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Diet Quality, Inflammation and Quality of Life in Breast Cancer Survivors; a Cross-Sectional Analysis of Pilot Study Data

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Abstract

Background—Modifiable lifestyle factors, such as diet quality, could reduce inflammation and improve quality of life (QOL) in breast cancer survivors, but data are inconclusive.

Objective—To determine if diet quality, as measured by Healthy Eating Index-2010 (HEI-2010) score, is associated with inflammation, health status or functional outcomes affecting QOL in early-stage breast cancer survivors.

Design—This is a cross-sectional, secondary analysis of baseline data collected from breast cancer survivors after completion of primary therapy and prior to randomization in a pilot nutritional intervention aimed at reducing side effects of aromatase inhibitor treatment.

Participants/setting—Participants were 44 postmenopausal women with stage I–III endocrine receptor positive breast cancer receiving outpatient care at a Mid-Western cancer center between 11/2011–10/2013.

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Clinical Trial Registration: NCT01478477 (clinicaltrials.gov)

COI Disclosure:
All authors declare that they have no conflicts of interest to disclose.

Main outcome measures—Primary outcomes were serum pro-inflammatory cytokines [interleukin-6 (IL-6), IL-17, and tumor necrosis factor alpha receptor 2 (TNFR-2)]. Secondary outcomes included QOL measured by the Stanford Health and Disability Questionnaire and the Functional Assessment of Cancer Therapy- Breast with Endocrine Subscale.

Statistical analyses performed—Pearson correlation coefficients (*r*) and linear regression models were used to evaluate the relationship of dietary variables with inflammatory cytokines and QOL measures.

Results—A higher overall HEI-2010 score (healthier diet) was associated with lower IL-6 (r= −0.46; p=0.002) and TNFR-2 (r=−0.41; p=0.006); however, associations were attenuated by BMI [IL=6 (r=−0.26; p=0.10); TNFR-2 (r=−0.30; p=0.06)]. In women with prior chemotherapy, higher HEI-2010 score was strongly associated with lower IL-6 (r= −0.67; p=0.009) and TNFR-2 (r= −0.59; p=0.03) after BMI adjustment. There were no significant correlations between HEI-2010 score and QOL measures after BMI adjustment.

Conclusions—These data suggest the need for more rigorous investigation into the relationship between diet quality, BMI and inflammation in breast cancer survivors.

Keywords

Diet quality; inflammation; breast cancer survivors; Healthy Eating Index; quality of life

Introduction

Breast cancer is the most common cancer among women in the United States (U.S.) with the exception of skin cancer; nearly 3.1 million U.S. women are currently breast cancer survivors [1]. As the prognosis for women diagnosed with early stage breast cancer continues to improve, patients and clinicians are shifting their focus from survival alone, to improving quality of life (QOL) and patient-centered functional outcomes [2]. Chronic inflammation has been associated with fatigue [3] and multiple other conditions affecting QOL in early stage breast cancer survivors including worse physical functioning and less vitality[4]. Pre-treatment inflammatory status may predict the development of common musculoskeletal side effects, which reduce QOL and may affect treatment adherence, in postmenopausal breast cancer survivors beginning commonly prescribed adjuvant cancer treatment with aromatase inhibitors (AIs) [5]. Furthermore, higher levels of the inflammatory cytokine interleukin-6 (IL-6) have been associated with negative cognitive side effects of chemotherapy in breast cancer survivors [6]. Most importantly, lower inflammation is associated with improved survival in women diagnosed with early stage breast cancer [7,8], potentially by promoting a less favorable microenvironment for tumor growth and metastasis [9]. Thus, identifying modifiable lifestyle factors, such as diet quality or specific dietary components, which can be targeted to reduce chronic inflammation, may be an important approach to improving QOL and breast cancer survival.

Overall diet quality (i.e. a healthier diet pattern) has been associated with lower inflammation in various cohorts [10,11], but results are inconsistent [12]. One study in newly diagnosed head and neck cancer patients found associations between better diet quality and lower levels of the inflammatory cytokines IL-6 and tumor necrosis factor alpha (TNFα) [13].

Research on diet quality and inflammation is sparse in breast cancer survivors, but results of one large cross-sectional study suggest that better diet quality is associated with lower levels of some inflammatory markers, such as C-reactive protein (CRP), but not others[14].

The relationship between diet quality and QOL in cancer survivors is ambiguous. For example, Wayne and colleagues [15] found a direct positive association between diet quality and QOL in breast cancer survivors; however, results of recent research are less clear and seem to suggest that improving diet quality after individuals have completed primary cancer treatment, as opposed to during treatment, might be most effective in improving QOL [16]. It is not known if diet quality after primary cancer treatment influences response to commonly prescribed adjuvant endocrine treatment such as AIs, or development of common musculoskeletal side effects related to this treatment. A preliminary step in addressing this question is determining the relationship of diet quality to inflammation and QOL measures in breast cancer survivors beginning AI treatment.

The primary objective of this research was to determine if overall diet quality, as measured by the Healthy Eating Index-2010 (HEI-2010), was associated with systemic inflammation in postmenopausal women diagnosed with early stage breast cancer that had completed primary cancer treatment and were scheduled to begin adjuvant endocrine treatment with AIs. The secondary objective was to determine if diet quality was associated with health/disability status and functional outcomes important to QOL. The authors hypothesized that women who had higher diet quality, (i.e. higher HEI-2010 scores) would have lower inflammatory markers [IL-6, IL-17, and tumor necrosis factor alpha receptor 2 (TNFR-2)], better health status (i.e. less disability) and better functional capacity.

Materials and Methods

Study Design and Participants

This is a cross-sectional secondary analysis of baseline data from 44 postmenopausal women with stage I–III hormone receptor positive breast cancer who were within two weeks of initiating first line adjuvant endocrine treatment with Food and Drug Administration approved third generation AIs (letrozole, anastrozole, or exemestane). Participants were enrolled in a pilot study testing effectiveness of a six month intervention of n-3 fatty acid supplementation versus placebo for joint symptoms, a common side effect of AI treatment[17]. The study was carried out at the Ohio State University Comprehensive Cancer Center (Clinical Trial #NCT01478477). Potentially eligible patients were recruited by physicians and the study coordinator during regularly scheduled clinic visits between November, 2011 and October, 2013. Exclusion criteria included concurrent malignancy, rheumatoid arthritis and other types of autoimmune and inflammatory joint disease (except fibromyalgia and osteoarthritis), known bleeding disorders, history of diabetes mellitus, heart disease or stroke, uncontrolled current illness, current daily use of anticoagulants or full dose aspirin (> 325 mg/d), non-steroidal anti-inflammatory drugs or steroids, or n-3 fatty acid supplements > 360 mg/d within six months of study initiation. A total of 277 women were assessed for eligibility; 146 did not meet eligibility criteria and 87 were unable or uninterested in participation, leaving a final sample size of 44 women for this baseline analysis. Data for this analysis were collected prior to randomization to the supplement intervention or the

placebo, and within two weeks of AI initiation. The Ohio State University Institutional Review Board approved the study protocol and all participants provided written informed consent.

Dietary assessment and HEI-2010

At the baseline study visit, women completed a food frequency questionnaire (FFQ) that was subsequently used to estimate nutrient intake and calculate HEI-2010 scores. The General Nutrition Assessment (GNA) FFQ was developed by the Nutrition Assessment Shared Resource of Fred Hutchinson Cancer Research Center, Seattle, Washington, based on a previously validated FFQ used in the Women's Health Initiative (WHI) [18]. The GNA and its parent WHI FFQ use the same format and analysis algorithms, with minor differences in specific items; however, unlike the WHI FFQ, the GNA nutrient database continues to be updated regularly as new nutrients and food components are added to the Nutrition Data Systems for Research (NDSR). In the current study, the GNA FFQ was used to assess usual diet intake over the previous three months; the FFQ contained 122 questions on foods or food groups, 19 adjustment questions designed to allow more precise analysis of fat intake, and four summary questions regarding usual intake of fat, fruits and vegetables. The Fred Hutchinson Cancer Research Center analyzed the FFQ data using the NDSR, version 2013, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN[19]. Briefly, component food items from the FFQ were linked to food items from the MyPyramid Equivalents Database[20] in order to estimate the food group equivalents for each line item on the FFQ. These food group equivalents, along with a few data items output by NDSR (e.g. alcohol, sodium, overall caloric intake and the ratio of poly- and mono-unsaturated to saturated fatty acids) were used to calculate the HEI-2010 scores.

The HEI-2010 is a scoring metric that measures diet quality in relation to conformity to the 2010 Dietary Guidelines for Americans [21], and has been used to examine relationships between diet and health-related outcomes [22]. The HEI-2010 was developed jointly by the National Cancer Institute and the U.S. Department of Agriculture, and is made up of 12 dietary components: nine adequacy components and three moderation components. A higher score (100 is maximal) corresponds to a higher quality diet; a higher score is given for increasing consumption of "adequacy" components and a lower score is given for increasing consumption of "moderation" components. Scoring standards for each component of the HEI-2010 are adjusted for energy intake (e.g. per 1000 kcal or as a percentage of total energy intake), except for the fatty acid component score, which is a ratio of unsaturated to saturated fatty acids[22].

Anthropometry

Height and weight of study participants were obtained by trained staff at the baseline study visit with women wearing light clothing and no shoes. Height was measured to the nearest 1 cm using a Seca stadiometer, and weight was measured to the nearest 0.1 kg using a Seca scale (Medical Measuring Systems and Scales, Chino, CA); an average of two measurements were used for calculation of body mass index (BMI) using the formula weight (kg)/height $(m)^2$.

Outcome measures

Enrolled participants had peripheral blood samples collected within two weeks of initiating AI treatment (baseline visit). Inflammatory cytokines (IL-6, TNFR-2, IL-17) were measured in baseline serum samples of study participants via electrochemilluminescence methodology with ultra-sensitive kits (Meso Scale Discovery, 1601 Research Boulevard, Rockville, MD, USA) using a Meso Scale Discovery Sector Imager 2400 at the Ohio State University Clinical Research Center in accordance with manufacturer instructions. The lower limit of detection was 0.7 pg/mL for IL-6, and 0.2 pg/mL for IL-17 and TNFR-2. The intra-assay and inter-assay coefficients of variation were typically less than 10% and 20%, respectively, for all inflammatory markers. These cytokines were selected because of data suggesting increased levels in arthritic joints [23], a role in mediating joint symptoms in models of arthritis treated with n-3 fatty acids [24] and associations with musculoskeletal symptoms in genetic studies of breast cancer survivors receiving AIs [25]. Although IL-17 seems to be particularly important in inflammation of joints, all three cytokines may contribute to a pro-inflammatory loop important in the progression of arthritis [26] and potentially AI-induced joint symptoms. Additionally, IL-6 and TNFα are among the crucial mediators of tumorigenesis and may be involved in tumor resistance to chemotherapy [27]. Because of the relatively short half-life and large variability of TNFα levels in the population [28], soluble receptors of TNFα are frequently measured as a more stable assay of long-term exposure to TNFα in investigations of disease relationships [29]. TNFR-2 was measured in this sample of breast cancer survivors.

The Functional Assessment of Cancer Therapy- Breast with Endocrine Subscale (FACT-ES) and the “short” two-page Stanford’s Health Assessment Questionnaire (SHAQ) are validated instruments that have been used to evaluate health and disability status, joint symptoms and functional capacity in our target population [17,30–32]. The FACT-ES (version four) is a composite of the FACT- General scale, which includes four well-being subscales with 27 items, the Breast Cancer Symptom Scale with nine items, and the Endocrine Symptom Scale with 19 items. This instrument was designed to provide a comprehensive assessment of the impact of cancer treatments on different aspects of patient functioning and well-being by using a five point Likert-type response scale. Higher scores reflect less symptom burden and better QOL [31]. The “short” SHAQ is comprised of a Disability Index, Visual Analog Scale for Pain, and the Patient Global Health Scale. It is designed to capture the long-term influence of chronic illness on QOL by assessing functional ability and pain. Lower scores indicate less disability and less pain [33]. Participants completed both the SHAQ and FACT-ES at baseline.

Statistical analysis

Pearson correlation coefficients (*r*) were used to quantify relationships between HEI-2010 scores, FACT scales, and inflammatory markers in all participants. SHAQ data were highly skewed, with 75% of participants scoring “0” at baseline, indicating no disability. Therefore, these scores were dichotomized into “no disability” (SHAQ=0) versus “some disability” (SHAQ>0) for analysis, and two-sample t-tests were used to assess relationships with other variables. Because cancer treatments such as chemotherapy and radiation may be inflammatory [34], but the role of inflammation in chemotherapy-induced side effects is

unclear [5,17,34], exploratory analyses were performed stratifying participants by prior chemotherapy or radiation treatment. There were no significant differences in primary outcome measures based on history of radiation therapy; therefore, only results stratified by chemotherapy status are reported in this manuscript. Linear regression models were used to estimate partial correlations adjusting for BMI. Adjustment for BMI was applied because of the significant inverse association of BMI with diet quality and positive association with inflammation. The distribution of IL-6 and IL-17 were right-skewed, and thus were natural log-transformed for all analyses to better approximate normality of residuals. Five women had IL-17 levels below limits of detection. These values were set at half of the limit of detection (i.e. 0.2 pg/mL * 0.5 = 0.1 pg/mL) for statistical analysis. Comparisons between women who had and did not have prior chemotherapy were conducted using two-sample t-tests and Fisher's exact tests. No adjustments for multiple comparisons were made in this exploratory pilot study. Results were considered statistically significant with a $p < 0.05$. The analyses for this paper were generated using SAS software, version 9.4. Copyright © 2013 SAS Institute Inc[35].

Results

Participant characteristics

Forty-four women enrolled in the clinical trial (Table 1). Median age of participants was 60, with a range of 43–76 years. Women ranged in BMI from 21–46 kg/m^2, with a mean BMI of 30 kg/m^2. The majority of participants had stage I breast cancer (T1a and T1b, n=31, 71%) and had received radiation treatment (n=26, 59%). Approximately one third (n=15, 34%) had undergone previous chemotherapy. There were no significant differences in tobacco use, chronic health conditions, disease stage or grade between women with previous chemotherapy versus women with no history of chemotherapy. Significantly fewer women treated with chemotherapy had progesterone receptor positive breast cancer when compared to women not treated with chemotherapy (73% vs. 97%; p =0.04).

Health and functional outcomes of participants were assessed by FACT-ES and SHAQ prior to randomization to study capsules (Table 1). The mean FACT-ES score, which is a composite of all FACT subscales, was 181.9 (SD 19.4; range 117–212) out of 220 possible points, indicating a relatively low symptom burden and high QOL. There were no significant differences in scores by chemotherapy status, with the exception of a significantly higher score on the FACT-ES Social Well Being scale in women previously treated with chemotherapy (p = 0.02). The majority of women (75%) reported no disability on the SHAQ; there were no differences by chemotherapy status.

As a measure of diet quality, FFQs completed at baseline visits were analyzed to obtain the HEI-2010 (Table 2). Participants had a mean total HEI-2010 score of 69.1 (SD 12.2); range 28.2–89.1) out of 100 possible points. The majority of women (82%) received the maximum score for the Total Protein Foods subscale, indicating consumption of ≥ 2.5 ounce equivalents per 1000 kcals. Less than 8% of participants received the maximum score on the subscales for Fatty Acids (maximum score requires unsaturated/saturated ratio of ≥ 2.5) or Empty Calories (maximum score requires ≤ 19% of energy), and only 2% received the maximum score for the Sodium subscale (maximum score requires ≤ 1.1 g per 1000 kcals).

There were no significant differences in overall HEI-2010 score or subscale scores by chemotherapy status.

Mean serum levels of inflammatory cytokines were calculated from baseline blood draws. Two women did not have blood collected. Two additional women, one with history of chemotherapy and one without, had extremely elevated IL-17 and IL-6 (respectively); values were nearly double the next highest observed value, and thus these outliers were removed from the cytokine analyses (Table 1). Women who had prior chemotherapy had significantly higher serum levels of IL-6 ($p = 0.03$) than women who had no chemotherapy; similarly, mean values of serum TNFR-2 and IL-17 were higher in women with prior chemotherapy, but neither reached statistical significance ($p = 0.13$ and 0.26 respectively). The mean TNFR-2 level was 7040 (SD 2071) pg/mL in women reporting some disability on the SHAQ, compared to 6166 (SD 1254) pg/mL in women reporting no disability; this difference was not statistically significant in unadjusted ($p=0.11$) or BMI-adjusted ($p=0.13$) analyses (Table 3, **online only**). Inflammatory cytokines were not significantly correlated with overall FACT-General, FACT-Breast Cancer Symptoms or FACT-Endocrine Symptom Scales (data not shown).

Association of diet quality with inflammatory cytokines

The relationship between HEI-2010 scores and inflammatory cytokines is presented in Table 4. A higher overall HEI-2010 score (i.e. healthier diet) was strongly associated with lower IL-6 ($r=-0.46$; $p=0.002$) and TNFR-2 ($r=-0.41$; $p=0.006$), but not IL-17, in unadjusted analyses of all participants. However, after adjusting for BMI, associations between HEI-2010 and IL-6 weakened ($r=-0.26$; $p=0.10$); similarly, a non-significant trend was seen in BMI-adjusted analysis of HEI-2010 and TNFR-2 ($r=-0.30$; $p=0.06$). In the subgroup with a history of chemotherapy ($n=15$) significant inverse associations were found between diet quality score and IL-6 ($r= -0.67$; $p=0.009$) and TNFR-2 ($r= -0.59$; $p=0.03$) in models adjusted for BMI. In women without history of chemotherapy, no significant associations were found between HEI-2010 and measured cytokines; likewise, there were no significant associations when analyses of this subgroup excluded women with a history of radiation (data not shown).

Association of diet quality with health and functional status

The relationship between health-related QOL as measured by the FACT scales and diet quality as measured by the HEI-2010 was assessed using Pearson correlations (Table 5). After adjustment for BMI, there were no significant associations between overall HEI-2010 score and functional outcomes measured by the FACT-ES scale or any of the FACT subscales in all participants or in analyses by chemotherapy status, including the subgroup of women ($n=10$) with no history of chemotherapy or radiation (data not shown). Self-reported health and disability were assessed using the SHAQ. Table 6 shows mean HEI-2010 scores by SHAQ category. The 11 women reporting some disability (SHAQ > 0) had a mean HEI-2010 score of 64.1, while the 33 women with no disability (SHAQ = 0) had a mean HEI-2010 score of 70.7, but this difference was not significant in unadjusted or BMI adjusted models. In women with no chemotherapy, a healthier diet score was significantly associated with no reported disability on the SHAQ in unadjusted analyses ($p = 0.03$), but

was attenuated by BMI (p=0.13). In the subgroup of women with no history of radiation or chemotherapy, diet quality score was not associated with SHAQ category (data not shown).

Discussion

Identifying modifiable lifestyle factors such as diet quality, that may reduce inflammation, could be beneficial to improve the prognosis and QOL of breast cancer survivors [3,4,8]. The postmenopausal women in this analysis had mean HEI-2010 scores indicative of a “mixed quality diet” comparable to a prior analysis using HEI-2005 that examined diet quality in postmenopausal women with invasive breast cancer in the WHI [36]. The vast majority of women in this pilot study had lower than recommended ratios of unsaturated/saturated fat and higher than recommended intake of added sugars and solid fats, and nearly all women consumed more than the recommended amount of sodium. Similar to previous research [14], higher diet quality was associated with lower inflammation in this analysis; interestingly, these inverse correlations were particularly strong in women who had undergone prior chemotherapy. Diet quality was not significantly associated with disability or functional status, factors important in QOL, after adjusting for BMI.

Higher HEI-2010 score was strongly correlated with lower levels of IL-6 and TNFR-2 in the overall sample of this pilot study, but these relationships weakened after adjustment for BMI. This suggests that the anti-inflammatory benefits of a healthy diet may be related to a combination of indirect effects mediated by BMI, and direct effects of diet quality, perhaps involving anti-inflammatory properties of foods or nutrients in a healthy dietary pattern [37]. However, because the small sample size of this study did not allow for statistical adjustment for multiple confounders, it is possible that factors in addition to BMI may have influenced results. Nonetheless, these results are similar to those reported from the Healthy Eating And Lifestyle (HEAL) study, a large prospective study of breast cancer survivors in which regression models were adjusted for multiple potential confounders, including BMI. Analysis of HEAL data found that diet quality was inversely related to levels of the inflammatory marker, CRP, in breast cancer survivors 30 months post-diagnosis, and that BMI attenuated, but did not fully explain, the relationship [14]. Although CRP was not measured in the present study, IL-6 was measured; IL-6 is a cytokine that induces CRP production by hepatocytes [38]. Both IL-6 and CRP have been correlated with nutritional status in cancer patients [39], and IL-6 has been associated with unwanted side effects of chemotherapy in breast cancer survivors [6].

Women with a history of chemotherapy in the current study had even stronger, significant, inverse associations between diet quality and inflammation, before and after adjustment for BMI. This may be because inflammatory cytokines were higher and more variable in these women, making relationships with dietary patterns and components more evident. A somewhat comparable situation was noted by George and colleagues, who reported that only in breast cancer survivors with no physical activity and higher CRP values did HEI-2005 scores predict CRP [14]. The relationship between chemotherapy and inflammation is unclear; chemotherapy could have a direct effect on inflammation [34,40], or inflammation could be an indicator of response to chemotherapy [41]. Alternatively, chemotherapy may be a surrogate for the stage of cancer, progesterone receptor status, or biology of the cancer that resulted in

women choosing to undergo chemotherapy treatment. Because of the pilot nature of this study, these potential relationships were unable to be parsed out.

No significant correlations were found between health-related QOL measures (i.e. FACT and SHAQ scores) and HEI-2010 score after BMI adjustment. This is in contrast to results from the HEAL study [15], in which higher QOL was associated with higher diet quality, as measured by the Diet Quality Index. Other researchers [42] also have reported inverse associations with the FACT scale specific to fatigue (FACT-F) and dietary components such as fiber in breast cancer survivors; however, these researchers did not investigate overall diet quality in relation to functional outcomes. Differing results in the present study could be related to different instruments used to measure diet quality and QOL, or to sample size considerations.

Strengths and Limitations

Strengths of this study include assessment of inflammation using multiple cytokines, assessment of health and functional status important to QOL using two different instruments, and exploratory subgroup analysis by history of chemotherapy. This pilot study also had several limitations; most notably, was the small sample size, which limited the power to detect relationships and prevented adjustment for multiple comparisons and multiple confounders in the statistical models. Because of this, BMI was the only covariate included in models. In addition, the sample lacked racial and ethnic diversity, and limited resources did not allow for measurement of a larger number of inflammatory markers, including CRP. Also, this was a cross-sectional analysis with limitations inherent to this design such as potential for selection bias, inability to determine temporal relationships or investigate associations with changes in outcomes over time, and inability to draw conclusions regarding cause and effect relationships. Another limitation is the self-reported dietary data used to estimate intake and calculate HEI-2010 scores. Nonetheless, a recent report from the WHI suggests that the HEI-2010 is a valid measure of diet quality in comparison to other indices, and is useful to capture essential elements of a healthy diet in women, particularly in obese postmenopausal breast cancer survivors [43].

Conclusions

Better diet quality was associated with lower inflammatory markers in postmenopausal women beginning adjuvant AI treatment for breast cancer. However, these associations were attenuated by BMI except in women who had undergone previous chemotherapy. Diet quality was not associated with QOL. More rigorous prospective studies are needed to investigate the relationship of BMI, diet quality and inflammation, and determine if diet quality improves response to AIs or reduces common side effects associated with treatment.

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Table 1

Baseline characteristics of 44 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

	All Participants (n=44)		Previous Chemotherapy[a] (n=15)		No Chemotherapy[b] (n=29)		
	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	P-value[c]
Demographics							
Age (years)	59.5 (8.1)		58.0 (8.6)		60.3 (7.8)		0.37
Race							0.46
White		43 (98%)		15 (100%)		28 (97%)	
African American		1 (2%)		0 (0%)		1 (3%)	
Body Mass Index (kg/m^2)	29.8 (6.2)		30.3 (7.2)		29.4 (5.6)		0.66
Tobacco Use							0.52
Current		1 (2%)		1 (7%)		0 (0%)	
Previous		11 (25%)		3 (20%)		8 (28%)	
Never		32 (73%)		11 (73%)		21 (72%)	
Prior Chronic Conditions							
Osteoarthritis		5 (11%)		1 (7%)		4 (14%)	0.65
Fibromyalgia		1 (2%)		0 (0%)		1 (3%)	1.00
Hyperlipidemia		5 (11%)		1 (7%)		4 (14%)	0.65
Hypertension		14 (32%)		5 (33%)		9 (31%)	1.00
Other		28 (64%)		10 (67%)		18 (62%)	1.00
Disease Characteristics							
Estrogen Receptor Positive		43 (98%)		14 (93%)		29 (100%)	0.34
Progesterone Receptor Positive		39 (89%)		11 (73%)		28 (97%)	0.04
T-stage [d]							0.20
T1a		6 (14%)		2 (13%)		4 (14%)	
T1b		25 (57%)		6 (40%)		19 (66%)	
T2		11 (25%)		6 (40%)		5 (17%)	
T3		2 (5%)		1 (7%)		1 (3%)	
T4		0 (0%)		0 (0%)		0 (0%)	

	All Participants (n=44)		Previous Chemotherapy[a] (n=15)		No Chemotherapy[b] (n=29)		
	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	P-value[c]
Her2Neu [e]							0.52
Positive		2 (5%)		1 (7%)		1 (3%)	
Negative		42 (95%)		14 (93%)		28 (97%)	
Cancer Treatment							
Radiation		26 (59%)		7 (47%)		19 (66%)	0.33
Chemotherapy		15 (34%)		15 (100%)		0 (0%)	--
Functional Assessment of Cancer Therapy [f]							
FACT-General [g h]	91.6 (11.0)		95.4 (8.0)		89.6 (11.9)		0.10
-Physical Well Being	24.9 (2.8)		24.9 (2.2)		24.9 (3.1)		0.94
-Social Well Being	24.5 (4.1)		26.4 (2.0)		23.5 (4.5)		0.02
-Emotional Well Being	20.1 (2.8)		20.4 (3.0)		20.0 (2.7)		0.63
-Functional Well Being	22.1 (5.4)		23.7 (3.7)		21.3 (6.0)		0.17
Breast Cancer Subscale	26.5 (4.0)		25.8 (4.3)		26.9 (3.8)		0.39
FACT-Breast [g i]	118.1 (13.6)		121.2 (11.4)		116.5 (14.5)		0.28
Endocrine Symptom Subscale	63.8 (8.1)		63.5 (7.4)		64.0 (8.5)		0.88
FACT-ES [g j]	181.9 (19.4)		184.7 (17.3)		180.4 (20.5)		0.49
Stanford Health Assessment Questionnaire							
SHAQ [k]	0.13 (0.34)		0.06 (0.12)		0.16 (0.41)		0.34
SHAQ > 0 [k l]		11 (25%)		3 (19%)		8 (29%)	0.72
Serum inflammatory cytokines							
Interleukin-6 (pg/mL) [m]	1.8 (1.2)	N=41	2.4 (1.6)	N=15	1.5 (0.88)	N=26	0.03
TNFR-2 (pg/mL) [n]	6374 (1507)	N=42	6853 (1427)	N=15	6108 (1510)	N=27	0.13
Interleukin-17 (pg/mL) [m]	0.52 (0.45)	N=41	0.57 (0.49)	N=14	0.49 (0.43)	N=27	0.26

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] P-values from two-sample t-tests and Fisher's exact tests comparing previous chemo to no chemo

[d] T-Stage is a classification of primary tumor size. A tumor that is larger and/or has grown into nearby tissues receives a higher number.

[e] Her2Neu (human epidermal growth factor receptor 2) positive cancers grow faster and are more likely to spread; patients can receive specific medication to target these cancers.

[f] For all Functional Assessment of Cancer Therapy scales, higher score = higher quality of life

[g] FACT, Functional Assessment of Cancer Therapy

[h] FACT-General includes all well-being subscales

[i] FACT-Breast = FACT General + Breast Cancer Subscale

[j] FACT-ES (Breast with Endocrine Subscale) = FACT General + Breast Cancer Subscale + Endocrine Symptom Subscale

[k] SHAQ, Stanford Health Assessment Questionnaire

[l] SHAQ >0 = some reported disability

[m] T-tests performed on log transformed data for Interleukin-6 and Interleukin-17

[n] TNFR-2, Tumor necrosis factor alpha receptor 2

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Table 2

Healthy Eating Index-2010 [22] mean scores and percentage with maximum score among 44 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

		All Participants (n=44)		Previous Chemotherapy [a] (n=15)		No Chemotherapy [b] (n=29)		
	HEI-2010 Dietary Component[c] (maximum score)	**Mean (SD)**	**N (%) at Max Score**	**Mean (SD)**	**N (%) at Max Score**	**Mean (SD)**	**N (%) at Max Score**	**P-value**
	Total HEI-2010 score (100) [c]	69.1 (12.2)	0	67.4 (12.8)	0	69.9 (12.0)	0	0.53 [d]
Adequacy [e]	Total Fruit (5) [f]	3.3 (1.5)	14 (32%)	3.1 (1.6)	4 (27%)	3.4 (1.5)	10 (34%)	0.74 [g]
	Whole Fruit (5) [h]	3.9 (1.3)	22 (50%)	3.9 (1.2)	7 (47%)	4.0 (1.4)	15 (52%)	1.00 [g]
	Total Vegetables (5) [i]	4.1 (1.1)	20 (45%)	4.0 (1.2)	6 (40%)	4.1 (1.1)	14 (48%)	0.75 [g]
	Greens and Beans (5) [j]	3.5 (1.6)	16 (36%)	3.1 (1.7)	3 (20%)	3.6 (1.6)	13 (45%)	0.19 [g]
	Whole Grains (10) [k]	5.3 (3.4)	8 (18%)	4.1 (3.8)	4 (27%)	5.9 (3.1)	4 (14%)	0.41 [g]
	Dairy (10) [l]	6.4 (2.4)	7 (16%)	6.4 (2.4)	2 (13%)	6.4 (2.4)	5 (17%)	1.00 [g]
	Total Protein Foods (5) [m]	4.8 (0.6)	36 (82%)	4.9 (0.3)	13 (87%)	4.7 (0.6)	23 (79%)	0.70 [g]
	Seafood and Plant Proteins (5) [n]	4.1 (1.3)	26 (59%)	4.1 (1.3)	9 (60%)	4.1 (1.3)	17 (59%)	1.00 [g]
	Fatty Acids (10) [o]	5.0 (2.8)	3 (7%)	5.0 (2.7)	1 (7%)	5.0 (2.8)	2 (7%)	1.00 [g]
	Refined Grains (10)[q]	8.8 (1.9)	25 (57%)	8.9 (1.8)	9 (60%)	8.8 (2.0)	16 (55%)	1.00 [g]
	Sodium (10) [r]	4.7 (2.6)	1 (2%)	5.1 (2.4)	0 (0%)	4.4 (2.7)	1 (3%)	1.00 [g]
Moderation [p]	Empty Calories (20) [s]	15.1 (3.6)	3 (7%)	14.7 (3.6)	1 (7%)	15.3 (3.6)	2 (7%)	1.00 [g]

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] HEI-2010, Healthy Eating Index-2010

[d] P-values from Fisher's exact tests comparing previous chemotherapy to no chemotherapy groups

[e] Higher score given for higher consumption

[f] Includes 100% fruit juice; maximum score given for ≥ 0.8 cup equivalents per 1000 kcal

[g] P-values from Fisher's exact tests (comparing % at the max) in previous chemotherapy and no chemotherapy groups

[h] Includes all forms except juice; maximum score given for ≥ 0.4 cup equivalents per 1000 kcal

[i] Includes any beans and peas not counted as total protein foods; maximum score given for ≥ 1.1 cup equivalents per 1000 kcal

[j] Includes any beans and peas not counted as total protein foods; maximum score given for ≥ 0.2 cup equivalents per 1000 kcal

[k] Maximum score given for ≥ 1.5 oz equivalents per 1000 kcal

[l] Includes all milk products and fortified soy beverages; maximum score given for ≥ 1.3 cup equivalents per 1000 kcal

[m] Beans and peas are included here (and not with vegetables) when total protein foods standard is otherwise not met; maximum score given for ≥ 2.5 oz equivalents per 1000 kcal

[n] Includes seafood, nuts, seeds, soy products (other than beverages) and beans and peas counted as total protein foods; maximum score given for ≥ 0.8 oz equivalents per 1000 kcal

[o] Ratio of poly + monounsaturated fatty acids/saturated fatty acids; maximum score given for (PUFAs + MUFAs)/SFAs ≥ 2.5

[p] Higher score given for lower consumption

[q] Maximum score given for ≤ 1.8 oz equivalents per 1000 kcal

[r] Maximum score given for ≤ 1.1 grams per 1000 kcal

[s] Calories from solid fats, alcohol (if >13 g/1000 kcal), and added sugars; maximum score given for ≤ 19% energy

Table 3

Mean cytokine levels by Stanford Health Assessment Questionnaire status among 42 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

		All Participants				Previous Chemotherapy [a]				No Chemotherapy [b]			
				P-value				P-value				P-value	
Cytokine (pg/mL)		n	Mean (SD)	Unadj.[c]	Adj.[d]	n	Mean (SD)	Unadj. [c]	Adj.[d]	n	Mean (SD)	Unadj.[c]	Adj.[d]
IL-6 [e]	SHAQ [f]= 0	31	0.45 (0.55)	0.99	0.72	12	0.77 (0.60)	0.35	0.45	19	0.24 (0.42)	0.32	0.97
	SHAQ> 0	10	0.44 (0.61)			3	0.40 (0.55)			7	0.47 (0.68)		
TNFR-2 [g]	SHAQ= 0	32	6166 (1254)	0.11	0.13	12	6672 (1352)	0.34	0.34	20	5863 (1116)	0.16	0.40
	SHAQ> 0	10	7040 (2071)			3	7578 (1793)			7	6810 (2270)		
IL-17 [h]	SHAQ= 0	31	−0.94 (0.85)	0.69	0.70	11	−0.68 (0.67)	0.34	0.37	20	−1.07 (0.92)	0.92	0.78
	SHAQ> 0	10	−1.05 (0.54)			3	−1.09 (0.29)			7	−1.03 (0.63)		

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] two-sample t-test, unadjusted for body mass index

[d] linear regression, adjusting for body mass index

[e] IL-6, interleukin-6; log transformed due to skewness

[f] SHAQ, Stanford Health Assessment Questionnaire

[g] TNFR-2, tumor necrosis factor alpha receptor 2

[h] IL-17, interleukin-17; log transformed due to skewness

Table 4

Pearson correlations between Healthy Eating Index-2010 scores and inflammatory cytokines among 42 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

Cytokine (pg/mL)		All Participants			Previous Chemotherapy [a]			No Chemotherapy [b]		
		N	*r*	(P-value)	N	*r*	(P-value)	N	*r*	(P-value)
IL-6 [c]	Unadjusted	41	−0.46	(0.002)	15	−0.69	(0.005)	26	−0.29	(0.15)
	Adjusted [d]		−0.26	(0.10)		−0.67	(0.009)		−0.02	(0.93)
TNFR-2 [e]	Unadjusted	42	−0.41	(0.006)	15	−0.46	(0.08)	27	−0.37	(0.06)
	Adjusted [d]		−0.30	(0.06)		−0.59	(0.03)		−0.19	(0.35)
IL-17 [f]	Unadjusted	41	0.04	(0.80)	14	0.03	(0.91)	27	0.07	(0.73)
	Adjusted [d]		0.03	(0.87)		0.10	(0.73)		0.02	(0.94)

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] IL-6, interleukin-6; log transformed due to skewness

[d] Linear regression was used to estimate partial correlation, adjusted for body mass index

[e] TNFR-2, tumor necrosis factor alpha receptor 2

[f] IL-17, interleukin-17; log transformed due to skewness

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Table 5

Pearson correlations between baseline Healthy Eating Index-2010 score and FACT scales among 44 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

		All Participants (n=44)		Previous Chemotherapy [a] (n=15)		No Chemotherapy [b] (n=29)	
FACT [c]		***r***	**(P-value)**	***r***	**(P-value)**	***r***	**(P-value)**
FACT-G [d]	Unadjusted	0.11	(0.46)	−0.06	(0.82)	0.22	(0.24)
	Adjusted [e]	−0.22	(0.15)	−0.14	(0.65)	−0.26	(0.18)
-Physical Well Being	Unadjusted	0.05	(0.73)	−0.30	(0.27)	0.19	(0.32)
	Adjusted [e]	0.28	(0.07)	0.21	(0.48)	0.30	(0.12)
-Social Well Being	Unadjusted	0.17	(0.27)	0.54	(0.04)	0.16	(0.41)
	Adjusted [e]	0.12	(0.44)	0.04	(0.88)	0.17	(0.38)
-Emotional Well Being	Unadjusted	0.01	(0.94)	−0.29	(0.29)	0.20	(0.29)
	Adjusted [e]	0.03	(0.86)	0.13	(0.66)	0.05	(0.79)
-Functional Well Being	Unadjusted	0.07	(0.65)	−0.02	(0.96)	0.13	(0.49)
	Adjusted [e]	−0.06	(0.71)	−0.39	(0.17)	0.13	(0.52)
Breast Cancer Subscale	Unadjusted	0.19	(0.23)	−0.05	(0.87)	0.31	(0.10)
	Adjusted [e]	0.19	(0.21)	0.00	(1.00)	0.28	(0.15)
FACT-B [f]	Unadjusted	0.15	(0.34)	−0.06	(0.83)	0.26	(0.17)
	Adjusted [e]	0.07	(0.64)	−0.12	(0.68)	0.17	(0.38)
Endocrine Symptom Subscale	Unadjusted	0.23	(0.13)	0.21	(0.46)	0.24	(0.21)
	Adjusted [e]	0.17	(0.28)	−0.14	(0.64)	0.31	(0.11)
FACT-ES [g]	Unadjusted	0.20	(0.20)	0.05	(0.87)	0.29	(0.13)
	Adjusted [e]	0.11	(0.49)	−0.14	(0.64)	0.22	(0.25)

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] FACT, Functional Assessment of Cancer Therapy

[d] FACT-G, Functional Assessment of Cancer - General; includes all well-being subscales

[e] Linear regression was used to estimate partial correlation, adjusted for body mass index

[f] FACT-B, Functional Assessment of Cancer – Breast; includes FACT-G + Breast Cancer Subscale

[g] FACT-ES, Functional Assessment of Cancer - Breast with Endocrine Scale; includes FACT-G + Breast Cancer Subscale + Endocrine Symptom Subscale

Table 6

Mean Healthy Eating Index-2010 scores by SHAQ status among 44 postmenopausal breast cancer survivors after completion of primary therapy and prior to randomization in a dietary supplement intervention

	All Participants (n=44)				Previous Chemotherapy [a] (n=15)				No Chemotherapy [b] (n=29)			
	n	HEI-2010 [c] Score Mean (SD)	P-value		n	HEI-2010 [c] Score Mean (SD)	P-value		n	HEI-2010 [c] Score Mean (SD)	P-value	
			Unadj. [d]	Adj. [e]			Unadj. [d]	Adj. [e]			Unadj. [d]	Adj. [e]
SHAQ=0 [f g]	33	70.7 (11.0)	0.12	0.26	12	66.9 (14.1)	0.78	0.88	21	72.9 (8.5)	0.03	0.13
SHAQ>0 [f h]	11	64.1 (14.5)			3	69.4 (6.6)			8	62.1 (16.5)		

[a] Participants with history of chemotherapy prior to study enrollment

[b] Participants without history of chemotherapy prior to study enrollment

[c] HEI-2010, Healthy Eating Index 2010

[d] two-sample t-test, unadjusted for body mass index

[e] linear regression adjusting for body mass index

[f] SHAQ, Stanford Health Assessment Questionnaire

[g] SHAQ = 0 indicates no reported disability

[h] SHAQ > 0 indicates some reported disability