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ORIGINAL REPORT

Fatigue, Inflammation, and ω-3 and ω-6 Fatty Acid Intake Among Breast Cancer Survivors

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ABSTRACT

Purpose
Evidence suggests that inflammation may drive fatigue in cancer survivors. Research in healthy populations has shown reduced inflammation with higher dietary intake of ω-3 polyunsaturated fatty acids (PUFAs), which could potentially reduce fatigue. This study investigated fatigue, inflammation, and intake of ω-3 and ω-6 PUFAs among breast cancer survivors.

Methods
Six hundred thirty-three survivors (mean age, 56 years; stage I to IIIA) participating in the Health, Eating, Activity, and Lifestyle Study completed a food frequency/dietary supplement questionnaire and provided a blood sample assayed for C-reactive protein (CRP) and serum amyloid A (30 months after diagnosis) and completed the Piper Fatigue Scale and Short Form-36 (SF-36) vitality scale (39 months after diagnosis). Analysis of covariance and logistic regression models tested relationships between inflammation and fatigue, inflammation and ω-3 and ω-6 PUFA intake, and PUFA intake and fatigue, controlling for three incremental levels of confounders. Fatigue was analyzed continuously (Piper scales) and dichotomously (SF-36 vitality ≤ 50).

Results
Behavioral ($P = .003$) and sensory ($P = .001$) fatigue scale scores were higher by increasing CRP tertile; relationships were attenuated after adjustment for medication use and comorbidity. Survivors with high CRP had 1.8 times greater odds of fatigue after full adjustment ($P < .05$). Higher intake of ω-6 relative to ω-3 PUFAs was associated with greater CRP ($P = .01$ after full adjustment) and greater odds of fatigue (odds ratio, 2.6 for the highest *v* lowest intake; $P < .05$).

Conclusion
Results link higher intake of ω-3 PUFAs, decreased inflammation, and decreased physical aspects of fatigue. Future studies should test whether ω-3 supplementation may reduce fatigue among significantly fatigued breast cancer survivors.

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INTRODUCTION

Fatigue is common among breast cancer survivors[1-3] and may persist for years after cancer treatment,[3] clustering with comorbid symptoms such as depression, anxiety, sleep disturbance, and pain[4-9] that reduce participation in life activities and quality of life.[10] Determining the mechanisms driving fatigue will inform interventions to prevent or ameliorate fatigue and preserve functioning and quality of life.

Animal and clinical studies suggest that fatigue among cancer survivors may be driven by altered cytokines and stress hormones contributing to inflammation.[11-16] Inflammatory cell signaling in the periphery may influence a CNS-mediated syndrome of sickness behavior inducing fatigue[13] through decreased glucocorticoid signaling and upregulation of nuclear factor-κB activity.[17] However, research on these mechanisms is limited and has not assessed how the multiple dimensions of fatigue relate to inflammation. Nonetheless, it seems plausible that interventions that reduce inflammation may reduce fatigue.

Observational data from healthy samples link inflammation to dietary intake of ω-3 and ω-6 polyunsaturated fatty acids (PUFAs). Higher ω-3 PUFAs relate to lower levels of proinflammatory markers, including interleukin (IL) -6, IL-1 receptor antagonist, tumor necrosis factor (TNF) α, and C-reactive protein (CRP),[18-23] and to higher levels of anti-inflammatory markers, including IL-10 and transforming growth factor β.[18] These relationships also are seen in patients with elevated inflammation (eg,

with coronary artery disease).[24,25] Given interest in the balance of ω-3 and ω-6 PUFAs, some studies investigated the ω-6:ω-3 ratio. A higher ω-6:ω-3 ratio has been related to higher levels of proinflammatory markers (IL-6, IL-1 receptor antagonist, TNF-α, and CRP)[18,23] and lower levels of anti-inflammatory markers (IL-10 and transforming growth factor β).[18] The ω-6:ω-3 ratio may be a stronger predictor of inflammation than either fatty acid alone.[23]

Supplementing healthy people with ω-3 PUFAs, especially long-chain ω-3 PUFAs, can reduce inflammation by suppressing synthesis of IL-1β, IL-1α, IL-2, and TNF-α.[26-29] Omega-3 supplementation in obese individuals[30] and patients with advanced cancer[31-33] reduces levels of serum CRP, serum amyloid A (SAA), IL-6, and TNF-α.[34] Because ω-3 and ω-6 PUFA intake relates to inflammation, which can produce fatigue, ω-3 and ω-6 PUFA intake may also be related to fatigue.

Only one study examined ω-3 intake, inflammation, and fatigue among cancer survivors and showed reduced fatigue among patients with advanced lung cancer after ω-3 PUFA supplementation.[33] To our knowledge, no studies have investigated ω-3 and ω-6 intake, inflammation, and fatigue among breast cancer survivors. This study assessed the relationships between multidimensional fatigue, inflammation (CRP and SAA), and intake of ω-3 and ω-6 PUFAs among breast cancer survivors.

METHODS

Study Population

The Health, Eating, Activity, and Lifestyle (HEAL) Study is a multicenter, multiethnic, prospective study of women diagnosed with in situ or stage I to IIIA breast cancer. Study protocols were approved by the institutional review boards of participating centers, and informed consent was obtained from participants.

Eligibility, Recruitment, and Data Collection

Women (n = 1,183) diagnosed with their first primary breast cancer were recruited from three Surveillance, Epidemiology, and End Results (SEER) registries in New Mexico, western Washington, and Los Angeles County, California. In New Mexico, we recruited 615 women age 18 years or older diagnosed between 1996 and 1999 living in Bernalillo, Santa Fe, Sandoval, Valencia, or Taos counties. In Washington, we recruited 202 women age 40 to 64 years diagnosed between 1997 and 1998 living in King, Pierce, or Snohomish counties. The age range for the Washington patients was restricted because of other ongoing studies. The accrual rate for the Washington and New Mexico sites was 41%.[35] In Los Angeles, we recruited 366 black women diagnosed between 1995 and 1998 who participated in the Women's Contraceptive and Reproductive Experiences Study (accrual rate, 72%[36]) or a parallel case-control study (accrual rate, 75%[37]) and were age 35 to 64 years at diagnosis. HEAL participants completed assessments at the following three time points: baseline (on average 6 months after diagnosis; range, 2 to 12 month after diagnosis) and two follow-up assessments at 30 months after diagnosis (range, 24 to 41 months) and 39 months after diagnosis (range, 24 to 59 months). The baseline and 30-month follow-ups assessed demographic and clinical variables, sleep, and physical activity. The 30-month assessment also included measures of dietary intake and a blood draw. The 39-month follow-up assessed symptoms and health-related quality of life (HRQOL; hereafter called the HRQOL assessment). Of 1,183 women completing the baseline survey, 944 (80%) participated in the 30-month assessment, 921 (78%) completed the food frequency questionnaire (FFQ), 858 (73%) participated in the HRQOL assessment, and 814 (69%) provided a blood sample. We excluded seven women missing data for CRP and SAA, 73 women with improbable FFQ values, and 31 women diagnosed with recurrent or new primary breast cancer before the 39-month follow-up assessment, leaving a final sample of 633 women.

Measures

Fatigue. Multidimensional fatigue (past month) was measured at the HRQOL assessment using the 22-item revised Piper Fatigue Scale[38] including a total score and four subscales (coded 0 to 10) measuring behavioral changes in activities from fatigue (behavioral/severity subscale), emotional meaning of fatigue (affective meaning subscale), physical symptoms (sensory subscale), and emotional symptoms (cognitive/mood subscale). Dichotomous fatigue was assessed using the vitality subscale of the Short Form-36 (SF-36)[39] (0 to 100 scale; lower scores indicate higher fatigue); women with vitality scores of 50 and lower were classified as fatigued.[7]

Inflammatory markers. CRP and SAA were chosen as inflammatory markers because they respond to physical activity and weight changes,[40] are more stable than cytokines, and are being investigated in HEAL as mechanisms linking lifestyle factors to survival. A fasting blood sample was collected at the 30-month interview and processed within 3 hours. Serum was stored at −70 to −80°C until analysis. CRP and SAA were measured by high-sensitivity assay using latex-enhanced nephelometry (Behring Nephelometer II analyzer; Dade-Behring Diagnostics, Deerfield, IL) at the University of Washington. The lower detection limits were 0.2 mg/L and 0.7 mg/L for CRP and SAA, respectively, with interassay coefficients of variation of 5% to 9% and 4% to 8%, respectively.

ω-3 and ω-6 PUFA intake. Dietary intake over the last month or last year (New Mexico) was assessed at the 30-month follow-up using a self-administered FFQ[41]; nutrient data were converted using Nutrition Data Systems for Research (version 2005; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). Mean daily intake of long-chain ω-3 PUFAs was calculated by adding eicosapentaenoic acid (20:5 ω-3) and docosahexaenoic acid (22:6 ω-3) intake. The ω-6:ω-3 ratio was calculated by dividing the ω-6 PUFA value by the ω-3 PUFA value.

Participants reported the type and duration of dietary supplements. Individuals taking fish or cod liver oil or flax seed oil were considered ω-3 supplement users. The continuous ratio of ω-6:ω-3 PUFA intake from FFQ and the dichotomous ω-3 supplement variable were combined, creating subgroups of ω-6 and ω-3 PUFA intake, similar to an analysis of fiber intake combining FFQ and supplement data.[42]

Potential covariates. A combined race/ethnicity/study site variable was used as a result of high correlations between these variables. Body mass index (BMI) at 30 months was calculated in kilograms per meter squared from clinic-measured height and weight at Washington and New Mexico and self-reported measures in Los Angeles. Average weekly hours of moderate to vigorous sports/recreation physical activity and sleep (past year) were assessed at 30 months using the Modifiable Activity Questionnaire.[43,44] Daily alcohol intake (grams per day at 30 months) was assessed by FFQ. Self-reported smoking habits at 30 months were coded as current, past (smoked > five packs of cigarettes), or never.

Comorbid conditions (at 30 months; self-reported physician diagnosis of angina/chest pain, heart attack, congestive heart failure, deep venous thrombosis, pulmonary embolism, stroke, arthritis, diabetes/high blood sugar, or other cancer) were categorized as zero, one, or ≥ two conditions. Two variables assessed prescribed or over-the-counter medication use at 30 months of anti-inflammatory medications (angiotensin I converting enzyme inhibitors, β-blockers, antihyperlipidemic agents, antigout agents, nonsteroidal anti-inflammatory drugs, antipyretics, and respiratory corticosteroids[45,46]) and antidepressant/anxiolytic medications (antidepressants, anxiolytics, or sedatives/hypnotics). Tumor stage (in situ, local, or regional) and hormone receptor status were obtained from SEER. Cancer treatment data were obtained from medical record abstraction and SEER. Use of tamoxifen was obtained from medical record abstraction and self-reported use at baseline and 30 months.

Data Analysis

Analysis of covariance (ANCOVA) models tested differences in multidimensional fatigue scores (Piper scales) by tertiles of CRP or SAA. Logistic regression models tested differences in the odds of fatigue (SF-36) by tertiles of CRP or SAA. Analyses for CRP were repeated using a dichotomous CRP risk variable (high risk, CRP > $v \leq 3.0$ mg/L).[47]

ANCOVA models tested differences in CRP and SAA levels by subgroup of ω-3 and ω-6 intake. Women in the lowest tertile of ω-6:ω-3 ratio who also

Table 1. Demographic and Clinical Characteristics of HEAL Study Participants

Characteristic	No. of Participants (N = 633)	%	Mean	SD
Baseline				
Age, years			55.6	10.1
29-49	183	28.9		
50-59	245	38.7		
60-69	142	22.4		
70+	63	10.0		
Race/ethnicity and location				
Non-Hispanic white, Washington	132	20.9		
Non-Hispanic white, New Mexico	268	42.3		
Black	146	23.1		
Hispanic	65	10.3		
Other	22	3.5		
Education				
High school or less	153	24.2		
Some college	227	35.9		
College graduate	127	20.1		
Graduate school	125	19.8		
Stage at diagnosis				
In situ	151	23.9		
Local	349	55.1		
Regional	133	21.0		
ER status				
ER positive	357	56.4		
ER negative	93	14.7		
ER borderline or unknown	183	28.9		
PR status				
PR positive	282	44.6		
PR negative	127	20.1		
PR borderline or unknown	224	35.4		
Treatment type				
Surgery only	210	31.6		
Surgery/radiation	251	37.8		
Surgery/chemotherapy	63	9.5		
Surgery/radiation/chemotherapy	140	21.1		
Time since diagnosis, months				
Diagnosis to baseline			6.0	2.2
Diagnosis to post-treatment follow-up			30.5	3.5
Diagnosis to QOL assessment			40.8	6.6
30-month follow-up assessment				
Menopausal status				
Premenopausal	111	17.5		
Postmenopausal	486	76.8		
Unclassifiable	36	5.7		
Tamoxifen use				
Used at both baseline and follow-up	192	30.3		
Used at baseline only	40	6.3		
Used at follow-up only	94	14.9		
No use during study period	307	48.5		
Medications				
Anti-inflammatory medications*	359	56.7		
Antidepressant use	105	16.6		
Anxiolytic use	25	4.0		
Hypnotic/sedative use	20	3.2		
No. of comorbid conditions				
0	222	35.1		
1	210	33.2		
2+	201	31.8		
Fatigue by Piper Fatigue Scale				
Behavioral/severity (n = 633)			2.4	2.6
Affective meaning (n = 629)			2.7	2.5
Sensory (n = 632)			4.1	2.3
Cognitive/mood (n = 633)			3.8	2.0
Total fatigue (n = 633)			3.9	2.0
Fatigue by SF-36				
Fatigued (vitality score ≤ 50)	263	41.6		
Score (range, 0-100)			56.1	22.1
Inflammation				
SAA, mg/L			10.2	30.0
CRP, mg/L			4.4	8.6
CRP > 3.0 mg/L	248	39.2		
Intake of ω-3 and ω-6 fatty acids, g/d				
ω-6			14.0	7.7
ω-3			1.4	0.8
Long-chain polyunsaturated fatty acid			0.1	0.2
ω-6:ω-3 ratio			10.6	3.7
ω-3 supplement use	93	14.7		
Body mass index, kg/m^2			28.0	6.4
Physical activity, hours per week of moderate-vigorous sports/ recreational activity			2.6	3.6
Sleep, hours per day			7.0	1.2
Alcohol intake, g/d			4.6	9.6
Smoking				
Currently smoking	77	12.2		
Previously smoked	251	39.7		
Never smoked	305	48.2		

(continued in next column)

Abbreviations: CRP, C-reactive protein; ER, estrogen receptor; HEAL, Health, Eating, Activity, and Lifestyle; SD, standard deviation; PR, progesterone receptor; QOL, quality of life; SAA, serum amyloid A; SF-36, Short Form-36.
*Anti-inflammatory medications includes nonsteroidal anti-inflammatory drugs, corticosteroids, antigout agents, antihyperlipidemic agents, β-blockers, and angiotensin-converting enzyme inhibitors.

used ω-3 supplements constituted the reference group. Analyses for CRP were repeated using logistic regression for the dichotomous CRP risk variable.

Multidimensional fatigue scores were compared across subgroups of ω-3 and ω-6 intake using ANCOVA. Logistic regression models tested differences in the odds of fatigue by level of ω-6 and ω-3 intake. To explore potential mediation of the ω-6:ω-3 intake-fatigue relationship by CRP, these models were adjusted for CRP.

Overadjustment for factors including those likely to be mediators can lead to bias and erroneous conclusions.[48,49] To evaluate potential bias, three incrementally adjusted models were run for each set of analyses, adjusting for age, race/study site, tamoxifen use, and menopausal status (model 1); model 1 plus antidepressant/anxiolytic use and number of comorbidities (model 2); and model 2 plus BMI (model 3). Other variables were considered as covariates (eg, anti-inflammatory medication, physical activity, hormone receptor status, cancer treatment type) but not included in final models because of multicollinearity or lack of improvement in model fit.

CRP and SAA were log-transformed as a result of non-normal distributions. Sensitivity analyses excluding extreme CRP values (n = 31 using the 95th percentile cutoff values from the National Health and Nutrition Examination Survey[50]) yielded similar results, so results presented use all data. PUFA analyses were repeated using only long-chain ω-3 PUFAs; these results were similar and thus are not presented. All analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

Table 2. Fatigue Levels Across Tertiles of CRP and CRP Risk Categories

Measure	CRP (mg/L)		Piper Fatigue Scale										Frequency of Fatigue (SF-36 vitality score ≤ 50)			
			Behavioral (n = 632)		Affective (n = 629)		Sensory (n = 632)		Cognitive (N = 633)		Total Score (N = 633)		Not Fatigued (n = 370)		Fatigued (n = 263)	
	Geometric Mean	95% CI	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	No. of Participants	%	No. of Participants	%
CRP tertile																
Lowest tertile	0.5	0.4 to 0.5	2.1	2.5	2.5	2.5	3.8	2.3	3.7	2.1	3.7	2.0	142	67.0	70	33.0
Middle tertile	2.1	2.0 to 2.2	2.4	2.5	2.7	2.5	4.1	2.3	3.7	1.9	3.8	1.9	125	60.1	83	39.9
Highest tertile	8.0	7.3 to 8.7	2.9	2.8	2.9	2.6	4.5	2.4	3.9	2.1	4.1	2.2	103	48.4	110	51.6
Trends of fatigue levels across CRP tertiles																
Model 1* P_{trend}†			.003		.08		.001		.28		.02					
Model 2‡ P_{trend}			.07		.50		.04		.88		.26					
Model 3§ P_{trend}			.10		.82		.21		.54		.47					
CRP risk category																
Average, ≤ 3.0 mg/L			2.2	2.5	2.6	2.5	3.9	2.3	3.7	2.0	3.7	2.0	245	63.6	140	36.4
High, > 3.0 mg/L			2.8	2.8	2.8	2.6	4.4	2.3	3.9	2.0	4.1	2.1	125	50.4	123	49.6
Differences in fatigue between CRP risk categories																
Model 1* *P*			.009		.22		.006		.34		.03					
Model 2‡ *P*			.16		.96		.15		.68		.46					
Model 3§ *P*			.23		.72		.47		.42		.74					

Abbreviations: CRP, C-reactive protein; SD, standard deviation; SF-36, Short Form-36.
*Model 1 adjusts for age, race/study site, tamoxifen use, and menopausal status.
†P_{trend} determined testing a trend of fatigue scores across the subgroup determined by tertiles of CRP.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§Model 3 adjusts for model 2 plus body mass index.

RESULTS

Sample Characteristics

Participants were, on average, 55.6 years old at baseline (Table 1); two thirds were non-Hispanic white. More than 50% had localized breast cancer. At 30 months, 76.8% of women were postmenopausal, 45.2% were taking tamoxifen, 56.7% were taking anti-inflammatory medications, 16.6% were taking antidepressants (used for treatment of hot flashes[51] and depression), and 31.8% had two or more comorbidities.

Mean multidimensional fatigue scores ranged from 2.4 (behavioral/severity subscale) to 4.1 (sensory subscale); 41.6% of participants were classified as fatigued. Mean serum CRP and SAA levels were 4.4 mg/L and 10.2 mg/L, respectively. Approximately 40% of participants had high-risk CRP levels.

Fatigue and Inflammation

There was a significant linear trend (Tables 2 and 3) for higher CRP levels, with higher scores for behavioral (P_{trend} = .003), sensory (P_{trend} = .001), and total fatigue (P_{trend} = .02, model 1). These findings were attenuated after adjusting for medication use, comorbidity, and BMI (models 2 and 3). Results were similar when CRP was dichotomized as high versus average risk. There were no significant associations for SAA in this analysis or any of the analyses; thus, results for SAA are not presented.

The odds ratios (ORs) for fatigue among the middle and highest tertile groups were 1.4 (95% CI, 0.9 to 2.1) and 2.4 (95% CI, 1.6 to 3.7), respectively, compared with the lowest tertile group (model 1). The OR for fatigue in the highest CRP tertile remained significant (OR, 1.8; 95% CI, 1.1 to 2.9) in model 3. There was an 80% (OR, 1.8; 95% CI, 1.3 to 2.6) increased risk of fatigue among individuals with high-risk CRP (model 1), which became nonsignificant after adjusting for BMI (model 3).

Table 3. Odds Ratios for Fatigue by CRP Tertile and CRP Risk Category

CRP Measure	Odds Ratio	95% CI
Tertile for CRP		
Model 1*		
Middle *v* lowest	1.4	0.9 to 2.1
Highest *v* lowest	2.4†	1.6 to 3.7
Model 2‡		
Middle *v* lowest	1.3	0.8 to 2.0
Highest *v* lowest	2.0†	1.3 to 3.0
Model 3§		
Middle *v* lowest	1.2	0.8 to 1.9
Highest *v* lowest	1.8‖	1.1 to 2.9
CRP risk categories		
Model 1*		
High *v* average risk	1.8†	1.3 to 2.6
Model 2‡		
High *v* average risk	1.5‖	1.1 to 2.1
Model 3§		
High *v* average risk	1.4	0.9 to 2.0

Abbreviation: CRP, C-reactive protein.
*Model 1 adjusts for age, race/study site, tamoxifen use, and menopausal status.
†$P < .01$ comparing odds ratios for being categorized as fatigued across subgroups determined by tertiles of CRP.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§Model 3 adjusts for model 2 plus body mass index.
‖$P < .05$ comparing odds ratios for being categorized as fatigued across subgroups determined by tertiles of CRP.

Table 4. Relationships Between ω-6 and ω-3 Intake and CRP

ω-6:ω-3 Ratio Tertile and Supplement Use	No. of Participants (N = 633)	CRP (mg/mL)		CRP Risk Category			
				Average-Risk CRP (n = 385)		High-Risk CRP (n = 248)	
		Geometric Mean	95% CI	No. of Participants	%	No. of Participants	%
Lowest, supplement users	47	1.0	0.7 to 1.5	40	85.1	7	14.9
Lowest, supplement nonusers	164	1.9	1.6 to 2.4	103	62.8	61	37.2
Middle, supplement users	31	1.3	0.8 to 2.0	23	74.2	8	25.8
Middle, supplement nonusers	180	2.2	1.8 to 2.6	105	58.3	75	41.7
Highest, supplement users	15	2.3	1.4 to 3.7	10	66.7	5	33.3
Highest, supplement nonusers	196	2.5	2.1 to 2.9	104	53.1	92	46.9
P_{trend}*							
Model 1†			.002				
Model 2‡			.01				
Model 3§			.01				

Abbreviation: CRP, C-reactive protein.
*P_{trend} determined testing a trend of CRP levels across subgroups determined by ω-6:ω-3 ratio tertile and supplement use.
†Model 1 age, race/study site, tamoxifen use, menopausal status.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§Model 3 adjusts for model 2 plus body mass index.

ω-6 and ω-3 PUFAs and Inflammation

A significant linear association between CRP and ω-6 and ω-3 intake was observed (Tables 4 and 5). Women with the highest ω-6:ω-3 ratio who were not taking ω-3 supplements (considered the most proinflammatory dietary condition) had the highest serum CRP levels, whereas women with the lowest ω-6:ω-3 ratio who were taking ω-3 supplements had the lowest serum CRP levels. This linear trend remained significant in model 3 ($P_{trend} = .01$). *P* values from ANCOVA models not assuming a linear trend were equivalent to the P_{trend} values reported earlier.

Results were similar for dichotomous CRP. The OR for high-risk CRP among individuals with the highest tertile of ω-6:ω-3 ratio who were not using ω-3 supplements (compared with those in the lowest tertile who used supplements) was 4.6 (95% CI, 1.9 to 11.0), which remained significant in model 3 (OR, 4.5; 95% CI, 1.7 to 11.5).

Table 5. Odds Ratios for Having High-Risk CRP Level

ω-6:ω-3 Ratio Tertile and Supplement Use	Odds Ratio	95% CI
Model 1*		
Lowest, nonusers *v* lowest, users	3.1	1.3 to 7.4
Middle, users *v* lowest, users	1.8	0.6 to 5.6
Middle, nonusers *v* lowest, users	3.6	1.5 to 8.7
Highest, users *v* lowest, users	2.4	0.6 to 5.6
Highest, nonusers *v* lowest, users	4.6†	1.9 to 11.0
Model 2‡		
Lowest, nonusers *v* lowest, users	2.7	1.1 to 6.5
Middle, users *v* lowest, users	1.8	0.5 to 5.6
Middle, nonusers *v* lowest, users	2.9	1.2 to 7.1
Highest, users *v* lowest, users	2.2	0.6 to 9.0
Highest, nonusers *v* lowest, users	3.8§	1.6 to 9.3
Model 3‖		
Lowest, nonusers *v* lowest, users	3.2	1.2 to 8.4
Middle, users *v* lowest, users	1.8	0.5 to 6.5
Middle, nonusers *v* lowest, users	3.3	1.3 to 8.6
Highest, users *v* lowest, users	2.6	0.6 to 11.4
Highest, nonusers *v* lowest, users	4.5§	1.7 to 11.5

Abbreviation: CRP, C-reactive protein.
*Model 1 adjusts for age, race/study site, tamoxifen use, and menopausal status.
†$P < .01$ comparing odds ratios for being fatigued across subgroups determined by ω-6:ω-3 ratio tertile and supplement use.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§$P < .05$ comparing odds ratios for being fatigued across subgroups determined by ω-6:ω-3 ratio tertile and supplement use.
‖Model 3 adjusts for model 2 plus body mass index.

ω-6 and ω-3 PUFAs and Fatigue

Significant linear associations were observed between ω-6 and ω-3 intake and multidimensional fatigue, specifically for the behavioral, sensory, and cognitive aspects of fatigue, and the total score ($P_{trend} < .05$; Tables 6 and 7). The associations became nonsignificant after adjusting for use of antidepressants/anxiolytics and comorbidities except for the sensory subscale (model 3, $P_{trend} = .02$). Further adjustment with CRP attenuated these relationships, whereas the association remained statistically significant for sensory and total fatigue scores ($P_{trend} < .05$; results not shown). *P* values from ANCOVA models not assuming a linear trend were significant for the sensory scale but not for other fatigue scales.

For dichotomous fatigue, women who were not taking ω-3 supplements (lowest tertile, nonusers: OR, 2.6; 95% CI, 1.2 to 5.5; middle tertile, nonusers: OR, 2.4; 95% CI, 1.1 to 5.2; highest tertile, nonusers: OR, 3.5; 95% CI, 1.7 to 7.4) all had increased risk of fatigue (*v* women with lowest ω-6:ω-3 ratio taking ω-3 supplements); however, the differences were no longer statistically significant after adjusting for use of antidepressants/anxiolytics and comorbidities. The relationship persisted in model 3 for the highest group; there was a 2.6-fold increased risk of fatigue among individuals with the highest ω-6:ω-3 ratio who were not taking ω-3 supplements compared with the reference group (model 3: OR, 2.6; 95% CI, 1.2 to 5.5). Adjusting the dichotomous fatigue models for CRP further attenuated the

Table 6. Fatigue Levels by Subgroup of ω-3 and ω-6 Fatty Acid Intake

ω-6:ω-3 Ratio Tertile and Supplement Use	No. of Participants	Piper Fatigue Scale										Frequency of Fatigue (SF-36 vitality score ≤ 50)			
		Behavioral (n = 632)		Affective (n = 629)		Sensory (n = 632)		Cognitive (N = 633)		Total Score (N = 633)		Not Fatigued (n = 370)		Fatigued (n = 263)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	No. of Participants	%	No. of Participants	%
Lowest, supplement users	47	1.8	2.1	2.1	2.3	3.1	2.1	3.2	1.9	3.1	1.8	36	76.6	11	23.4
Lowest, supplement nonusers	164	2.4	2.7	2.7	2.7	4.0	2.3	3.8	2.1	3.9	2.1	97	59.2	67	40.9
Middle, supplement users	31	2.2	2.4	2.8	2.4	4.2	2.3	3.7	1.3	3.9	1.7	19	61.3	12	38.7
Middle, supplement nonusers	180	2.3	2.5	2.6	2.5	4.0	2.3	3.8	2.0	3.8	2.0	109	60.6	71	39.4
Highest, supplement users	15	3.4	3.1	3.4	2.6	4.3	2.9	3.7	2.2	4.1	2.4	9	60.0	6	40.0
Highest, supplement nonusers	196	2.7	2.8	2.8	2.6	4.5	2.3	4.0	2.0	4.1	2.0	100	51.0	96	49.0
P_{trend}* of differences in fatigue levels across subgroups															
Model 1†		.03		.40		.002		.03		.02					
Model 2‡		.14		.88		.02		.19		.12					
Model 3§		.14		.90		.02		.20		.12					

Abbreviations: SD, standard deviation; SF-36, Short Form-36.
*P_{trend} determined testing a trend of C-reactive protein levels across the subgroup of ω-3 and ω-6 intake.
†Model 1 adjusts for age, race/study site, tamoxifen use, and menopausal status.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§Model 3 adjusts for model 2 plus body mass index.

ORs, but the trend remained statistically significant ($P < .05$; results not shown).

DISCUSSION

To our knowledge, this is the first study investigating multidimensional fatigue, inflammation, and intake of ω-3 and ω-6 PUFAs among breast cancer survivors. Results extend previous research using unidimensional fatigue scales[11-16] by showing that physical fatigue symptoms and their impact on functioning (ie, physical fatigue) are significantly associated with increased inflammation, whereas the more psychological aspects of fatigue are less related to inflammation. These relationships were nonsignificant after adjustment for antidepressant/anxiolytic medications, comorbidities, and BMI, suggesting that residual depression or anxiety symptoms in users of these medications or comorbid conditions including BMI may mediate the relationship between inflammation and physical fatigue. Alternatively, the attenuated relationships could be a result of overlap in the symptoms of fatigue and depression or a result of the shared role of inflammation in the etiology of physical fatigue and comorbid conditions. Results using the SF-36 dichotomous fatigue variable also suggest a direct relationship between inflammation and fatigue for survivors with higher levels of fatigue. Higher CRP was associated with greater odds of fatigue even after adjusting for multiple covariates.

Table 7. Odds Ratios for Fatigue by ω-6:ω-3 Ratio Tertile and Supplement Use

ω-6:ω-3 Ratio Tertile and Supplement Use	Odds Ratio	95% CI
Model 1*		
Lowest, nonusers *v* lowest, users	2.6	1.2 to 5.5
Middle, users *v* lowest, users	2.3	0.9 to 6.4
Middle, nonusers *v* lowest, users	2.4	1.1 to 5.2
Highest, users *v* lowest, users	2.7	0.8 to 9.4
Highest, nonusers *v* lowest, users	3.5†	1.7 to 7.4
Model 2‡		
Lowest, nonusers *v* lowest, users	2.1	1.0 to 4.5
Middle, users *v* lowest, users	2.3	0.8 to 6.4
Middle, nonusers *v* lowest, users	1.9	0.9 to 4.1
Highest, users *v* lowest, users	2.2	0.6 to 8.1
Highest, nonusers *v* lowest, users	2.6	1.2 to 5.6
Model 3§		
Lowest, nonusers *v* lowest, users	2.1	0.9 to 4.5
Middle, users *v* lowest, users	2.3	0.8 to 6.3
Middle, nonusers *v* lowest, users	1.8	0.8 to 4.0
Highest, users *v* lowest, users	2.2	0.6 to 8.1
Highest, nonusers *v* lowest, users	2.6	1.2 to 5.5

*Model 1 adjusts for age, race/study site, tamoxifen use, and menopausal status.
†$P < .05$ comparing odds ratios for being categorized as fatigued across subgroups determined by ω-6:ω-3 ratio tertile and supplement use.
‡Model 2 adjusts for model 1 plus antidepressant/anxiolytic use and number of comorbidities.
§Model 3 adjusts for model 2 plus body mass index.

Increased intake of ω-3 relative to ω-6 PUFAs was associated with reduced inflammation in these breast cancer survivors, consistent with observational data in healthy populations[18-23] and from ω-3 supplementation studies among patients with advanced cancer.[31-34] The magnitude of the association is clinically significant; women with the lowest intake of ω-3 relative to ω-6 PUFAs had 4.5 times the increased odds of having a high-risk CRP level compared with women with the highest intake of ω-3 relative to ω-6 PUFAs. Increased inflammation is associated with reduced survival among women with breast cancer[52] and with risk for atherosclerosis[53] and other serious medical problems faced by cancer survivors after treatment. Future studies should confirm these associations and potentially test whether supplementation with ω-3 PUFAs can reduce inflammation in breast cancer survivors. Because ω-3 supplementation has been inconsistently related to tumor development and proliferation,[54] such a trial should also measure recurrences and second cancers.

Finally, to our knowledge, this is the first study of breast cancer survivors showing significant associations between ω-6 and ω-3 intake and the behavioral, sensory, and cognitive aspects of fatigue. These results are consistent with research from noncancer samples showing that ω-3 supplementation reduces psychological symptoms, including depression and fatigue,[55] and with the study by Cerchietti et al[33] showing reduced fatigue in patients with lung cancer. The attenuation of these relationships after adjustment for medications and comorbidities may be a result of the same reasons cited earlier for the relationship between CRP and fatigue. Together, these results suggest that intake of ω-3 relative to ω-6 PUFAs is related to lower levels of inflammation, which relates to lower levels of fatigue, most consistently for the physical aspects of fatigue. Further, as with the results linking inflammation to dichotomous fatigue, intake of ω-3 PUFAs in particular was associated with reduced risk of fatigue for those with the greatest intake of ω-3 PUFAs, regardless of medications or comorbidities.

Relationships between ω-6:ω-3 intake and the behavioral, sensory, and cognitive aspects of fatigue were only somewhat attenuated after adjusting for serum CRP, suggesting that inflammation may partially mediate the association between ω-3 and ω-6 intake and fatigue but that other pathways are also involved. Future studies should examine ω-3–induced changes in muscle sympathetic nerve activity[56] and in the ratio of serum arachidonic to eicosapentaenoic acid, which has been related to fatigue,[57] independent of inflammation.[58]

Strengths of this study include assessment of diet, fatigue, and inflammation in a large, diverse group of breast cancer survivors recruited through registries and careful adjustment for three levels of confounders. Limitations include only one assessment of each construct, with fatigue measured after the blood draw, so it is unknown how changes in diet or inflammation relate to changes in fatigue. Selection bias may occur from including only survivors healthy enough to participate several years after cancer treatment; however, more than 40% of participants were classified as fatigued, similar to another large sample of breast cancer survivors,[7] and 40% of the sample had high-risk CRP scores. Furthermore, why significant results were obtained for CRP but not SAA is unknown. SAA is associated with radiation or chemotherapy treatment,[59] and differential effects of treatment on SAA versus CRP may account for this difference. Alternatively, the acute-phase response of SAA is different and more rapid than CRP[60] and potentially more influenced by unmeasured recent factors.

In sum, if confirmed by other studies, these results point toward a future trial testing whether ω-3 PUFA supplements may reduce inflammation among breast cancer survivors and whether they may also reduce fatigue, especially physical fatigue, among those suffering most from this potentially debilitating condition. Considering the high prevalence of fatigue among cancer survivors, effective treatment could have a significant health impact.

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