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Dietary fiber is associated with circulating concentrations of C-reactive protein in breast cancer survivors: the HEAL study

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Abstract

Inflammation is a suspected risk factor for breast cancer and its subsequent prognosis. The extent to which dietary and lifestyle factors might influence inflammation is important to examine. Specifically, dietary fiber may reduce systemic inflammation, but this relationship has not been examined among breast cancer survivors. We examined associations between dietary fiber and serum concentrations of C-reactive protein (CRP) and serum amyloid-A (SAA), among 698 female breast cancer survivors from the Health, Eating, Activity, and Lifestyle (HEAL) Study. Data are from interviews and clinical visits conducted 24 months post-study enrollment. Multivariate-adjusted linear regression estimated associations of total, soluble and insoluble fiber with serum concentrations of CRP and SAA. Logistic regression estimated the odds of elevated CRP (defined as >3.0 mg/L) across tertiles of dietary fiber intake. Mean total dietary fiber intake was 13.9 ± 6.4 g/day. Mean CRP and SAA were 3.32 ± 3.66 mg/L and 7.73 ± 10.23 mg/L, respectively. We observed a multivariate-adjusted inverse association between total dietary fiber intake and CRP concentrations (β , -0.029; 95% CI, -0.049, -0.008). Results for insoluble fiber were similar (β , -0.039; 95% CI, -0.064, -0.013). Among survivors who consumed >15.5 g/day of insoluble dietary fiber, a 49% reduction in the likelihood of having elevated CRP concentrations (OR, 0.51; 95% CI, 0.27, 0.95) was observed compared to those who consumed <5.4 g/day ($p = 0.053$). Our results suggest that diets high in fiber may benefit breast cancer survivors via reductions in systemic inflammation; elevated inflammation may be prognostic for reduced survival.

Keywords

dietary fiber; breast cancer; C-reactive protein; serum amyloid A; inflammation

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Introduction

Epidemiological evidence supports a role for inflammation in the etiology of several chronic diseases; the most notable being cardiovascular disease (CVD), diabetes, and several types of cancer [1–4]. Various markers of inflammation have been examined with respect to their association with these chronic diseases [3, 5–11]. C-reactive protein (CRP), a non-specific acute phase protein and biomarker of inflammation, consistently predicts positive associations with chronic conditions, including malignant disease [11–20]. The specific mechanisms by which dietary fiber modulates inflammatory response in humans are unclear. However, evidence suggests that dietary fiber may mediate systemic inflammatory response by multiple mechanisms, such as regulating body weight, slowing absorption of glucose, increasing sensitivity to insulin and shifts in microbial community [21–25]. The latter mechanism has been shown to increase the production of short chain fatty acids (SCFAs) and decrease inflammatory responses within the colon [26]. Epidemiological evidence from both cross-sectional and cohort studies suggests that higher intake of dietary fiber is associated with lower concentrations of inflammatory markers [27–29]. Findings from these studies have sparked interest in elucidating the role dietary fiber plays in modulating inflammatory response.

Research examining the impact of dietary fiber on inflammation and has been conducted primarily in healthy men and women and patients with diabetes or cardiovascular risk factors; yet little is known about the effects of fiber on inflammation in breast cancer patients [29–31]. Investigating this association may help determine whether increasing dietary fiber intake improve prognosis among breast cancer survivors, by reducing the risk of elevated concentrations of cytokines and other inflammatory markers and potentially reducing the risk of recurrence and mortality [32]. We therefore examined the relationship between self-reported usual intake of dietary fiber (total, soluble and insoluble) and the inflammatory markers CRP and serum amyloid A (SAA) in a cohort of breast cancer survivors enrolled in the Health, Eating, Activity and Lifestyle (HEAL) Study. We also examined the association between the amount of dietary fiber and race/ethnicity, since Hispanic women have both the lowest breast cancer rates of any major racial/ethnic group in the U.S. [33], and the highest dietary fiber intake reported by other racial/ethnic groups [34].

Materials and Methods

Study Participants and Procedures

A total of 1,183 women, between 18–64 years, were enrolled in the HEAL Study, a multicenter, multiethnic cohort of female breast cancer patients. Details of the aims, study design, and methods have been previously published [35–37]. Recruitment eligibility was restricted to women with *in situ* or Stage I to IIIA disease, who participated in a baseline interview within 12 months of diagnosis, and resided and identified from Surveillance Epidemiology and End Results (SEER) registry in one of three distinct regions in western United States: north-central New Mexico, Los Angeles (CA), and western Washington. All participants completed an in-person interview and clinical visit at baseline entry into the cohort, which was within their first year following diagnosis. Participants completed an additional visit 24 months after enrollment consisting of an in-person interview, a self-administered food frequency questionnaire (FFQ), anthropometry and a 30 mL fasting blood draw. Written informed consent was obtained from each participant. The study was performed with the approval of the Institutional Review Boards of participating centers, in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Dietary Fiber Measurement

The primary exposures of interest are total daily intake of dietary fiber (g/day), soluble fiber (g/day), and insoluble fiber (g/day). Daily fiber intake was assessed using a FFQ, designed for the Women's Health Initiative. Collection procedures and information pertaining to the questionnaire are described in an earlier publication [38]. In brief, 24 months post-enrollment participants were asked the usual frequency of consumption and portion size for 122 food items or food groups.

Other Data

Other data collected either at baseline or the 24-month post-enrollment interview included age at breast cancer diagnosis, body mass index (BMI), current smoking status, menopausal status, number of cardiovascular or potential inflammatory related conditions, physical activity, total energy intake, alcohol consumption and fat intake, and medication use. Participants disease stage (*in situ* and stage I-IIIa) was obtained from the local SEER registries and breast cancer treatment data were obtained from the participant's medical records.

Measures of Inflammation: CRP and SAA

Trained laboratory staff measured CRP and SAA concentration from a single 30 mL 12-hour fasting blood sample taken from participants at the 24 month follow-up clinical visit. All blood samples were processed and stored between -70° to -80°C , until assays were conducted. We measured high sensitivity CRP and SAA by latex-enhanced nephelometry using the Behring Nephelometer II analyzer (Dade Behring Diagnostics, Deerfield, IL) at the University of Washington Medical Center (Seattle, WA). There is evidence to indicate that this high sensitivity assay routinely performs well [39], and CRP values obtained using latex-enhanced method are highly correlated with validated enzyme-linked immunosorbent assay ($r = 0.95$) [40]. The lower limits of detection for the CRP and SAA assays were 0.2 and 0.7 mg/L, respectively and the inter-assay coefficients of variation were 5–9% and 4–8%, respectively. For each assay, quality-control procedures were conducted using control materials from Bio-Rad Laboratories (Hercules, CA).

Statistical Analysis

Our analytic goal was to characterize the association of dietary fiber with serum concentrations of CRP and SAA. For descriptive purposes, participants were divided into tertiles based on the dietary fiber intake distribution across the entire cohort. We compared participant characteristics by total fiber tertile using the overall F statistic from general linear model procedures to assess whether mean values for variables differed significantly from each other across total dietary fiber tertiles and the chi-squared statistic to assess whether values for categorical variables differed significantly across total dietary fiber tertiles.

For the primary aim, we used multiple linear regression analysis to compute the beta coefficients (β), standard errors (SE) and 95 percent confidence intervals (95% CI) between dietary fiber intake and each inflammatory marker. Tests for trend were performed by modeling the mean values of each fiber tertile as a continuous variable. In addition, logistic regression analysis was conducted to compute the odds ratios (OR) and 95% CI for the probability of having an elevated CRP concentration. We made an *a priori* decision to model total dietary fiber intake as a continuous variable in multivariate linear regression and as categories (highest and middle tertile vs. lowest tertile separately) in examining the likelihood of elevated serum CRP concentrations. We hypothesized a linear relationship and the continuous parameterization yields slightly more power when testing linear associations. In a similar fashion, we examined certain fractions of dietary fiber (i.e., soluble and

insoluble) to assess for similar trends. The inflammatory markers were modeled as continuous variables. Data for CRP and SAA were log transformed to produce a more linear relationship and normally distributed residuals when the tested parameters deviated from a normal distribution. The values for total fiber, soluble fiber, and insoluble fiber intake were normally distributed, therefore no transformations were necessary. For the logistic regression analysis, CRP was modeled as a dichotomous variable to determine the likelihood of elevated CRP, defined as ≥ 3 mg/L to compare to prior studies [11].

All models were adjusted for potential confounding variables, notably age (continuous, years) [41], BMI (continuous, kg/m²) [42, 43], current smoking status (yes/no) [44], post-menopausal status (yes/no) [45], physical activity by moderate and/or vigorous sport and recreational activities in the year prior to follow-up (continuous, MET-h/wk) [36, 46], daily total energy (continuous, kcal) [29, 31], daily alcohol consumption (continuous, g) [29, 31], daily fat intake (continuous, g) [29, 31, 47], number of self-reported history of any cardiovascular disease or inflammatory-related condition (including angina, myocardial infarction, heart failure, hypertension, stroke, diabetes, chronic kidney or liver disease, and arthritis) [42], current medication use (mutually exclusive variables for Tamoxifen, non-steroidal anti-inflammatory drugs (NSAIDs), Beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, lipid lowering, oral estrogen, vitamin E supplements, and multivitamins) [45, 48–50]. Furthermore, disease stage (*in situ* and stage I–IIIA) and breast cancer treatment (surgery only, surgery and radiation, surgery and chemotherapy, and surgery, radiation, and chemotherapy) were also examined to account for possible confounding [51]. An adjustment variable for race/ethnicity/study site was generated to adjust for the high correlation between race/ethnicity and study site and residual confounding [41].

All potential confounding variables were added to the multivariable-adjusted model if they (a) were associated with both CRP concentrations and with dietary fiber intake and changed the risk estimate of the model containing dietary fiber intake, age and BMI by at least 10% or (b) were previously reported to be associated with CRP and SAA levels among individuals without breast cancer [41–47]. Diagnostics were performed to test for multicollinearity among the covariates. In all models, tolerance was close to 1.0, indicating lack of multicollinearity.[52] We performed all analysis using SPSS version 16.0 (SPSS Inc, Chicago, IL), with a Type I error set at $p > 0.05$ (two-sided).

For the purposes of this report, we excluded women who did not complete a 24 month follow-up assessment, had missing dietary assessment data, had missing CRP or SAA measurements, or were not disease free at the 24 month follow-up, resulting in a sample size of $n = 731$. We further excluded 32 (4%) participants who had CRP values that were greater than the 95th percentile cutoffs of the age- and race-specific NHANES distributions [41]. These exclusions were intended to account for elevated CRP concentrations due to acute inflammation or infection at the time of blood draw; as such concentrations would not be reflective of true chronic inflammation. Lastly, we excluded a single outlier participant who reported an improbable total dietary fiber exceeding 85 g/day, leaving $n = 698$ women for this analysis.

Results

The mean intake for total dietary fiber was 13.96 g/d, and mean intakes for soluble and insoluble fiber were 3.71 g/d and 10.16 g/d, respectively. Table 1 gives means, standard deviations (SD) and proportions of participant characteristics across total dietary fiber. Based on the descriptive statistics, there were no significant differences in participant characteristics across tertiles of total dietary fiber intake, except for race/ethnicity,

education, vitamin E supplementation, arthritis and hypertension. The majority of participants identified themselves as non-Hispanic whites, ranging from 49% to 70% across tertile of total dietary fiber ($p < 0.001$). HEAL participants were well educated as 74.3% reported having attended college or graduate school. Vitamin E supplementation varied across the tertile of total dietary fiber intake, with 50.0% taking supplements in tertile one, 64.8% in tertile two and 67.0% within tertile three ($p = 0.001$). Rates of arthritis were found to differ across the tertile of dietary fiber ($p = 0.04$), as well as hypertension ($p = 0.02$)

The overall mean serum CRP was 3.32 mg/L with significant differences across the fiber intake distribution (Table 2). Mean serum CRP concentrations were lowest among participants with the highest grouping (third tertile) of total dietary fiber intake, 2.93 mg/L; whereas those in the second and first fiber intake tertiles had a mean CRP concentration of 3.24 mg/L and 3.79 mg/L, respectively ($p < 0.036$). SAA concentrations did not differ across fiber distribution. Among those with the lowest intake of total dietary fiber, the mean total dietary fiber intake was 7.56 g/day, and correspondingly the mean intakes for soluble and insoluble fiber were 2.05 g/day and 5.45 g/day. For those classified into tertile two, the mean total dietary fiber intake was 12.95 g/day, with mean soluble fiber intake of 3.43 g/day and mean insoluble fiber intake of 9.43 g/day. Women classified into the highest intake of dietary fiber (tertile three), the mean total dietary fiber intake was 21.35 g/day, soluble fiber intake was 5.64 g/day, and insoluble fiber intake was 15.48 g/day.

Linear regression models tested associations of total, soluble, and insoluble dietary fiber intake with both CRP and SAA (Table 3). We constructed a multivariate-adjusted model (adjusting for age, BMI, race/ethnicity/site, and other known moderators of CRP, including current smoking status, postmenopausal status, physical activity, alcohol consumption, dietary fat intake, total energy, number of cardiovascular and inflammatory related conditions, medication use, disease stage and adjuvant treatment used), in which a strong inverse association of total dietary fiber with serum CRP was observed (β , -0.029; 95% CI, -0.049, -0.008; $p = 0.006$). We observed no associations between total dietary fiber intake and SAA.

We next examined the relationship between fiber types, soluble and insoluble, and measures of inflammation (Table 3). Insoluble fiber was strongly, inversely associated with CRP concentrations (multivariate-adjusted model: β , -0.039; 95% CI, -0.064, -0.013; $p = 0.003$). However, no relationship was observed between soluble fiber and CRP concentrations. No associations were found for either total fiber or any fraction with serum SAA concentrations.

The odds of elevated CRP, defined as having a serum CRP concentration ≥ 3 mg/L, was examined. For these analyses, participants in the highest two tertiles of total, soluble and insoluble dietary fiber intake were compared to participants in the lowest tertile of corresponding fraction of dietary fiber intake (Table 4). While there was a suggestion that total dietary fiber intake may protect against elevated CRP, the association did not reach statistical significance in the multivariate-adjusted model (OR, 0.57; 95% CI, 0.30, 1.07). Soluble dietary fiber was also inversely related to elevated CRP, but the association was not statistically significant (OR, 0.86; 95% CI, 0.45, 1.63). However, participants in the highest tertile of insoluble dietary fiber intake had a 49% reduced likelihood of having elevated CRP when compared to the lowest tertile (OR, 0.51; 95% CI, 0.27, 0.95, p for trend = 0.044).

Table 5 presents mean, SD, median, and interquartile range (IQR) for serum concentrations of CRP and SAA by racial/ethnic groups. Serum CRP concentrations were highest among non-Hispanic black women, (4.46 mg/l), followed by Hispanics (3.60 mg/l), and non-Hispanic white women (2.83 mg/l, $p < 0.001$). Concentrations of SAA were similar across

racial/ethnic groups. In multivariate linear regression analysis, non-Hispanic white women had an inverse association of both total dietary fiber intake (β , -0.031; 95% CI, -0.057, -0.006) and insoluble fiber intake (β , -0.042; 95% CI, -0.074, -0.010) with circulating concentrations of CRP. For every one gram increase in total and insoluble fiber intake, one may expect to see an approximate 3% and 4% decrease in serum CRP concentration (mg/L), respectively. A similar relationship was seen among non-Hispanic black women, but the associations were not statistically significant. No associations were observed between total, soluble, and insoluble dietary fiber intake and CRP among Hispanic women.

Discussion

In this multiethnic cohort of early-stage breast cancer survivors, we investigated the relationship between intake of total, soluble, and insoluble dietary fiber with two acute phase markers of inflammation, CRP and SAA. Our principal finding was an inverse association of total and insoluble dietary fiber with CRP concentrations. The importance of identifying modifiable factors, such as diet, that influence inflammatory response may provide the means for reducing the risk of several diseases, as well decrease poor prognosis among women diagnosed with breast cancer. Recent findings from HEAL study participants found that elevated levels of CRP were associated with poor prognosis [32].

Several hypothesized mechanisms have been put forth to explain how dietary fiber may reduce inflammation. First, fiber may have an effect on systemic inflammation by contributing to regulation of healthy body weight. Many weight loss studies have shown a concurrent reduction in CRP with weight loss [43, 53, 54], and it is well-recognized that obesity is associated with low-grade, chronic inflammation [55]. Dietary fiber also slows the absorption of glucose and helps to regulate insulin sensitivity [56]. It has been suggested that reduction in lipid oxidation may have favorable effects on systemic inflammation [19, 21, 54]. Consumption of fermentable fiber has been associated with beneficial shifts in gut microbial composition [57]; gut microbes play an important role in immune function through interaction with toll-like receptors [58]. Finally, a diet rich in fiber also contains other micronutrients such as vitamins, minerals, and other bioactive compounds or secondary metabolites that may work through other pathways (e.g., antioxidant support and detoxification) to ultimately affect expression of cytokines and other mediators of inflammation [53, 59, 60].

Our findings are consistent with previous observational and clinical intervention studies that have examined the relationship between dietary fiber and concentrations of CRP in persons without cancer [28–31, 61]. A 43% reduction in the likelihood of elevated CRP was seen among participants in the highest tertile of total dietary fiber intake vs. the lowest tertile and a 49% reduction in the likelihood of elevated CRP among participants in the highest tertile of insoluble dietary fiber vs. the lowest tertile. A study conducted by Ma et al. [30] used cross sectional and longitudinal data from 524 persons in the Seasonal Variation of Blood Cholesterol Levels Study (SEASONS). The authors reported a 63% reduction (OR, 0.37; 95% CI, 0.16, 0.87) in the likelihood of elevated CRP concentration was reported among participants in the highest quartile of total dietary fiber (i.e., 22.36 gm/day) compared to participants in the lowest quartile (i.e., 10.22 gm/day). When comparing participants who reported intake in the highest quartile of insoluble dietary fiber (i.e., 14.39 g/d), a 68% reduction in the likelihood of elevated CRP was found when compared to the participants in the lowest quartile (i.e., 6.37 g/d; OR, 0.32; 95% CI, 0.14, 0.72). Similarly, in a randomized crossover intervention trial of 35 participants, King et al. [28] demonstrated that fiber intake of approximately 30 g/day reduced serum CRP concentrations by 14% using a diet naturally rich in fiber and an 18% reduction in a fiber-supplemented diet. Two separate investigations using data from the 1999–2000 NHANES, reported similar trends [29, 31]. Ajani et al.

reported a 51% reduction (OR, 0.49; 95% CI, 0.37, 0.65) in the likelihood of elevated CRP concentration among participants in the highest quintile of dietary fiber (32.0 g/d) compared to participants in the lowest quintile (5.1 g/d) [31], and a 42% reduction (OR 0.49; 95% CI, 0.38, 0.88) in the likelihood of elevated CRP concentration was reported by King et al. [29] when comparing participants in the highest quartile of dietary fiber intake to those in the lowest quartile.

Strengths of this study include being a large study among breast cancer survivors to assess the relationship between dietary fiber and inflammation. We recently reported that inflammatory status may be an important prognostic factor for breast cancer prognosis [32], therefore it is worthwhile to recognize what modifiable factors, such as diet, can reduce systemic inflammation. The HEAL cohort consisted of a diverse race/ethnic sample, composed of non-Hispanic white, non-Hispanic blacks, and Hispanic women, which permitted the assessment and adjustment of race/ethnic effects. The FFQ was developed for use in multicultural populations, including African Americans and Hispanics [38]. In addition, this study collected data on various factors known to affect CRP concentrations (i.e., current medication use and comorbid conditions), allowing for their adjustment in multivariate analysis. However, the cross-sectional nature of this study is a limitation that does not allow the evaluation of causality due to uncertain temporality of this association. Furthermore, due to the timing of measurements for CRP and SAA (taken approximately 31 months after diagnosis), it is unclear if consumption practices for dietary fiber or CRP concentrations were results of a participants long-term health status or their potentially newly adopted habits of “health.” Another limitation is that the HEAL study included women with early stage disease and so we do not know the association among women with late stage disease. The HEAL dietary data are based on a FFQ, and evidence is increasing that measurement error from dietary self-report may attenuate odds ratios and relative risk estimates in disease associations studies [62]. However, in general, FFQ provide good measures of overall relative trends in consumption of specific food groups. Finally, this sample is not representative of the U.S. general population, but can be applicable to women with breast cancer.

In conclusion, in a multiethnic cohort of early-stage breast cancer survivors, we found that a diet high in dietary fiber (near 20 g/d) is associated with lower concentrations of CRP. The findings indicate that increased consumption of dietary fiber may be helpful in decreasing systemic inflammation. Further research is needed to understand the relationship of dietary fiber with inflammation and whether specific types of fiber have differential influences on specific inflammatory markers.

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Table 1

Anthropometric and lifestyle characteristics by tertiles of total dietary fiber levels among 698 female breast cancer survivors

	Tertile of Total Dietary Fiber Intake ^a						P value ^b
	<10.0 g/d (n = 232)		10.0-16.1 g/d (n = 233)		>16.1 g/d (n = 233)		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	
Weight (kg)	75.06	18.08	73.10	17.26	73.23	16.70	0.40
Height (cm)	163.20	7.25	163.37	6.82	163.66	6.88	0.78
Body mass index (kg/m ²)	28.13	6.29	27.35	6.01	27.39	6.24	0.30
Hip circumference (cm)	108.93	13.49	107.55	12.59	107.86	12.61	0.49
Waist circumference (cm)	90.68	14.59	88.86	14.29	89.09	14.48	0.34
Waist:Hip ratio	0.831	0.072	0.802	0.073	0.820	0.074	0.49
Physical Activity (MET h/week)	10.92	19.52	12.61	16.50	15.35	18.65	0.03 [*]
Percentages							
Race/ethnicity (%)							< 0.001 ^{**}
Non-Hispanic white	48.3		64.4		70.4		
African American	37.5		21.5		18.0		
Hispanic	11.2		10.7		9.9		
Other	3.0		3.4		1.7		
Education (%)							0.001 ^{***}
High school or less	31.1		6.9		20.2		
College	57.7		52.8		53.3		
Graduate School	11.2		18.9		26.6		
Study Site (%)							< 0.001 ^{***}
FHCRC	19.8		21.5		24.0		
UNM	42.7		57.1		58.4		
USC	37.5		21.5		17.6		
Smoking Status (%)							0.21
Current	47.0		46.4		51.1		
Former	37.1		42.5		39.5		
Never	15.9		11.2		9.4		

	Tertile of Total Dietary Fiber Intake ^a						P value ^b
	<10.0 g/d (n = 232)		10.0-16.1 g/d (n = 233)		>16.1 g/d (n = 233)		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	
Body Mass Index (%)							0.79
< 25 kg/m ²	37.8		42.2		39.2		
25-29.9 kg/m ²	31.7		30.4		34.1		
30 kg/m ²	30.4		27.4		26.7		
Menopausal (yes, %)	81.5		82.4		79.0		0.62
Current medications use (yes, %)							
Tamoxifen	45.7		38.6		48.1		0.10
NSAIDs	37.5		34.3		43.3		0.13
Beta blockers	7.3		9.0		4.7		0.19
ACE inhibitors	12.1		11.2		6.9		0.14
Lipid lowering	6.5		10.7		6.4		0.14
Oral estrogens	3.4		4.7		4.7		0.74
Vitamin E supplement	50.9		64.8		67.0		0.001***
Multivitamin	69.8		75.5		74.2		0.35
History of medical problems (yes, %)							
Arthritis	40.9		31.3		43.8		0.04*
Coronary Heart Disease	8.2		12.0		6.9		0.13
Cardiovascular Disease	16.4		17.6		10.7		0.09
Diabetes	7.8		12.0		9.0		0.34
Hypertension	39.2		36.5		26.6		0.02*
Kidney disease	1.7		3.4		3.0		0.50
Liver disease	1.3		4.3		2.1		0.25
SEER summary stage (%)							0.87
In situ	23.3		23.6		20.6		
Localized	53.0		55.4		55.8		
Regional by direct extension only	23.7		21.0		23.6		
Adjuvant Treatment (%)							0.46
No chemotherapy or radiation	31.0		31.3		30.9		

	Tertile of Total Dietary Fiber Intake ^a					
	<10.0 g/d (n = 232)		10.0-16.1 g/d (n = 233)		>16.1 g/d (n = 233)	
	Mean or %	SD	Mean or %	SD	Mean or %	SD
Radiation only	39.2		40.3		35.6	
Chemotherapy only	12.5		8.2		9.4	
Radiation and chemotherapy	17.2		20.2		24.0	

Abbreviations: MET, Moderate Exercise Time; FHCRC, Fred Hutchinson Cancer Research Center, Seattle, WA; UNM, University of New Mexico, Albuquerque, NM; USC, University of Southern, Los Angeles, CA; SEER,

Note: Menopausal status defined as age 55 or older or not menstruating in the last 12 months, an oophorectomy, or a hysterectomy. Coronary Heart Disease was defined as positive report of angina, myocardial infarction, or heart failure. Cardiovascular Disease was defined as positive report of angina, myocardial infarction, heart failure, stroke, pulmonary embolism or deep vein thrombosis.

^aTertiles based on dietary fiber intake distribution across entire cohort

^bP-value represent test for variation across tertiles

* P < 0.05,

** P < 0.01,

*** P < 0.001

Table 2
Inflammatory markers and dietary intake by tertiles of dietary fiber intake among 689 female breast cancer survivors

	All Participants	Tertile of Total Dietary Fiber Intake ^a			P value ^b				
		<10.0 g/d (n = 232)	10.0–16.0 g/d (n = 233)	16.1 g/d (n = 233)					
Inflammatory Markers									
C-reactive protein (mg/L)					0.04*				
Mean (SD)	3.32 (3.66)	3.79 (4.15)	3.24 (3.30)	2.93 (3.44)					
Median (IQR)	2.00 (0.80–4.33)	2.15 (0.90–5.28)	2.10 (0.80–3.45)	1.80 (0.80–3.50)					
Serum amyloid A (mg/L)					0.44				
Mean (SD)	7.73 (10.23)	8.44 (14.98)	7.38 (7.08)	7.37 (6.33)					
Median (IQR)	5.40 (3.38–9.20)	5.30 (3.20–10.08)	5.50 (4.60–8.80)	5.40 (3.75–8.65)					
Dietary Factors									
Total fiber (g/d)									
Mean (SD)	14.0 (6.4)	7.6 (1.8)	12.9 (1.6)	21.4 (4.4)					
Median (IQR)	12.9 (9.1–18.2)	7.9 (6.4–9.1)	12.9 (11.5–14.3)	20.4 (18.1–23.0)					
Soluble fiber (g/d)									
Mean (SD)	3.7 (1.7)	2.1 (0.5)	3.4 (0.6)	5.6 (1.3)					
Median (IQR)	3.4 (2.4–4.9)	2.1 (1.7–2.4)	3.4 (2.9–3.9)	5.4 (4.9–6.2)					
Insoluble fiber (g/d)									
Mean (SD)	10.2 (4.7)	5.5 (1.3)	9.4 (1.3)	15.6 (3.4)					
Median (IQR)	9.4 (6.5–13.0)	5.6 (4.6–6.5)	9.4 (8.4–10.5)	14.9 (13.0–17.1)					
Daily energy (kcal)	1455	694.1	990	422.5	1415	778.6	<0.001***		
Carbohydrate (% of daily energy)	48.2	9.6	45.8	9.5	46.9	8.8	51.8	9.3	<0.001***
Protein (% of daily energy)	16.7	3.6	16.2	3.9	17.2	3.4	16.8	3.5	0.01**
Fat (% of daily energy)	34.8	8.1	36.5	8.0	35.8	7.5	32.2	8.3	<0.001***
Alcohol (g/d)	4.5	10.1	4.9	10.9	4.5	9.8	4.3	9.7	0.81

Abbreviations: mg, milligram; l, liter; IQR, interquartile range; kcal, kilocalories; g, grams; d, day; %, percentage

^aTertiles based on dietary fiber intake distribution across entire cohort

^bP-value represent test for variation across tertiles

* $P < 0.05$,
** $P < 0.01$,
*** $P < 0.001$

Table 3

Regression coefficients from analysis of covariance using total dietary fiber intake, soluble dietary fiber intake, and insoluble dietary fiber intake level as the primary independent variable and CRP and SAA as the dependent variable.

	Age-adjusted Log CRP			Age-adjusted Log SAA		
	β	SE	95% CI	β	SE	95% CI
Total Dietary Fiber						
Model 1	-0.013	0.007	-0.027, 0.001	0.000	0.004	-0.009, 0.008
Model 2	-0.029**	0.010	-0.049, -0.008	-0.002	0.007	-0.016, 0.012
Soluble Dietary Fiber						
Model 1	-0.027	0.026	-0.078, 0.025	0.011	0.016	-0.020, 0.042
Model 2	-0.073	0.041	-0.153, 0.007	0.024	0.028	-0.031, 0.078
Insoluble Dietary Fiber						
Model 1	-0.021*	0.009	-0.039, -0.002	-0.002	0.006	-0.014, 0.009
Model 2	-0.039**	0.013	-0.064, -0.013	-0.006	0.009	-0.024, 0.012

Abbreviations: CRP, C-reactive protein; SAA, serum amyloid A; β , beta; SE, standard error; CI, confidence interval Note: Model 1 was adjusted for age, Model 2 was adjusted for age, BMI, race/site, smoking status, postmenopausal status, physical activity, alcohol intake, dietary fat intake, total caloric intake, number of inflammatory related-diseases, medications, disease stage, and adjuvant therapy used.

* $P < 0.05$,
** $P < 0.01$,
*** $P < 0.001$

Table 4

Odds ratios of elevated CRP (>3.00 mg/l) risk comparing across tertile of total, soluble and insoluble dietary fiber intake, HEAL study.

Elevated CRP ^a					
<i>Unadjusted</i>		<i>Multivariate Adjusted</i>			
	OR	95% CI	OR	95% CI	
Total Dietary Fiber Intake					
Tertile 1	1.00	Referent	1.00	Referent	
Tertile 2	0.91	0.63, 1.32	0.87	0.55, 1.39	
Tertile 3	0.68 [*]	0.47, 0.99	0.57	0.30, 1.07	
<i>P</i> for trend	0.05		0.09		
Soluble Dietary Fiber Intake					
Tertile 1	1.00	Referent	1.00	Referent	
Tertile 2	0.99	0.68, 1.44	1.00	0.63, 1.60	
Tertile 3	0.83	0.57, 1.22	0.86	0.45, 1.63	
<i>P</i> for trend	0.35		0.67		
Insoluble Fiber Intake					
Tertile 1	1.00	Referent	1.00	Referent	
Tertile 2	0.92	0.64, 1.34	0.92	0.58, 1.48	
Tertile 3	0.37 [*]	0.43, 0.92	0.51 [*]	0.27, 0.95	
<i>P</i> for trend	0.02		0.04		

Abbreviations: CRP, C-reactive protein; OR, odds ratio; CI, confidence interval

Note: Model adjusted for age, BMI, race/site, smoking status, postmenopausal status, physical activity, alcohol intake, dietary fat intake, total caloric intake, number of inflammatory related-diseases, medications, disease stage, and adjuvant therapy used ^aElevated serum CRP concentrations defined >3.00 mg/l

^{*} P<0.05

TABLE 5

Distribution of Inflammatory Markers and Age-adjusted regression coefficients (β) from analysis of covariance between total dietary fiber intake, soluble dietary fiber intake, and insoluble dietary fiber intake level with CRP and SAA by race/ethnicity

Biomarker Concentrations	Non-Hispanic White (n = 426)				Non-Hispanic Black (n = 179)				Hispanic (n = 74)			
	Mean	SD	Median		Mean	SD	Median		Mean	SD	Median	
C-reactive Protein (mg/L)	2.83	3.13	1.75		4.46	4.70	2.80		3.60	3.13	2.70	
Serum Myloid A (mg/L)	8.07	12.28	5.45		6.75	4.85	5.10		8.23	5.93	6.05	
Log CRP												
	β	SE	95% CI		β	SE	95% CI		β	SE	95% CI	
Total Dietary Fiber Intake												
Model 1	-0.010	0.009	-0.027, 0.008		-0.023	0.014	-0.050, 0.005		0.053**	0.020	0.013, 0.093	
Model 2	-0.031*	0.013	-0.057, -0.006		-0.044	0.023	-0.091, 0.002		-0.010	0.037	-0.085, 0.065	
Soluble Dietary Fiber Intake												
Model 1	-0.20	0.033	-0.084, 0.045		-0.081	0.054	-0.188, 0.026		0.210	0.068	0.074, 0.346	
Model 2	-0.086	0.048	-0.181, 0.009		-0.172	0.102	-0.372, 0.029		0.067	0.148	-0.230, 0.364	
Insoluble Fiber Intake												
Model 1	-0.016	0.012	-0.039, 0.008		-0.031	0.019	-0.068, 0.006		0.065*	0.028	0.009, 0.121	
Model 2	-0.042**	0.016	-0.074, -0.010		-0.055	0.029	-0.113, 0.003		-0.021	0.046	-0.114, 0.071	

Abbreviations: CRP, C-reactive protein; SAA, serum amyloid A; β , beta; SE, standard error; CI, confidence interval.

Note: Excluded 19 participants who reported a race/ethnicity not classified into one of the three race/ethnicity categories; Model 1 was adjusted for age; Model 2 was adjusted for age, BMI, smoking status, postmenopausal status, physical activity, alcohol intake, dietary fat intake, total caloric intake, number of inflammatory related-diseases, medications, disease stage, and adjuvant therapy used (Method = Enter).

* $P < 0.05$,

** $P < 0.001$