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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Postdiagnosis Diet Quality Is Inversely Related to a Biomarker of Inflammation among Breast Cancer Survivors

Stephanie M. George[1,2], Marian L. Neuhouser[6], Susan T. Mayne[1], Melinda L. Irwin[1], Demetrius Albanes[2], Mitchell H. Gail[3], Catherine M. Alfano[4], Leslie Bernstein[7], Anne McTiernan[6], Jill Reedy[5], Ashley W. Smith[5], Cornelia M. Ulrich[6,8], and Rachel Ballard-Barbash[5]

Abstract

Background: Inflammation and immune response have potential prognostic implications for breast cancer survivors. We examined how postdiagnosis diet quality is cross-sectionally related to biomarkers of inflammation and adipose-derived hormones among breast cancer survivors and determined whether physical activity or body size modified any observed associations.

Methods: Participants included 746 women diagnosed with stage 0 to IIIA breast cancer. Thirty months after diagnosis, the women completed food frequency questionnaires. We scored diet quality with the Healthy Eating Index (HEI)-2005. Serum concentrations of C-reactive protein (CRP), serum amyloid A, leptin, and adiponectin were measured in fasting 30 mL blood samples. Log biomarker values were regressed on quartiles of HEI-2005 scores in multivariate models, and β scores were exponentiated and expressed as geometric means within quartiles of HEI-2005 scores.

Results: Women with better versus poor quality postdiagnosis diets, as defined by higher HEI-2005 scores (Q4 versus Q1), had lower concentrations of CRP (1.6 mg/L versus 2.5 mg/L), but no significant difference in concentrations of serum amyloid A, leptin, or adiponectin. Among women not engaging in recreational physical activity after diagnosis, better diet quality was associated with lower CRP concentrations (2.5 mg/L versus 5.0 mg/L), but no association was observed among women engaging in any recreational physical activity (1.4 mg/L versus 1.6 mg/L; *P* heterogeneity = 0.03).

Conclusions: Among breast cancer survivors, a better-quality diet seems to be associated with lower levels of chronic inflammation.

Impact: Lower levels of chronic inflammation have been associated with improved survival after breast cancer. *Cancer Epidemiol Biomarkers Prev; 19(9); 2220–8. ©2010 AACR.*

Introduction

In the United States, approximately 2.5 million women are thought to be living with a personal history of breast cancer and the many morbidities associated with life as a survivor (1). There is some evidence that a modifiable health habit that women can change, which is the quality of the diet, may be related to survival after breast cancer (2, 3). However, the mechanisms linking postdiagnosis diet to survival are not well known.

Recent studies have highlighted the potential prognostic importance of inflammation and immune response for women with early-stage breast cancer. Among breast cancer survivors, higher concentrations of C-reactive protein (CRP) and serum amyloid A (SAA), biomarkers of chronic inflammation, have been associated with poorer survival (4). Additionally, a higher concentration of adiponectin, a hormone involved in metabolism and inflammation (5-7), has been associated with improved survival (8).

These biomarkers that have been related to survival are of interest to study in relation to the dietary patterns women choose after a diagnosis of breast cancer, because certain dietary components and nutrients have anti-inflammatory properties (9), which may have synergistic or antagonistic effects on the biomarkers in the context of total diet (10). Among obese women without cancer, overall diet quality has been associated with inflammation (11), whereas caloric restriction (12) and lower carbohydrate consumption (13) have been shown to be associated with favorable adipokine profiles. In animal studies, high-fat diets have resulted in diminished

Authors' Affiliations: [1]Yale School of Public Health, Division of Chronic Disease Epidemiology, New Haven, Connecticut; [2]Nutritional Epidemiology Branch and [3]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, and [4]Office of Cancer Survivorship and [5]Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland; [6]Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Seattle, Washington; [7]Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, California; and [8]German Cancer Research Center and National Center for Tumor Diseases, Heidelberg, Germany

Corresponding Author: Stephanie M. George, National Cancer Institute, 6120 Executive Boulevard, Suite 320, MSC 7232, Bethesda, MD 20892. Phone: 301-496-7031; Fax: 301-496-6829. E-mail: materess@mail.nih.gov

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inflammatory response to adipose-derived hormones like leptin and adiponectin (14, 15).

Diet quality could be directly or indirectly related to inflammation and immune function through changes in body mass (11, 16, 17), being that higher body fat mass is associated with higher concentrations of CRP, SAA, and leptin, and with lower concentrations of adiponectin (18, 19). We investigated these potential mechanistic pathways of inflammation biomarkers (CRP, SAA) and adipose-derived hormones (adiponectin, leptin) for postdiagnosis diet quality among women with early-stage breast cancer.

Materials and Methods

The Health, Eating, Activity, and Lifestyle (HEAL) study is a multiethnic prospective cohort study that has enrolled 1,183 breast cancer survivors, women diagnosed with their first primary breast cancer (0-IIIA), who were drawn from Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries in New Mexico, Los Angeles County, and Western Washington. These breast cancer survivors are being followed to determine whether lifestyle, hormones, and other exposures affect breast cancer prognosis. Details of the study have been published elsewhere (20-22).

In the HEAL study, women completed extensive assessments, which were conducted at baseline, approximately 6 months after diagnosis, and at approximately 30 months after diagnosis. At the 30-month assessment, a blood draw was also taken.

A total of 944 participants were alive and completed the 30-month assessment. We excluded women who may have been receiving treatment for subsequent recurrences or new primaries at the time of their 30-month assessment (n = 32), because active treatment may be associated with changes in diet. We retained women who had subsequent recurrences or new primaries well in advance of the 30-month assessment such that treatment would not affect exposure measurements (n = 25). Sensitivity analyses confirmed that including these women did not change results. Of the remaining 912 women, we excluded women with incomplete data for diet (n = 21), follow-up time (n = 3), biomarkers (n = 124), or body mass index (BMI; n = 18). Our final sample included 746 women. We obtained written informed consent from all study participants. The study was approved by the institutional review board at each participating center, in accord with assurances filed with and approved by the U.S. Department of Health and Human Services.

Biomarker assessment

Inflammation biomarkers and adipose-derived hormones. A 30 mL fasting blood sample was collected from participants at the 30-month assessment. Blood was

Table 1. The Healthy Eating Index-2005 components and standards for scoring (41)

Component	Maximum points	Standard for maximum score	Standard for minimum score of zero
Total fruit (includes 100% juice)	5	≥0.8 cup equiv. per 1,000 kcal	No fruit
Whole fruit (not juice)	5	≥0.4 cup equiv. per 1,000 kcal	No whole fruit
Total vegetables	5	≥1.1 cup equiv. per 1,000 kcal	No vegetables
Dark green and orange vegetables and legumes*	5	≥0.4 cup equiv. per 1,000 kcal	No dark green or orange vegetables or legumes
Total grains	5	≥3.0 oz equiv. per 1,000 kcal	No grains
Whole grains	5	≥1.5 oz equiv. per 1,000 kcal	No whole grains
Milk†	10	≥1.3 cup equiv. per 1,000 kcal	No milk
Meat and beans	10	≥2.5 oz equiv. per 1,000 kcal	No meat or beans
Oils‡	10	≥12 g per 1,000 kcal	No oil
Saturated fat	10	≤7% of energy§	≥15% of energy
Sodium	10	≤0.7 g per 1,000 kcal§	≥2.0 g per 1,000 kcal
Calories from solid fats, alcoholic beverages, and added sugars (SoFAAS)	20	≤20% of energy	≥50% of energy

NOTE: Intakes between the minimum and maximum levels are scored proportionately, except for saturated fat and sodium (see footnote §).

*Legumes counted as vegetables only after standard of meat and beans is met.

†Includes all milk products, such as fluid milk, yogurt, cheese, and soy beverages.

‡Includes nonhydrogenated vegetable oils and oils in fish, nuts, and seeds.

§Saturated fat and sodium get a score of 8 for the intake levels that reflect the 2005 Dietary Guidelines, <10% of calories from saturated fat and 1.1 grams of sodium/1,000 kcal, respectively.

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Table 2. Characteristics of 746 breast cancer survivors in the Health, Eating, Activity, Lifestyle study by quartiles of HEI-2005 scores

	Postdiagnosis diet quality				*P**
	HEI-2005 quartile 1 (35-57) "Poor" No. (%)	HEI-2005 quartile 2 (57-67) "Mixed" No. (%)	HEI-2005 quartile 3 (67-75) "Mixed" No. (%)	HEI-2005 quartile 4 (75-87) "Better" No. (%)	
Number of participants	186	187	187	186	
Age†					
Mean (SE)	55.7 (0.7)	58.1 (0.8)	57.7 (0.7)	60.1 (0.8)	<0.0001
Race/Ethnicity					<0.0001
White, non-Hispanic	86 (46)	102 (55)	126 (67)	134 (72)	
Hispanic	29 (16)	24 (13)	17 (9)	1 (6)	
Black, non-Hispanic	67 (36)	55 (29)	39 (21)	35 (19)	
American Indian, Asian, Other	4 (2)	6 (3)	5 (3)	6 (3)	
Recruitment site					0.001
Western Washington	39 (21)	40 (21)	43 (23)	44 (24)	
New Mexico	80 (43)	93 (50)	105 (56)	107 (58)	
Los Angeles County, California	67 (36)	54 (29)	39 (21)	35 (19)	
Menopausal status†					0.01
Premenopausal	65 (35)	62 (33)	63 (34)	54 (29)	
Postmenopausal	106 (57)	116 (62)	114 (61)	128 (69)	
Unknown	15 (8)	9 (5)	10 (5)	4 (2)	
Treatment					0.69
Surgery only	65 (35)	59 (32)	54 (29)	58 (31)	
+ Radiation	71 (38)	68 (36)	74 (40)	72 (39)	
+ Chemotherapy	20 (11)	16 (9)	19 (10)	18 (10)	
+ Radiation and chemotherapy	30 (16)	44 (24)	40 (21)	38 (20)	
Stage					
In situ	50 (27)	41 (22)	46 (25)	39 (21)	
Localized	97 (52)	108 (58)	97 (52)	103 (55)	
Regional	39 (21)	38 (20)	44 (24)	44 (24)	
Current tamoxifen use					0.14
No	111 (60)	106 (57)	104 (56)	97 (52)	
Yes	75 (40)	81 (43)	83 (44)	89 (48)	
Estrogen receptor status‡					0.33
Positive	94 (51)	105 (56)	106 (57)	113 (61)	
Negative	31 (17)	35 (19)	29 (16)	22 (12)	
HEI-2005 score (100 points possible)					
Mean (SE)	50.3 (0.4)	62.6 (0.2)	70.8 (0.2)	79.0 (0.2)	<0.0001
Energy/day (kcal)					
Mean (SE)	1,723 (87)	1,514 (50)	1,396 (45)	1,256 (34)	<0.0001
Fruit (c eq/1,000 kcal)					
Mean (SE)	0.5 (0.03)	0.9 (0.04)	1.2 (0.06)	1.7 (0.06)	<0.0001
Whole fruit (c eq/1,000 kcal)					
Mean (SE)	0.3 (0.02)	0.6 (0.03)	0.8 (0.05)	1.2 (0.06)	<0.0001
Vegetables (c eq/1,000 kcal)					
Mean (SE)	0.8 (0.03)	1.0 (0.05)	1.1 (0.03)	1.3 (0.04)	<0.0001
Dark green vegetables, orange vegetables, and legumes (c eq/1,000 kcal)§					
Mean (SE)	0.1 (0.01)	0.2 (0.03)	0.2 (0.01)	0.3 (0.01)	<0.0001
Total grains (oz eq/1,000 kcal)					
Mean (SE)	2.5 (0.07)	2.7 (0.07)	2.8 (0.07)	2.9 (0.06)	0.0002

(*Continued on the following page*)

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Table 2. Characteristics of 746 breast cancer survivors in the Health, Eating, Activity, Lifestyle study by quartiles of HEI-2005 scores (Cont'd)

	Postdiagnosis diet quality				*P**
	HEI-2005 quartile 1 (35-57) "Poor" No. (%)	HEI-2005 quartile 2 (57-67) "Mixed" No. (%)	HEI-2005 quartile 3 (67-75) "Mixed" No. (%)	HEI-2005 quartile 4 (75-87) "Better" No. (%)	
Whole grains (oz eq/1,000 kcal)					
Mean (SE)	0.4 (0.03)	0.6 (0.03)	0.7 (0.04)	0.9 (0.04)	<0.0001
Meat and beans (oz eq/1,000 kcal)‖					
Mean (SE)	3.0 (0.09)	3.0 (0.08)	3.0 (0.07)	2.9 (0.07)	0.38
Oils (g/1,000 kcal)					
Mean (SE)	9.6 (0.35)	11.1 (0.36)	11.5 (0.37)	11.2 (0.40)	0.003
Milk (c eq/1,000 kcal)					
Mean (SE)	0.7 (0.03)	0.9 (0.04)	0.9 (0.05)	1.0 (0.05)	<0.0001
Sodium (g/1,000 kcal)					
Mean (SE)	1.5 (0.02)	1.7 (0.02)	1.6 (0.02)	1.7 (0.02)	<0.0001
Percent calories from saturated fat					
Mean (SE)	14.1 (0.24)	12.4 (0.18)	10.6 (0.16)	8.6 (0.14)	<0.0001
Percent discretionary calories from solid fat, alcoholic beverages, and added sugars					
Mean (SE)	40.5 (0.55)	31.9 (0.40)	27.1 (0.33)	20.8 (0.33)	<0.0001
MET-hours/week of postdiagnosis recreational physical activity					
Mean (SE)	8.5 (1.0)	11.4 (1.1)	13.4 (1.2)	18.1 (1.8)	<0.0001
BMI†					
Mean (SE)	28.6 (0.5)	28.9 (0.5)	27.4 (0.4)	26.6 (0.4)	0.003
Current smoker†	37 (20)	22 (12)	21 (11)	13 (7)	0.003
Current use of nonsteroidal anti-inflammatory drugs†	78 (42)	56 (30)	71 (38)	78 (42)	1.00

*P values are for likelihood ratio χ^2tests contrasting means (continuous variables) and percentages (categorical variables) for women with a better quality diet compared with those with a poor-quality diet.
†At 30-month assessment.
‡Confirmed positive/negative status for 535 participants.
§Includes legumes only after meat and beans standard has been met.
‖Includes legumes only if meat and beans standard is otherwise not met.

processed within 3 hours of collection and serum was stored in 1.8-mL tubes at −70°C to −80°C until analysis.

CRP and SAA were measured by latex-enhanced nephelometry using high-sensitivity assays (23) on the Behring Nephelometer II analyzer (Dade Behring Diagnostics) at the University of Washington Medical Center (Seattle, WA). Adiponectin was measured using a highly sensitive RIA (Linco Research) at the Northwest Research Lipid Laboratories at the University of Washington. Leptin was measured using the Linco ^{125}RIA kit at the Reproductive and Endocrine Research Laboratory at the University of Southern California for California participants and at the Aging and Genetic Epidemiology Program Laboratory at the University of New Mexico for New Mexico and Washington participants. The lowest detection limits for CRP, SAA, leptin, and adiponectin assays were 0.2 mg/L, 0.7 mg/L, 0.5 ng/mL, and 0.78 ng/mL, respectively. Interassay coefficients of variation were 5% to 9% for CRP, 4% to 8% for SAA, 5% to 8% for leptin, and 19% for adiponectin.

Diet

To measure diet at the 30-month assessment, we used a 122-item self-administered food-frequency questionnaire (FFQ) developed and validated for the Women's Health Initiative (WHI; ref. 24), adapted from the Health Habits and Lifestyle Questionnaire (25). The WHI-FFQ was designed to capture foods relevant for multiethnic and geographically diverse population groups and has been shown to produce reliable ($r_{\text{all nutrients}} = 0.76$) and comparable estimates to 8 days of dietary intake from 24-hour dietary recalls and 4-day food records ($r = 0.37, 0.62, 0.41$, and 0.36, with energy, percent energy from fat, carbohydrate,

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and protein, respectively; ref. 24). New Mexico participants reported their usual dietary intake for the previous year, whereas participants at the other two centers reported usual intake for the previous month.

The nutrient database used to analyze the WHI-FFQ was derived from the Nutrition Data Systems for Research (NDS-R, version 2005, University of Minnesota, Minneapolis, MN; refs. 26, 27). NDS-R provides necessary estimates for energy, saturated fat, and sodium, but does not link to the MyPyramid Equivalents Database (MPED; ref. 28). Thus, we established a customized link between the MPED and the WHI-FFQ database to calculate servings of total fruit, whole fruit, total vegetables, dark green vegetables, orange vegetables, legumes, total grains, whole grains, milk, meat and beans, oils, solid fats, and added sugars, in units that reflect US dietary guidance. We also created variables for calories from solid fat, added sugar, alcohol, and calories from saturated fat.

We measured diet quality with the Healthy Eating Index-2005 (HEI-2005; refs. 29-32), which uses an energy-adjusted density approach and was jointly developed by the National Cancer Institute and the U.S. Department of Agriculture to align with the U.S. Dietary Guidelines for Americans-2005 (33). Table 1 lists the 12 components and standards for scoring. For each participant, we scored each component and calculated a total score (100 possible points). We classified HEI-2005 scores into quartiles. The strength of HEI-2005 is its ability to distinguish those scoring well on virtually all of the components (Q4) versus those scoring poorly on virtually all the components (Q1), and this is the comparison of our analysis. Scores in the middle quartiles (Q2-Q3) are more likely to reflect "mixed quality" diets, thus including individuals with somewhat similar total scores, but more widely varying component scores.

Anthropometry

BMI. Height was measured postdiagnosis at the baseline assessment. For participants missing measured height, self-reported height at age 18 was used. At the 30-month assessment, trained staff measured weight to the nearest 0.1 kg, with women wearing light indoor clothing and no shoes. All measurements were done twice and averaged for a final value. BMI was calculated as weight (kg)/height (m^2).

Recreational physical activity

We collected information on recreational aerobic physical activity using the Modifiable Activity Questionnaire developed by Kriska, which has high validity and reliability ($r = 0.73$ with total energy expenditure assessed by doubly-labeled water, and $r = 0.92$ for 3-week test-retest; ref. 34). At the 30-month assessment, participants reported the type, duration, and frequency of aerobic recreational physical activities (e.g., brisk walking, biking, dancing, swimming, jogging) in the previous year. Activities were classified according to their corresponding metabolic equivalent of task value (MET; ref. 35). For all activities with MET values ≥ 3, we summed the products of activity MET values and hours spent in each activity to arrive at the MET-hours/week spent in moderate/vigorous-intensity aerobic activity for each participant.

Similar to Irwin et al. (36), we classified recreational physical activity into three categories (inactive, 0; somewhat active, >0 to <9; active, ≥ 9 MET-hours/week), with 9 MET-hours/week approximately equal to 150 minutes/week of moderate-intensity physical activity, and meeting the general population guidelines (37). Given the benefit observed in HEAL for doing any postdiagnosis recreational physical activity (36), for stratified analyses we dichotomized physical activity as none (0 MET-hours/week) versus any (>0 MET-hours/week).

Additional risk factors

For participants' initial breast cancer diagnoses, disease stage and estrogen receptor status were obtained from SEER cancer registry records, and detailed information on treatment and surgical procedures were obtained from SEER registry, physician, and hospital records. At baseline, information was collected on recruitment site, date of birth, and race, and information on chronic conditions was abstracted from medical records. We calculated age at 30-month assessment using date of birth and the 30-month assessment date. At the 30-month assessment, we collected information on tamoxifen use, use of nonsteroidal anti-inflammatory drugs, smoking status, and physician-diagnosed type II diabetes. We determined participants' menopausal status (premenopausal, postmenopausal, undetermined) at the 30-month assessment from medical records, hormone levels, and questionnaires. We considered each of these risk factors in model development.

Statistical analyses

Differences in descriptive characteristics of women with better versus poor quality diets were tested using likelihood ratio χ^2 tests.

We examined the residuals of the analytes on their regressions and found that a logarithmic transformation yielded nearly homoscedastic variation about zero. The resulting normal quantile-quantile plots were nearly linear, confirming the suitability of the logarithmic transformation. Log biomarker values were regressed on quartiles of HEI-2005 scores in multivariate models, and β scores were exponentiated and expressed as geometric means and 95% confidence intervals (95% CI) within quartiles of HEI-2005 scores.

We adjusted for factors that changed the magnitude of β values by $\geq 10\%$, improved model fit, and/or allowed comparison to the published literature. We presented a parsimonious model (model 3) meeting these criteria that adjusts for age (continuous), total energy (kcal), BMI (continuous), race/ethnicity (non-Hispanic White, Hispanic, Black/African American, American Indian/Asian/Other), and MET-hours/week of recreational physical activity (continuous). For the adipose-derived hormones, we also presented a model (model 4) with additional adjustments

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for stage, menopausal status, and smoking, which were confounders in age and energy-adjusted models for these hormones; however, adding these to the parsimonious model did not improve model fit. Using our biomarker-specific models, we also investigated each HEI-2005 component separately, controlling for other components.

For any association observed, we investigated heterogeneity by postdiagnosis recreational physical activity and BMI by using likelihood ratio tests for both the interaction of diet quality with these factors ($\alpha = 0.1$) and the difference in model fit of full and reduced models. If an interaction was present, we stratified by the relevant factor and calculated a Cochran's Q heterogeneity statistic (38). All statistical tests were based on *a priori* hypotheses, and therefore there was no adjustment for multiple testing. All analyses were conducted with SAS (version 9.1.3).

Results

Women with better- versus poor-quality diets, defined as having higher HEI-2005 scores (Q4 versus Q1), were older, more likely to be non-Hispanic White and postmenopausal, engaged in more postdiagnosis recreational physical activity, had lower BMIs, and were less likely to be current smokers (Table 2).

As shown in Table 3, women with better-quality diets had significantly lower CRP concentrations (1.6 mg/L versus 2.4 mg/L; $P = 0.004$), but similar serum concentrations of SAA, leptin, or adiponectin. Controlling for BMI in models resulted in attenuation of all diet quality–biomarker associations and a noticeable improvement in model fit, especially for CRP and leptin. The addition of other confounders on top of models already including BMI did not change model fit.

Table 3. Adjusted geometric means and 95% confidence intervals for biomarkers of inflammation and adipose-derived hormone concentrations of 746 breast cancer survivors by quartiles of HEI-2005 scores

		Postdiagnosis diet quality				
	Model r^2*	HEI-2005 quartile 1 (35-57) "Poor"	HEI-2005 quartile 2 (57-67) "Mixed"	HEI-2005 quartile 3 (67-75) "Mixed"	HEI-2005 quartile 4 (75-87) "Better"	*P* for contrast "Better vs. Poor"
n		186	187	187	186	
C-reactive protein (mg/L)						
Model 1	0.05	2.6 (2.1-3.1)	2.2 (1.9-2.5)	2.1 (1.8-2.5)	1.4 (1.2-1.7)	<0.0001
Model 2	0.30	2.4 (2.1-2.8)	2.0 (1.7-2.3)	2.2 (1.9-2.6)	1.6 (1.4-1.9)	0.0005
Model 3	0.30	2.4 (1.9-2.9)	2.0 (1.6-2.4)	2.2 (1.8-2.7)	1.6 (1.4-2.0)	0.004
Serum amyloid A (mg/L)						
Model 1	0.07	6.6 (5.9-7.4)	5.5 (4.9-6.2)	6.2 (5.5-6.9)	5.8 (5.2-6.6)	0.17
Model 2	0.15	6.5 (5.8-7.2)	5.2 (4.8-5.9)	6.3 (5.6-7.0)	6.1 (5.4-6.8)	0.48
Model 3	0.15	6.5 (5.7-7.5)	5.4 (4.7-6.2)	6.4 (5.5-7.3)	6.3 (5.4-7.2)	0.63
Leptin (ng/mL)						
Model 1	0.01	21.4 (19.3-23.8)	19.5 (17.5-21.6)	18.3 (16.5-20.4)	17.2 (15.4-19.1)	0.004
Model 2	0.58	20.5 (19.1-21.9)	17.8 (16.6-19.0)	19.1 (17.8-20.4)	19.0 (17.7-20.3)	0.13
Model 3	0.59	19.7 (18.1-21.4)	17.4 (16.0-18.9)	18.9 (17.4-20.6)	19.0 (17.5-20.7)	0.63
Model 4	0.60	19.8 (17.9-21.9)	17.2 (15.6-19.1)	18.8 (16.9-20.8)	18.7 (16.9-20.8)	0.36
Adiponectin (μg/mL)						
Model 1	0.05	12.8 (11.7-14.0)	13.5 (12.4-14.8)	14.0 (12.8-15.3)	14.1 (12.9-15.5)	0.15
Model 2	0.11	13.0 (11.9-14.2)	14.0 (12.8-15.2)	13.8 (12.7-15.1)	13.7 (12.5-15.0)	0.43
Model 3	0.19	12.7 (11.4-14.1)	13.3 (12.0-14.8)	12.7 (11.4-14.2)	12.6 (11.3-14.1)	0.94
Model 4	0.19	13.0 (11.4-14.7)	13.6 (12.0-15.4)	13.0 (11.4-14.8)	12.9 (11.3-14.7)	0.94

NOTE: Model 1: adjusted for age (continuous), energy (kcals/day); model 2: model 1+ BMI (continuous); model 3: model 2+ recreational moderate/vigorous physical activity (continuous), race/ethnicity (non-Hispanic White; Hispanic; Black, African American; American Indian, Asian, other; missing); model 4: model 3+ stage (*in situ*, localized, regional), menopausal status (premenopausal, postmenopausal, undetermined), smoking (current, former, never, missing).

*r^2 for models only adjusting for age, energy, and BMI without HEI score were 0.29, 0.14, 0.58 and 0.11 for C-reactive protein, serum amyloid A, leptin, and adiponectin, respectively.

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Table 4. Adjusted geometric means and 95% confidence intervals for C-reactive protein concentrations of 746 breast cancer survivors by quartiles of HEI-2005 scores and recreational moderate/vigorous physical activity

	Postdiagnosis diet duality				*P* for contrast "Better vs. Poor"	*P* heterogeneity
	HEI-2005 quartile 1 (35-57) "Poor "	HEI-2005 quartile 2 (57-67) "Mixed"	HEI-2005 quartile 3 (67-75) "Mixed"	HEI-2005 quartile 4 (75-87) "Better"		
No recreational physical activity after diagnosis (0 MET-hours/week)						
n	89	71	62	54		
C-reactive protein, mg/L	5.0 (3.4-7.4)	4.2 (2.8-6.4)	3.5 (2.4-5.5)	2.5 (1.6-4.0)	0.001	
						0.03
Any recreational physical activity after diagnosis (>0 MET-hours/week)						
n	97	115	125	131		
C-reactive protein, mg/L	1.6 (1.2-2.1)	1.4 (1.1-1.8)	1.8 (1.4-2.3)	1.4 (1.1-1.8)	0.39	

NOTE: Adjusted for age (continuous), energy (continuous), BMI (continuous), race/ethnicity (Non-Hispanic White; Hispanic; Black, African American; American Indian, Asian, other; missing).

When we evaluated each HEI-2005 component individually, controlling for all other components, higher component scores for consumption of dark green and orange vegetables and legumes were significantly associated with lower CRP concentrations (data not shown). However, this component did not account for the full association observed for overall diet quality.

We found evidence of effect modification (*P* heterogeneity = 0.03) of the diet quality–CRP association by postdiagnosis recreational physical activity level (Table 4 and Fig. 1). A better-quality diet was associated with lower CRP concentrations among women engaging in no recreational physical activity (2.5 mg/L versus 5.0 mg/L) but not among women who were engaging in any recreational physical activity (1.4 mg/L versus 1.6 mg/L), whose concentrations of CRP were lower overall across quartiles of HEI-2005. We did not find evidence of effect modification of the diet-CRP relationship by BMI.

Discussion

This study fills an important gap in the literature by defining inflammation as a potential mechanism by which diet quality could affect survival, regardless of age, energy intake, BMI, recreational physical activity, and race. This study complements our previous work in the HEAL study showing a positive relationship between elevated CRP and mortality (4), independent of obesity.

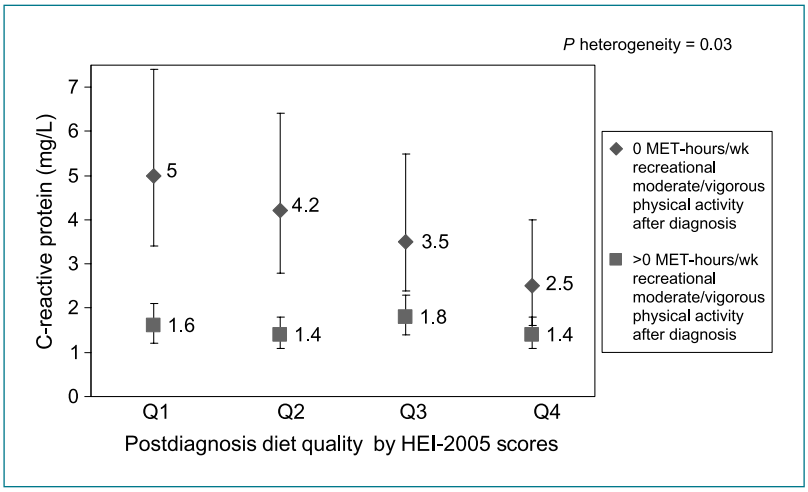

Figure 1. Adjusted geometric means and 95% confidence intervals of C-reactive protein concentrations by quartiles of HEI-2005 scores and recreational moderate/vigorous physical activity.

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We did not find evidence of associations between diet quality and SAA, leptin, or adiponectin. Although CRP and SAA are both biomarkers of inflammation, we found diet quality to be more strongly associated with CRP than with SAA, which had also been reported our previous study of women without cancer (11). Given that both CRP and SAA were associated with mortality in our cohort (4), it is possible that, in contrast to CRP, SAA marks inflammation related to tumor progression or cardiovascular disease that is possibly less related to diet quality and less directly dependent on BMI. Future work is needed to investigate if our measure of diet quality is related to other important biomarkers of inflammation among survivors. If a better-quality diet does influence adipose-derived hormone concentrations, it is possible that larger contrasts of diet quality are needed to see the difference in these biomarkers.

Although relationships between diet quality and the biomarkers investigated were not explained by body size, controlling for BMI (model 2) resulted in noticeable attenuation of relationships and greatly increased the explanatory power of models. Our results therefore suggest diet quality might also work indirectly to reduce inflammation through improving body size. Observational studies indicate that being in a normal weight range at the time of breast cancer diagnosis, as well as during and after treatment, is associated with improved prognosis (39).

In our study, the association between CRP and diet quality only held among women who were not engaging in recreational physical activity after diagnosis. It is possible that after a diagnosis of breast cancer, better diet quality may be anti-inflammatory, but relationships between diet quality and chronic inflammation are only evident when inflammation is high, as was the case among inactive survivors in our study. Because physical activity has been shown to reduce CRP concentrations among overweight and obese women (40), inactive women may show more room for the inflammation-lowering effects of the diet.

Few large studies of breast cancer survivors have been published, and this multiethnic cohort provides an important opportunity to investigate relationships between postdiagnosis diet, a modifiable factor, and biomarkers related to survival. Given that blood was collected after primary treatment was completed, the biomarkers measured in our study reflect ongoing host factors that may influence prognosis, as opposed to acute effects that may have been a result of the breast cancer treatments that participants received. We collected high-quality extensive data on clinical characteristics and treatment from physician and hospital records in addition to SEER cancer registry records, and objectively measured weight at the 30-month assessment. To assess diet, we used a valid and reliable dietary questionnaire designed for use by multiethnic postmenopausal women (37). Using the multidimensional HEI-2005, we were able to distinguish survivors with better- versus poor-quality diets based on current dietary guidance. We also had a detailed postdiagnosis assessment of recreational physical activity (36).

In this cross-sectional analysis, we were unable to determine temporality. It also remains possible that underlying conditions of chronic inflammation or confounding by unmeasured factors could explain the results observed for CRP, given that we did not find associations with the other analytes. The self-report nature of our diet assessments may have resulted in exposure misclassification, although we would not expect this misclassification to be differential. There was a difference in response timeframe (last month versus last year) for the FFQ by study site; however, it is reasonable to assume that women did not differentially make diet changes across sites during that time in the absence of an intervention. Our results are only generalizable to women who have completed treatment and survived at least 30 months after diagnoses of breast cancer. Lastly, we had insufficient statistical power to examine clinically important subpopulations of breast cancer survivors that may have poor prognosis (such as by race, estrogen receptor status, stage, and BMI).

Our study suggests that among inactive survivors, a better-quality diet may be related to lower levels of chronic inflammation, which has been linked to improved survival. Future larger cohort studies of breast cancer survivors with sufficient follow-up and multiple measurements over time are needed to confirm our findings, investigate how inflammation may mediate the relationship between diet quality and improved survival, and understand potential heterogeneity of findings among clinically important subpopulations of patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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