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Dietary fiber intake and risk of breast cancer by menopausal and estrogen receptor status

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Abstract

Purpose—Evaluate the hypothesis that relation of breast cancer associated with dietary fiber intakes varies by type of fiber, menopausal, and the tumor's hormone receptor status.

Methods—A case-control study of female breast cancer was conducted in Connecticut. A total of 557 incident breast cancer cases and 536 age frequency-matched controls were included in the analysis. Information on dietary intakes was collected through in-person interviews with a semi-quantitative food frequency questionnaire and was converted into nutrient intakes. Odds ratios and 95% confidence intervals were estimated by unconditional logistic regression.

Results—Among pre-menopausal women, higher intake of soluble fiber (highest versus lowest quartile of intake) was associated with a significantly reduced risk of breast cancer (OR = 0.38, 95% CI, 0.15–0.97, $P_{\text{trend}} = 0.08$). When further restricted to pre-menopausal women with ER^- tumors, the adjusted OR for the highest quartile of intake was 0.15 (95% CI, 0.03–0.69, $P_{\text{trend}} = 0.02$) for soluble fiber intake. Among post-menopausal women, no reduced risk of breast cancer was observed for either soluble or insoluble fiber intakes or among ER^+ or ER^- tumor groups.

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Conclusions—The results from this study show that dietary soluble fiber intake is associated with a significantly reduced risk of ER^- breast cancer among pre-menopausal women. Additional studies with larger sample size are needed to confirm these results.

Keywords

Dietary fiber intake; Breast cancer; Estrogen receptor; Menopausal status; Case-control studies

Introduction

More than one million women will be diagnosed with breast cancer and over 460,000 of them will die from the disease each year worldwide [1]. While tremendous effort has been made, the known risk factors can only explain about half of the disease [2]. Among various factors that have been linked to breast cancer risk in epidemiologic studies, low dietary fiber intake has been linked to a reduced risk of breast cancer [3–6].

Evidence linking dietary fiber intake and breast cancer risk, however, has been inconsistent. A meta-analysis of 12 case-control studies by Howe et al. [3] reported a significantly reduced risk of breast cancer associated with dietary fiber intake in post-menopausal women. The study by Cho et al. [4] from the Nurses' Health Study cohort, on the other hand, found no association between fiber or fiber fractions and risk of breast cancer. The Canadian National Breast Screening Study [7] also did not find a relationship between fiber intake and breast cancer risk.

Several studies suggested that the risk of breast cancer associated with fiber intakes may vary by type of fiber intakes (soluble and insoluble), by menopausal status (pre-menopausal and post-menopausal) [5, 8, 9] and by the tumor's hormone receptor status (estrogen receptor (ER) positive or negative and progesterone receptor (PR) positive or negative) [6, 10–12]. For example, the National Institutes of Health-AARP Diet and Health Study found an inverse association between soluble fiber and breast cancer risk, and the relationship appearedtobestronger for ER^-/PR^- tumors than for ER^+/PR^+ tumors among post-menopausal women [6]. Another recent study by Cade et al. [5] reported a statistically significant inverse association between total fiber intake and risk of breast cancer among pre-menopausal women, but not among post-menopausal women.

Here, we report the results evaluating the hypothesis that risk of breast cancer associated with dietary fiber intakes varies by type of fiber, menopausal, and ER status of the tumor using the data from our case-control study of breast cancer in Connecticut, USA.

Subjects and methods

Study population

The study population and methods have been described elsewhere [13, 14]. In brief, cases chosen for the study were Connecticut residents pathologically diagnosed with incident breast cancer (ICD-O, 174.0–174.9) with an age range between 30 and 79, with no previous diagnosis of cancer except non-melanoma skin cancer, between January 1, 1994, and December 31, 1997.

Cases were recruited from New Haven County and Tolland County in Connecticut. In New Haven County, the cases were identified from Yale-New Haven Hospital (YNHH), where records of all newly performed breast-related surgeries were kept. We consecutively selected all breast cancer patients who met the study eligibility requirements as described above. A total of 561 incident breast cancer cases were identified from YNHH, with 432 of them (77%) completing in-person interviews. The 569 potential hospital controls from New Haven County were randomly selected from those who underwent breast-related surgery but who were histologically confirmed with either normal tissue or benign breast diseases without atypia. Of these, 404 (71%) participated in the study.

For Tolland County, the cases were ascertained by the Rapid Case Ascertainment Shared Resource of the Yale Comprehensive Cancer Center, where the staff was assigned geographically to survey all of the state's non-pediatric hospitals in order to identify newly diagnosed cases. Information for the cases identified in the field was regularly entered, verified, and screened against the Connecticut Tumor Registry database. Connecticut also has reciprocal reporting of cancer cases with adjacent states, facilitating complete ascertainment. A total of 238 such cases were identified from Tolland with 176 of them (74%) completing in-person interviews. The controls from Tolland County were population-based and recruited through either random digit dialing (for those below age 65) or from the Centers for Medicare & Medicaid Services (CMMS) files, previously known as the Health Care Finance Administration (HCFA) (for those aged 65 and above). The participation rate from random digit dialing-selected controls was 64% including the initial telephone screening and from HCFA controls, 54%. A total of 152 random digit dialing-selected controls and 53 HCFA controls participated in the study. Efforts were made to frequency match the cases and controls by age (within 5-year intervals) using a 1:1 ratio by adjusting the number of controls randomly selected in each age stratum every few months. As noted above, certain data used in this study were obtained from the Connecticut Tumor Registry located in the Connecticut Department of Public Health. The author(s) assume(s) full responsibility for analyses and interpretation of these data.

In this study, a total of 608 incident breast cancer cases and 609 controls were recruited and completed with inperson interviews. Among them, 42 participants (20 cases, 22 controls) were excluded due to incomplete information on fiber intake. An additional 82 participants were excluded because their estimated average daily energy intake was either < 800 kcal (27 cases, 46 controls) or > 4,000 kcal (4 cases, 5 controls). Thus, a total of 557 cases and 536 controls were included in the final analysis.

Interviews

After approval by the hospitals, the Connecticut Department of Public Health Institutional Review Board, and by each subject's physician, or following selection through random sampling, potential participants were approached by letter and then contacted by phone. Trained study interviewers conducted in-person interviews for those who agreed, either in the subject's home or at a convenient location to the participant to collect information on major or suspected risk factors for breast cancer, including dietary intake.

For dietary intake, a semi-quantitative food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center [15] was used to record information about usual dietary intake 1 year before the interview. Case interviews were completed 3 months after diagnosis, on average. The FFQs were sent to the Fred Hutchinson Cancer Research Center, and average daily nutrient intakes were calculated using the University of Minnesota Nutrition Coding Center Nutrient Data System database. Based on the Institute of Medicine report on US intakes of fiber [16], dietary fiber is found in plant foods: vegetables, fruit, and pulses (legumes), as well as in cereals, roots, tubers, and plantains. Based on reports, good sources of soluble fiber include oatmeal, oat cereal, lentils, apples, oranges, pears, oat bran, strawberries, nuts, flaxseeds, beans, dried peas, blueberries, psyllium, cucumbers, celery, and carrots. Sources of insoluble fiber include whole wheat, whole grains, wheat bran, corn bran, seeds, nuts, barley, couscous, brown rice, bulgur, zucchini, celery, broccoli, cabbage, onions, tomatoes, carrots, cucumbers, green beans, dark leafy vegetables, raisins, grapes, fruit, and root vegetable skins.

Statistical analysis

Unconditional logistic regression analyses were used to estimate the association, control for confounding factors and test for linear trend. The dietary fiber intakes were divided into quartiles based on the distributions of the control group. Formal statistical testing for trend was performed by treating each variable as a continuous variable rather than several indicator variables. The following potential confounders were included in the final model: age (continuous), race (white or nonwhite), body-mass index (BMI, continuous), age at first menarche period (B12, > 12), menopausal status, age at first full-term birth (nulliparous, < 25, 25–29, 30–35, > 35 years), lifetime months of lactation (continuous), family history of breast cancer in first-degree relatives, annual household income (< $25,000, $25,000–$45,000, $45,001–$67,500, > $67,500, or unknown), the presence of a positive history of cigarette smoking (ever or never) and alcohol consumption (ever or never), and total energy intake as a continuous variable. Data were further stratified by ER status for cases recruited from New Haven County where the information on ER status was available. Data cannot be analyzed by PR status since the information on PR status was available only from the small number of subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the strength of the association and the precision of the estimates using SAS (9.2 for Windows, SAS Institute Inc., Cary, NC, USA) statistical software.

Results

Cases were slightly older than the controls, despite an attempt at frequency matching; therefore, age was controlled for in all subsequent analyses. A slightly higher proportion of cases reported a higher BMI, positive family histories of breast cancer and cigarette smoking. In contrast, controls reported longer lifetime duration of lactation (Table 1).

The median total fiber intake (15.1 g/day) observed in controls in this study. For soluble fibers and insoluble fibers, the median intakes were 5.1 g/day (10th–90th percentile range: 2.8–7.8 g/day) and 10.0 g/day (10th–90th percentile range: 5.3–15.7 g/day), respectively. Fiber intake did not vary significantly with age at the age range of the study population. It also did not vary significantly with different racial groups. However, the fiber intake, including both soluble and insoluble fiber intake, was associated with a significant and positive association with income and months of lifetime breasting feeding in this study.

As shown in Table 2, while fiber intakes were associated with a reduced risk of breast cancer among pre-menopausal women when the highest quartile group was compared with the lowest, only soluble fiber intake was associated with a statistically significant association (OR = 0.38, 95% CI, 0.15, 0.97), although no dose-response trend was found (P_{trend} = 0.08). No statistically significant association was observed among post-menopausal women for either soluble or insoluble intake groups.

Table 3 shows the results further stratified by menopausal status and ER status for subjects recruited from New Haven County where information on ER status was available. As shown in Table 3, among pre-menopausal women, although both ER^+ and ER^- cancer patients showed a reduced risk of breast cancer associated with total, soluble and insoluble fiber intakes when the highest quartile intake group was compared with the lowest, only the ER^- cancer patients had a statistically significantly reduced risk associated with soluble fiber intake (OR = 0.15, 95% CI, 0.03, 0.69, P_{trend} = 0.02). There was no evidence that dietary fiber was associated with a reduced risk of breast cancer in post-menopausal women for either ER^+ or ER^- tumors, although there was a borderline statistically significant trend for an increased risk with increasing intake of insoluble fibers among post-menopausal women with ER^- tumors. The association, however, does not appear to be strong. Formal test of interactions at multiplicative model showed a *P* value of 0.036 between soluble fiber intake and menopausal status, and a *P* value of 0.021 for insoluble fiber and menopausal status. No other significant interaction was observed between dietary fiber intakes and other factors.

The data were further stratified by study site and the results for both the New Haven County and Tolland County were quite similar, while the results were less stable due to the further stratification of the study population.

Discussion

In this case-control study, we found a reduced risk of breast cancer associated with dietary soluble fiber intakes in pre-menopausal women, but not among post-menopausal women. The observed association appears to be stronger for ER^- tumors in our study.

The median total fiber intake observed in this study was quite similar to those reported in the study reported from other similar US population [6, 17]. The results are consistent with several, but not all, recent studies. For example, the UK women's cohort study by Cade et al. [5] recently reported a statistically significant inverse relationship between fiber intakes and risk of breast cancer in pre-menopausal women. A multi-center case-control study conducted in Italy by La Vecchia et al. [9] also showed that fiber intake may have a stronger protective effect on breast cancer for pre-menopausal women than for post-menopausal women. Several cohort studies were conducted in post-menopausal women and did not find a significant association between fiber intakes and breast cancer risk [18–21]. Earlier studies also reported a different relationship between dietary fat intakes and breast cancer risk for pre- and post-menopausal women. For example, it has been shown that dietary fat intakes may be related to breast cancer in post-menopausal women, but not in pre-menopausal women [3, 22].

Recent studies also showed a potential different relationship between fiber intakes and breast cancer risk by estrogen receptor status, although all studies were conducted among post-menopausal women. The National Institutes of Health-AARP Diet and Health Study by Park et al. [6] recently reported a stronger inverse association between fiber intake and breast cancer risk for ER^-/PR^- tumors (RR for the highest quintile compared with the lowest quintile = 0.56; 95% CI, 0.35, 0.90) than for ER^+/PR^+ tumors (RR = 0.95; 95% CI, 0.76, 1.20). The Melbourne Collaborative Cohort Study [10] observed a positive association with ER^+/PR^+ tumors (RR = 1.36; 95% CI, 1.10, 1.67), with higher fiber intake associated with increased risk. It should be noted, however, that three other cohort studies that examined breast cancer by hormone receptor status did not find a statistically significant association between dietary fiber intake and breast cancer risk by ER or PR status among post-menopausal women [11, 12, 20].

Risk of breast cancer associated with fiber intake also appears to vary by type of dietary fiber intakes. Park et al. [6] showed that while insoluble fiber intake was not associated with breast cancer risk, soluble fiber intake, however, was associated with a 17% significantly reduced risk of breast cancer when the highest quintile was compared with the lowest (RR = 0.83; 95% CI, 0.70, 0.98). These results are consistent with what we observed in this study. However, the borderline statistically significant trend was observed in our study for an increased risk with increasing intake of insoluble fibers among post-menopausal women with ER^- tumors. Larger studies, however, are needed to confirm the result of this study.

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 [23–

25]. An experimental study also showed that pectin, a soluble fiber, had an inhibitory effect on mammary tumor growth, angiogenesis, and metastasis [26]. Insoluble fiber, on the other hand, has been shown to increase the fecal excretion of estrogens [27, 28], which may be associated with a reduced risk of breast cancer through the reduction in circulating estrogen level [29]. Experimental studies have shown that higher soluble fiber intake reduces mammary tumor incidence in rats [30].

We should recognize that the relationship between dietary fiber intake and breast cancer risk remains unimpressive as compared to the relationship between fiber and other cancers (such as colorectal cancer and stomach cancer) as reviewed by an expert panel [31]. The reduced risk of breast cancer associated with dietary fiber intake observed in this study may in fact indirectly reflect the effects from other dietary nutrients, and thus dietary fiber here may simply act as a marker for other exposures which have been linked to a reduced risk of human cancer as well, such as folate, phytochemicals, carotenoids, vitamin C and E which are also like dietary fiber found in plant foods, such as vegetables, fruits, and pulses (legumes), as well as in cereals, roots, tubers, and plantains [31]. On the other hand, an increased consumption of fiber from foods of plant origin (such as vegetables, fruits, and cereals) may reflect a reduced consumption of foods of animal origin, particularly red meat and processed meat which have been associated with an increased risk of some human cancers.

As in any case-control study, recall bias is a potential limitation because women knew their disease status at the time that the interviews were conducted. However, recall bias would not explain the inverse association that we observed in pre- but not post-menopausal women. Non-differential misclassification bias on exposure, on the other hand, is likely and could be responsible for lack of statistical significance association in some of the analyses. The relatively small sample size of our study has made the point estimates less stable, especially for the results stratified by type of fiber and estrogen receptor status as reflected by the wide confidence intervals of the point estimates. Moreover, considering the relative small sample size, coupled with stratified analyses by estrogen receptor status, chance could not be excluded as the potential alternative explanation for some of the observed statistically significant findings.

In summary, the results from this case-control study show that dietary soluble fiber intake is associated with a significantly reduced risk of ER^- breast cancer among pre-menopausal women. Further studies with larger sample size are needed to confirm these results.

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Table 1

Selected characteristics of breast cancer cases and controls among Connecticut women

Characteristics	**Cases (n = 557)**		**Controls (n = 536)**	
	n	**%**	***n***	**%**
Age (years)				
< 50	164	29.44	201	37.50
50–59	177	31.78	147	27.43
≥ 60	216	38.78	188	35.07
Race				
White	507	91.02	492	91.79
Nonwhite	50	8.98	44	8.21
Body-mass index (kg/m^2)				
< 22.5	146	26.21	151	28.17
22.5 to < 25	136	24.42	140	26.12
25 to < 30	162	29.08	139	25.93
≥ 30	113	20.29	106	19.78
Age (years) at menarche				
≤ 12	285	51.17	286	53.36
> 12	272	48.83	250	46.64
Menopausal status				
Pre-menopausal	113	20.29	186	34.70
Post-menopausal	444	79.71	350	65.30
Age (years) at first full-term pregnancy				
Nulliparous	77	13.82	87	16.23
< 25	252	45.24	234	43.66
25–29	149	26.75	132	24.63
C30	79	14.18	83	15.49
Lifetime months of lactation				
No	362	64.99	316	58.96
≤ 12	125	22.44	134	25.00
> 12	70	12.57	86	16.04
Family history of breast cancer in a first-degree relative				
No	427	76.66	424	79.10
Yes	130	23.34	112	20.90
Cigarette smoking				
Never	244	43.81	259	48.32
Ever[a]	313	56.19	277	51.68
Alcohol drinking				
Never	473	84.92	461	86.01
Ever[b]	84	15.08	75	13.99
Annual household income				
< $25,000	128	22.98	102	19.03
$25,000–$45,000	138	24.78	122	22.76
$45,000–$67,500	105	18.85	116	21.64
≥ 67,500	92	16.52	122	22.76
Missing	94	16.88	74	13.81

[a]At least 100 cigarettes in the lifetime

[b]At least 12 drinks of any type of alcoholic beverage in a year

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Table 2

Risk of breast cancer associated with fiber intake among women, stratified by menopausal status, in Connecticut

Dietary intake	All (557/536)[a]			Pre-menopausal (113/186)[a]			Post-menopausal (444/350)[a]		
	Ca/Co[a]	OR[b]	95% CI	Ca/Co[a]	OR[c]	95% CI	Ca/Co[a]	OR[c]	95% CI
Total fiber (g/day)									
< 10.7	105/112	1.00		28/40	1.00		77/72	1.00	
10.7–14.0	144/139	1.08	(0.74, 1.56)	28/42	0.91	(0.44, 1.88)	116/97	1.14	(0.74, 1.74)
14.0–18.3	161/145	1.20	(0.82, 1.78)	37/47	1.14	(0.58, 2.27)	124/98	1.21	(0.79, 1.85)
> 18.3	147/140	1.17	(0.76, 1.80)	20/57	0.48	(0.23, 1.01)	127/83	1.50	(0.97, 2.32)
P-trend[d]			0.41			0.10			0.07
Soluble fiber (g/day)									
< 3.6	113/111	1.00		29/38	1.00		84/73	1.00	
3.6–4.7	142/141	0.95	(0.65, 1.37)	29/46	0.87	(0.41, 1.88)	113/95	1.07	(0.69, 1.66)
4.7–6.2	176/144	1.16	(0.79, 1.70)	37/44	1.20	(0.54, 2.70)	139/100	1.26	(0.81, 1.97)
> 6.2	126/140	0.84	(0.54, 1.30)	18/58	0.38	(0.15, 0.97)	108/82	1.15	(0.69, 1.93)
P-trend[d]			0.70			0.08			0.46
Insoluble fiber (g/day)									
< 7.0	107/111	1.00		28/43	1.00		79/68	1.00	
7.0–9.2	146/140	1.04	(0.72, 1.52)	31/38	1.27	(0.62, 2.60)	115/102	1.01	(0.66, 1.56)
9.2–12.1	149/144	1.08	(0.73, 1.59)	33/47	1.06	(0.53, 2.10)	116/97	1.06	(0.69, 1.63)
> 12.1	155/141	1.16	(0.76, 1.78)	21/58	0.54	(0.26, 1.13)	134/83	1.46	(0.95, 2.27)
P-trend[d]			0.48			0.08			0.07

CI confidence interval, *OR* odds ratio, *ER* estrogen receptor

[a] Cases/controls

[b] Adjusted for age (years, continuous), race (white, nonwhite), body-mass index (kg/m^2, continuous), age at first menarche (≤ 12 or > 12 years), menopausal status, family history of breast cancer (yes or no), age at first full-term birth (nulliparous, < 25, 25–29, 30–35, > 35 years), months of lifetime breast feeding (months, continuous), cigarette smoking (ever or never), alcohol drinking (ever or never), menopausal status, and total energy intake (kcal, continuous)

[c] Without adjusting for menopausal status

[d] Test for linear trend in adjusted OR for quartiles

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Table 3

Risk of breast cancer associated with the fiber intake, stratified by menopausal status and ER status, in New Haven County

Dietary intake	Pre-menopausal						Post-menopausal					
	ER$^+$ (36/132)[a]			ER$^-$ (45/132)[a]			ER$^+$ (158/228)[a]			ER$^-$ (125/228)[a]		
	Ca/Co[a]	OR[b]	95% CI	Ca/Co[a]	OR[b]	95% CI	Ca/Co[a]	OR[b]	95% CI	Ca/Co[a]	OR[b]	95% CI
Total fiber (g/day)												
< 10.7	8/28	1.00	(0.31, 3.67)	13/28	1.00		29/48	1.00		19/48	1.00	
10.7–14.0	10/28	1.06	(0.31, 3.67)	13/28	0.69	(0.22, 2.13)	41/72	0.95	(0.53, 1.80)	28/72	0.93	(0.45, 1.90)
14.0–18.3	12/38	0.84	(0.23, 3.11)	12/38	0.54	(0.16, 1.81)	46/59	1.22	(0.62, 2.39)	37/59	1.39	(0.67, 2.91)
> 18.3	6/38	0.39	(0.07, 2.05)	7/38	0.24	(0.06, 1.03)	42/49	1.36	(0.63, 2.95)	41/49	1.90	(0.84, 4.31)
P-trend[c]			0.27			0.06			0.32			0.06
Soluble fiber (g/day)												
< 3.6	8/27	1.00		13/27	1.00		30/52	1.00		22/52	1.00	
3.6–4.7	9/31	0.97	(0.27, 3.45)	13/31	0.58	(0.19, 1.79)	41/65	1.09	(0.58, 2.06)	31/65	1.16	(0.58, 2.31)
4.7–6.2	14/35	1.41	(0.38, 5.27)	13/35	0.47	(0.14, 1.59)	50/65	1.28	(0.67, 2.43)	40/65	1.27	(0.63, 2.57)
> 6.2	5/39	0.34	(0.07, 1.73)	6/39	0.15	(0.03, 0.69)	37/46	1.32	(0.61, 2.85)	32/46	1.36	(0.60, 3.09)
P-trend[c]			0.33			0.02			0.42			0.44
Insoluble fiber (g/day)												
< 7.0	8/30	1.00		13/30	1.00		30/45	1.00		22/45	1.00	
7.0–9.2	14/25	1.86	(0.55, 6.24)	12/25	0.99	(0.32, 3.06)	42/78	0.85	(0.45, 1.61)	22/78	0.54	(0.26, 1.12)
9.2–12.1	9/38	0.55	(0.14, 2.13)	11/38	0.58	(0.17, 1.95)	43/53	1.16	(0.58, 2.31)	37/53	1.20	(0.58, 2.47)
> 12.1	5/39	0.31	(0.06, 1.58)	9/39	0.44	(0.12, 1.70)	43/52	1.17	(0.55, 2.50)	44/52	1.55	(0.71, 3.36)
P-trend[c]			0.06			0.18			0.46			0.05

CI confidence interval, *OR* odds ratio, *ER* estrogen receptor

[a]Cases/controls

[b]Adjusted for age (years, continuous), race (white, nonwhite), body-mass index (kg/m^2, continuous), age at first menarche (≤ 12 or > 12 years), family history of breast cancer (yes or no), age at first full-term birth (nulliparous, < 25, 25–29, 30–35, > 35 years), months of lifetime breast feeding (months, continuous), cigarette smoking (ever or never), alcohol drinking (ever or never), and total energy intake (kcal, continuous)

[c]Test for linear trend in adjusted OR for quartiles