI: 0.82, 0.97).

When we examined the association by histologic types of breast cancer, we observed that dietary fiber intake was weakly inversely associated with ductal tumors, was significantly inversely related to lobular tumors, and was not related to ductal-lobular tumors. The associations, however, did not statistically significantly differ by histologic types. For an increment of 10 g/d of dietary fiber intake the multivariate RR was 0.94 (95% CI: 0.87, 1.02) for ductal tumors, 0.81 (95% CI: 0.65, 1.01) for lobular tumors, 0.96 (95% CI: 0.76, 1.21) for ductal-lobular tumors, and 1.05 (95% CI: 0.90, 1.23) for other tumors.

TABLE 1
Selective characteristics of postmenopausal women by dietary fiber intake (n = 185,598)

	Dietary fiber intake		
	Quintile 1	Quintile 3	Quintile 5
Dietary fiber intake (g/d)[1]	11	17	26
Age at baseline (y)	62 ± 5[2]	62 ± 5	63 ± 5
White, non-Hispanic (%)	90	90	87
College or postcollege education (%)	46	54	60
BMI (kg/m^2)	27.1 ± 6.3	27.0 ± 5.9	26.1 ± 5.6
Physical activity, ≥3 times/wk (%)	27	41	57
Current smoker (%)	28	12	7
Age at first birth and parity (%)			
Nulliparous	14	14	15
<30 y and ≤2 children	31	31	32
<30 y and ≥3 children	49	50	47
≥30 y	5	6	6
Age at menopause (%)			
<50 y	63	60	58
50 to <55 y	31	33	34
≥55 y	6	7	8
Family history of breast cancer (%)	12	12	12
Breast biopsy (%)	23	25	25
Menopausal hormone therapy use (%)			
Never	51	46	45
<5 y	19	19	19
5–9 y	11	14	14
≥10 y	19	21	22
Gynecological surgery (%)			
No	54	54	55
Both oophorectomy and hysterectomy	22	23	22
Oophorectomy only	4	4	3
Hysterectomy only	20	20	20
Fruit and vegetable intake (servings/1000 kcal)	2.6 ± 1.1	4.2 ± 1.2	6.8 ± 2.1
Alcohol intake (g/d)	11 ± 28	5 ± 11	3 ± 7
Total fat intake (% total energy/d)	34 ± 8	31 ± 7	25 ± 6
Total energy intake (kcal/d)	1580 ± 720	1577 ± 638	1543 ± 636

[1] Values are medians.
[2] Mean ± SD (all such values).

TABLE 2
Relative risks (RRs) and 95% CIs of breast cancer by histologic type for quintile of dietary fiber intake among postmenopausal women in the National Institutes of Health–AARP Diet and Health Study (n = 185,598)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Median intake (g/d)	11	14	17	20	26	
All breast cancer						
No. of cases	1098	1120	1130	1098	1015	
Age-adjusted RR	1.00 (referent)	1.00 (0.92, 1.08)	1.00 (0.92, 1.09)	0.97 (0.89, 1.05)	0.89 (0.82, 0.97)	0.003
Multivariate RR[1]	1.00 (referent)	0.96 (0.88, 1.05)	0.95 (0.86, 1.05)	0.91 (0.82, 1.01)	0.87 (0.77, 0.98)	0.02
Ductal tumors						
No. of cases	700	740	722	705	664	
Age-adjusted RR	1.00 (referent)	1.04 (0.94, 1.15)	1.01 (0.91, 1.12)	0.98 (0.88, 1.09)	0.92 (0.82, 1.02)	0.04
Multivariate RR[1]	1.00 (referent)	1.00 (0.90, 1.12)	0.96 (0.85, 1.09)	0.93 (0.81, 1.06)	0.90 (0.77, 1.04)	0.10
Lobular tumors						
No. of cases	116	110	119	114	91	
Age-adjusted RR	1.00 (referent)	0.91 (0.70, 1.19)	0.98 (0.76, 1.26)	0.92 (0.71, 1.20)	0.73 (0.56, 0.96)	0.03
Multivariate RR[1]	1.00 (referent)	0.85 (0.64, 1.13)	0.87 (0.64, 1.18)	0.80 (0.57, 1.12)	0.66 (0.44, 0.97)	0.04
Ductal or lobular tumors						
No. of cases	84	80	78	99	83	
Age-adjusted RR	1.00 (referent)	0.94 (0.69, 1.27)	0.91 (0.67, 1.24)	1.15 (0.86, 1.54)	0.96 (0.71, 1.30)	0.80
Multivariate RR[1]	1.00 (referent)	0.93 (0.66, 1.29)	0.88 (0.61, 1.27)	1.05 (0.72, 1.55)	0.83 (0.53, 1.29)	0.53
Other tumors						
No. of cases	198	190	211	180	177	
Age-adjusted RR	1.00 (referent)	0.93 (0.77, 1.14)	1.03 (0.85, 1.25)	0.87 (0.71, 1.07)	0.85 (0.69, 1.04)	0.08
Multivariate RR[1]	1.00 (referent)	0.90 (0.73, 1.12)	0.99 (0.78, 1.24)	0.85 (0.66, 1.10)	0.92 (0.69, 1.23)	0.60

[1] Cox proportional hazard models adjusted for race, education (less than high school, high school graduation, some college, and college or post-college education), BMI (in kg/m^2; <25, 25 to <30, 30 to <35, and ≥35), age at first birth and parity (nulliparous, <30 y and ≤2 children, <30 y and ≥3 children, and ≥30 y), family history of breast cancer (yes and no), age at menopause (<50, 50–54, and ≥55 y), physical activity (never, rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), smoking (never; former, ≤20 cigarettes/d; former, >20 cigarettes/d; current, ≤20 cigarettes/d; and current, >20 cigarettes/d), menopausal hormone therapy use (never, <5 y, 5–10 y, and ≥10 y), breast biopsy (no and yes), gynecologic surgery (none, both oophorectomy and hysterectomy, oophorectomy only, and hysterectomy only), and intakes of alcohol (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/d), total fruit and vegetables (quintiles), total fat (quintiles), and total energy (continuous).

We also observed that dietary fiber intake was related to a significantly lower risk of hormone receptor-negative tumors, but not hormone receptor-positive tumors. The multivariate RR comparing the highest with the lowest quintile of dietary fiber intake was 0.91 (95% CI: 0.74, 1.12; P for trend: 0.28; 1977 cases) for ER^+ tumors, 0.95 (95% CI: 0.76, 1.19; P for trend: 0.47; 1689 cases) for PR^+ tumors; 0.59 (95% CI: 0.38, 0.92; P for trend: 0.01; 414 cases) for ER^- tumors; and 0.64 (95% CI: 0.46, 0.89; P for trend: 0.009; 702 cases) for PR^- tumors. In analyses of breast cancer cases further defined by both ER and PR status, we observed a statistically significant inverse association with ER^-/PR^- tumors but not with ER^+/PR^+ or ER^+/PR^- tumors (**Table 3**). For 10-g/d increment of dietary fiber intake, the age-adjusted RR of ER^-/PR^- tumor was 0.83 (95% CI: 0.70, 0.99), and the multivariate RR of ER^-/PR^- tumor was 0.77 (95% CI: 0.60, 1.00). After correction for measurement error, the age-adjusted RR was 0.70 (95% CI: 0.51, 0.98).

The associations were different between ER^+/PR^+ and ER^-/PR^- tumors (P for test difference: 0.05). When we examined the associations by combinations of histology and ER status, we observed that the inverse relation with dietary fiber intake was more strongly related to ER negativity than to histology: dietary fiber intake tended to be associated with a lower risk of ER^- tumors across all histologic types (data not shown).

Fiber intake from grains, vegetables, and beans was not related to breast cancer (**Table 4**). Fiber intake from fruit was inversely associated with risk of breast cancer in the age-adjusted model. However, after adjusting for other breast cancer risk factors, the association was attenuated and no longer statistically significant. We also found that soluble fiber intake was inversely associated with risk of breast cancer, but insoluble fiber intake was not. When associations with dietary fiber from specific food sources and types of fiber were examined by ER/PR status, we found similar results.

We observed that the association between dietary fiber intake and risk of breast cancer was not significantly modified by total fat intake (P = 0.08). Compared with the high-fat–low-dietary fiber group, the multivariate RR was 0.86 (95% CI: 0.76, 0.97) in the low-fat–high-dietary fiber group, 0.85 (95% CI: 0.72, 0.99) in the high-fat–high-fiber group, and 1.10 (95% CI: 0.97, 1.24) in the low-fat–low-fiber group. The association between dietary fiber intake and breast cancer was not modified by alcohol intake, BMI, or use of menopausal hormone therapy (data not shown).

DISCUSSION

In this large prospective cohort study, we found that dietary fiber intake was associated with a 13% lower risk of breast cancer in postmenopausal women in the highest quintile of total dietary fiber as opposed to the lowest quintile. The association appeared to be stronger for lobular tumors than that for ductal tumors and for ER^-/PR^- tumors than for ER^+/PR^+ tumors. Fiber from grains, fruit, vegetables, and beans was not related to breast cancer. Soluble, but not insoluble, fiber intake was inversely associated with breast cancer. Total fat intake did not

TABLE 3
Relative risks (RRs) and 95% CIs of breast cancer by hormone receptor status for quintile of dietary fiber intake among postmenopausal women in the National Institutes of Health–AARP Diet and Health Study (n = 185,598)[1]

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Median intake (g/d)	11	14	17	20	26	
ER^+/PR^+						
No. of cases	284	318	357	347	335	
Age-adjusted RR	1.00 (referent)	1.09 (0.93, 1.28)	1.18 (1.01, 1.38)	1.11 (0.95, 1.29)	1.01 (0.86, 1.18)	0.84
Multivariate RR[2]	1.00 (referent)	1.04 (0.88, 1.24)	1.11 (0.92, 1.34)	1.02 (0.83, 1.25)	0.95 (0.76, 1.20)	0.47
ER^+/PR^-						
No. of cases	68	64	63	73	68	
Age-adjusted RR	1.00 (referent)	0.91 (0.64, 1.28)	0.86 (0.61, 1.21)	0.96 (0.69, 1.33)	0.84 (0.60, 1.18)	0.43
Multivariate RR[2]	1.00 (referent)	0.83 (0.57, 1.21)	0.75 (0.50, 1.13)	0.81 (0.52, 1.24)	0.74 (0.45, 1.21)	0.32
ER^-/PR^-						
No. of cases	81	73	88	60	64	
Age-adjusted RR	1.00 (referent)	0.89 (0.65, 1.22)	1.05 (0.77, 1.42)	0.69 (0.50, 0.97)	0.70 (0.51, 0.97)	0.01
Multivariate RR[2]	1.00 (referent)	0.84 (0.59, 1.18)	0.94 (0.65, 1.34)	0.58 (0.38, 0.89)	0.56 (0.35, 0.90)	0.008

[1] ER^+, estrogen receptor positive; PR^+, progesterone receptor positive; ER^-, ER negative; PR^-, PR negative.

[2] Cox proportional hazard models adjusted for race, education (less than high school, high school graduation, some college, and college or post-college education), BMI (in kg/m^2; <25, 25 to <30, 30 to <35, and ≥35), age at first birth and parity (nulliparous, <30 y and ≤2 children, <30 y and ≥3 children, and ≥30 y), family history of breast cancer (yes and no), age at menopause (<50, 50–54, and ≥55 y), physical activity (never, rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), smoking (never; former, ≤20 cigarettes/d; former, >20 cigarettes/d; current, ≤20 cigarettes/d; and current, >20 cigarettes/d), menopausal hormone therapy use (never, <5 y, 5–10 y, and ≥10 y), breast biopsy (no and yes), gynecologic surgery (none, both oophorectomy and hysterectomy, oophorectomy only, and hysterectomy only), and intakes of alcohol (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/d), total fruit and vegetables (quintiles), total fat (quintiles), and total energy (continuous).

significantly modify the association between dietary fiber intake and risk of breast cancer.

Although most prospective cohort studies have found no relation between dietary fiber intake and breast cancer in postmenopausal women (9–15), some studies did suggest an inverse association. The Nurses' Health Study (29) found a multivariate RR of 0.68 (95% CI: 0.43, 1.06; 4092 cases) for >30 g/d compared with ≤10 g/d of dietary fiber intake. In addition, 2 Swedish cohort studies (16, 17) found a suggestive inverse association of dietary fiber intake with breast cancer: the multivariate $RR_{Q5\ vs\ Q1}$ was 0.85 (95% CI: 0.69, 1.05; P for trend: 0.09; 1188 cases; median intake: 29 g/d) in the Swedish Mammography Cohort Study (17) and 0.58 (95% CI: 0.40, 0.84; P for trend: 0.056; 342 cases; median intake: 26 g/d) in the Malmo Diet and Cancer cohort study (16). The ranges of dietary fiber intake in the Swedish studies were comparable to those of other studies, but the main source of dietary fiber differed. The Swedish study population had higher consumption of fiber from grains [≈70% of fiber came from grains (17)], whereas in other studies most fiber derived from vegetables and fruit.

When dietary fiber from specific food sources was examined, most studies found that fiber intakes from grains, vegetables, and beans were not related to risk of breast cancer (10, 13, 14, 17). Fiber intake from fruit, however, was significantly inversely associated with risk of breast cancer in the Swedish Mammography Cohort Study ($RR_{Q5\ vs\ Q1}$: 0.66; 95% CI: 0.47, 0.93; P for trend: 0.007). Fiber from fruit was also weakly associated with risk of breast cancer in the Nurses' Health Study ($RR_{Q5\ vs\ Q1}$: 0.92; 95% CI: 0.81, 1.04; P for trend: 0.08) (29) and in our study. An experimental study showed that pectin, which is mainly from fruit and is soluble fiber, had an inhibitory effect on mammary tumor growth, angiogenesis, and metastasis (30). A few studies have examined types of dietary fiber in relation to breast cancer and found that both soluble and insoluble fiber intakes were not related to risk of breast cancer (10, 15, 29). In contrast, we found that soluble, but not insoluble, fiber intake was inversely related to breast cancer. It is possible that fiber type makes a difference in pathophysiologic processes related to breast cancer. Soluble fiber has been shown to be more effective in controlling blood glucose, insulin, and insulin-like growth factors, which have been positively related to risk of breast cancer (5–7). Insoluble fiber, however, may be more effective in binding and excreting estrogen in stool with a consequent decrease in serum estrone and estradiol (4). However, this result should be interpreted with caution because of high correlation between soluble and insoluble fiber intakes.

We found that an association between dietary fiber intake and risk of breast cancer was not significantly modified by total fat intake: compared with women with low-fiber–high-fat intake, both women with a high-fiber–high-fat intake and those with high-fiber–low-fat intake lowered risk of breast cancer. Although a high-fiber–low-fat diet has been hypothesized to lower risk of breast cancer, limited evidence supports this hypothesis. The Women's Health Initiative Randomized Controlled Dietary Modification Trial in postmenopausal women found that a high-fiber–low-fat diet may lower risk of breast cancer (RR: 0.91; 95% CI: 0.83, 1.01) (31). However, the Women's Healthy Eating and Living Randomized Trial in women with a history of breast cancer found no effect of a high-fiber–low-fat diet on survival or breast cancer progression (32).

Our study is the first study to examine the association between dietary fiber and breast cancer by histologic type. We found that the dietary fiber–breast cancer association was more apparent for lobular tumors than for ductal tumors. The incidence of lobular tumors continues to increase (33), but the cause of lobular tumor is largely unknown. Some studies have suggested that use of menopausal hormone therapy was more strongly associated with risk of lobular tumor than with risk of ducal tumor (34, 35). It may

TABLE 4
Relative risks (RR)s and 95% CIs of breast cancer by quintile of fiber intake from food sources and types of fiber among postmenopausal women in the National Institutes of Health–AARP Diet and Health Study (n = 185,598)

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for trend
Fiber from grains						
Median intake (g/d)	2.5	3.8	4.9	6.3	8.9	
No. of cases	1102	1067	1102	1111	1079	
Age-adjusted RR	1.00 (referent)	0.96 (0.88, 1.04)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)	0.95 (0.87, 1.03)	0.34
Multivariate RR[1]	1.00 (referent)	0.93 (0.86, 1.02)	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)	0.93 (0.85, 1.02)	0.27
Fiber from fruit						
Median intake (g/d)	1.1	2.4	3.7	5.3	8.2	
No. of cases	1097	1177	1124	1039	1024	
Age-adjusted RR	1.00 (referent)	1.05 (0.97, 1.14)	0.99 (0.92, 1.08)	0.91 (0.84, 0.99)	0.89 (0.82, 0.97)	<0.001
Multivariate RR[1]	1.00 (referent)	1.02 (0.94, 1.12)	0.96 (0.87, 1.06)	0.89 (0.80, 0.99)	0.93 (0.82, 1.05)	0.09
Fiber from vegetables						
Median intake (g/d)	2.9	4.4	5.6	7.2	10.4	
No. of cases	1047	1092	1114	1093	1115	
Age-adjusted RR	1.00 (referent)	1.04 (0.95, 1.13)	1.06 (0.98, 1.15)	1.04 (0.95, 1.13)	1.06 (0.97, 1.15)	0.28
Multivariate RR[1]	1.00 (referent)	1.02 (0.93, 1.12)	1.03 (0.94, 1.14)	1.02 (0.92, 1.13)	1.09 (0.97, 1.23)	0.16
Fiber from beans						
Median intake (g/d)	0.3	0.8	1.2	1.8	3.4	
No. of cases	1059	1118	1076	1131	1077	
Age-adjusted RR	1.00 (referent)	1.06 (0.97, 1.15)	1.02 (0.93, 1.11)	1.07 (0.98, 1.16)	1.02 (0.94, 1.11)	0.90
Multivariate RR[1]	1.00 (referent)	1.02 (0.94, 1.11)	0.97 (0.89, 1.05)	1.00 (0.92, 1.09)	0.96 (0.88, 1.05)	0.28
Soluble fiber						
Median intake (g/d)	3.8	4.9	5.9	7.0	9.0	
No. of cases	1082	1180	1079	1110	1010	
Age-adjusted RR	1.00 (referent)	1.07 (0.99, 1.16)	0.97 (0.89, 1.06)	0.99 (0.91, 1.08)	0.90 (0.82, 0.98)	0.01
Multivariate RR[1]	1.00 (referent)	1.02 (0.92, 1.13)	0.88 (0.77, 1.00)	0.88 (0.76, 1.02)	0.83 (0.70, 0.98)	0.02
Insoluble fiber						
Median intake (g/d)	6.8	9.2	11.0	13.1	17.0	
No. of cases	1081	1110	1140	1106	1024	
Age-adjusted RR	1.00 (referent)	1.01 (0.93, 1.10)	1.03 (0.95, 1.12)	0.99 (0.91, 1.08)	0.91 (0.84, 0.99)	0.02
Multivariate RR[1]	1.00 (referent)	0.99 (0.90, 1.10)	1.06 (0.94, 1.19)	1.05 (0.92, 1.20)	1.03 (0.88, 1.19)	0.76

[1] Cox proportional hazard models adjusted for race, education (less than high school, high school graduation, some college, and college or post-college education), BMI (in kg/m^2; <25, 25 to <30, 30 to <35, and ≥35), age at first birth and parity (nulliparous, <30 y and ≤2 children, <30 y and ≥3 children, and ≥30 y), family history of breast cancer (yes and no), age at menopause (<50, 50–54, and ≥55 y), physical activity (never, rarely, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), smoking (never; former, ≤20 cigarettes/d; former, >20 cigarettes/d; current, ≤20 cigarettes/d; and current, >20 cigarettes/d), menopausal hormone therapy use (never, <5 y, 5–10 y, and ≥10 y), breast biopsy (no and yes), gynecologic surgery (none, both oophorectomy and hysterectomy, oophorectomy only, and hysterectomy only), and intakes of alcohol (0, >0 to <5, 5 to <15, 15 to <30, and ≥30 g/d), total fruit and vegetables (quintiles), total fat (quintiles), and total energy (continuous).

be possible that hormonally sensitive lobular tumors may be more responsive to the effect of dietary fiber than are ductal tumors. However, we cannot exclude the possibility of chance in our finding. More studies are needed to identify potentially different risk factors for breast cancer according to histology and hormone receptor status.

Three of 4 cohort studies that examined breast cancer by hormone receptor status found that dietary fiber intake was not related to ER$^+$/PR$^+$ and ER$^-$/PR$^-$ tumors (15, 17, 36). However, the Melbourne Collaborative Cohort Study (13) observed a positive association with ER$^+$/PR$^+$ tumors (RR: 1.36; 95% CI: 1.10, 1.67; 154 cases), and an inverse association with ER$^-$/PR$^-$ tumors (RR: 0.65; 95% CI: 0.43, 0.99; 52 cases). In contrast, our study found no association with ER$^+$/PR$^+$ tumors, but a significant inverse association with ER$^-$/PR$^-$ tumors. It has been suggested that breast cancer risk factors differ by hormone receptor status (37): risk factors known to be linked to estrogen metabolism, eg, may have a stronger relation to ER$^+$ tumors than to ER$^-$ tumors. For ER$^+$ tumors, estrogen exposure may be the most important factor and thus override any effect of nonhormonal factors. ER$^-$ tumors, however, may be more susceptible to other exposures such as diet. Studies that have examined dietary patterns, glycemic index, and glycemic load found that the associations with ER$^-$ tumors were stronger than those for ER$^+$ tumors (15, 38, 39). The Women's Intervention Nutrition study, a randomized clinical trial of low-fat diet, also observed that the effect of dietary intervention on relapse-free survival was greater in women with ER$^-$ tumors (hazard ratio: 0.58; 95% CI: 0.37, 0.91) than in women with ER$^+$ tumors (hazard ratio: 0.85; 95% CI: 0.63, 1.14) (39).

Our study is the largest prospective cohort study of the association between dietary fiber intake and risk of breast cancer by hormone receptor status and by breast cancer histologic type. A wide range of dietary fiber intakes—which could offset intraindividual measurement error to some extent—and the large number of cases in our study may have provided adequate statistical power to detect modest associations. In addition, we found that the associations became stronger after adjustment for measurement error in dietary fiber intake, although we recognize that multivariate measurement error correction is complex and

a focus of current methodologic research (40). In that light, the use of alternative dietary assessment tools, such as multiple 24-h recalls, in conjunction with standard frequency questionnaires, may help reduce RR attenuation because of measurement error and thereby further clarify this question (41). More studies are needed to examine associations between dietary fiber and risk of breast cancer by hormone receptor status and histologic type. In addition, given that the effects of estrogen and some breast cancer risk factors differ by menopausal status (1), studies that investigate the fiber–breast cancer association among premenopausal women are warranted.

Our finding suggests that dietary fiber can play a role in preventing breast cancer through nonestrogen pathways among postmenopausal women. Nevertheless, the totality of evidence at this point is far from consistent, and additional research is needed before definitive public health recommendations for fiber and breast cancer can be made.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, State of Nevada Department of Health and Human Services.

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