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ORIGINAL REPORT

Yoga's Impact on Inflammation, Mood, and Fatigue in Breast Cancer Survivors: A Randomized Controlled Trial

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ABSTRACT

Purpose
To evaluate yoga's impact on inflammation, mood, and fatigue.

Patients and Methods
A randomized controlled 3-month trial was conducted with two post-treatment assessments of 200 breast cancer survivors assigned to either 12 weeks of 90-minute twice per week hatha yoga classes or a wait-list control. The main outcome measures were lipopolysaccharide-stimulated production of proinflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1β (IL-1β), and scores on the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), the vitality scale from the Medical Outcomes Study 36-item Short Form (SF-36), and the Center for Epidemiological Studies-Depression (CES-D) scale.

Results
Immediately post-treatment, fatigue was not lower ($P > .05$) but vitality was higher ($P = .01$) in the yoga group compared with the control group. At 3 months post-treatment, fatigue was lower in the yoga group ($P = .002$), vitality was higher ($P = .01$), and IL-6 ($P = .027$), TNF-α ($P = .027$), and IL-1β ($P = .037$) were lower for yoga participants compared with the control group. Groups did not differ on depression at either time ($P > .2$). Planned secondary analyses showed that the frequency of yoga practice had stronger associations with fatigue at both post-treatment visits ($P = .019$; $P < .001$), as well as vitality ($P = .016$; $P = .0045$), but not depression ($P > .05$) than simple group assignment; more frequent practice produced larger changes. At 3 months post-treatment, increasing yoga practice also led to a decrease in IL-6 ($P = .01$) and IL-1β ($P = .03$) production but not in TNF-α production ($P > .05$).

Conclusion
Chronic inflammation may fuel declines in physical function leading to frailty and disability. If yoga dampens or limits both fatigue and inflammation, then regular practice could have substantial health benefits.

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INTRODUCTION

Cancer survivors are more than twice as likely as individuals without a cancer history to have poor health and disability.[1] Reduced physical activity during cancer treatment can decrease the capacity for physical performance, and activity may be further limited by the late effects of cancer and its treatment in survivors.[2,3] With deconditioning, normal activities become more fatiguing, resulting in greater weariness and lessened functional capacity over time.[2,3] Breast cancer survivors with lower levels of physical activity have a higher risk for premature death.[4]

Inflammation is one of the key candidate mechanisms for age-related decrements in physical function and disability.[5-7] Chronic inflammation signals a heightened risk for disability and mortality, even in the absence of clinical disease.[5,6,8,9]

Inflammation is lower in active than in sedentary individuals.[10] Indeed, when cardiorespiratory fitness is assessed objectively by maximal exercise testing, better physical fitness is associated with lower inflammation.[11,12] In this context, it is noteworthy that cancer survivors' average cardiorespiratory fitness is consistently approximately 30% lower than that of their sedentary age mates without a cancer history.[13,14]

About a third of breast cancer survivors report that fatigue interferes with daily activities.[15] Persistent fatigue in survivors may be related in part to overactivation of the inflammatory network.[16] Regular exercise reduces fatigue[17] as well as

inflammation.[7,18] However, fatigue and pain often limit survivors' physical activity.[19,20] Yoga provides graded exercise that can be tailored for individuals who have been sedentary, and the postures can be modified to accommodate functional limitations.[20] In addition, studies with cancer survivors suggest that yoga practice lowers fatigue and improves mood and sleep quality.[20-25]

Accordingly, this study assessed the impact of yoga on inflammation, mood, and fatigue, our primary outcomes. We hypothesized that yoga would decrease inflammation, depressive symptoms, and fatigue in contrast to those characteristics in the wait-list control group.

PATIENTS AND METHODS

Study Design

This randomized controlled trial (RCT) compared a 12-week hatha yoga intervention with a wait-list control condition. Questionnaires and fasting blood samples were collected in the Clinical Research Center at baseline, immediately post-treatment, and 3 months post-treatment. The institutional review board approved this study, and each participant provided informed consent.

Participants

The 200 stage 0 to IIIa breast cancer survivors ranged in age from 27 to 76 years (Table 1). They had completed cancer treatment within the past 3 years (except for tamoxifen/aromatase inhibitors) and were at least 2 months post-surgery or adjuvant therapy or radiation, whichever occurred last. Women were recruited through oncologists' referrals, community print and web-based announcements, and breast cancer groups and events.

Exclusions included a prior history of breast or any other cancer except basal or squamous cell skin cancer, inflammatory breast cancer, anemia, diabetes, chronic obstructive pulmonary disease, uncontrolled hypertension, evidence of liver or kidney failure, symptomatic ischemic heart disease, conditions involving the immune system such as autoimmune and/or inflammatory diseases, cognitive impairment, alcohol/drug abuse, current yoga practice (within the last 6 months), and/or previous yoga practice for more than 3 months. Women reporting 5 hours or more of vigorous physical activity per week were excluded. Figure 1 shows screening, randomization, and participant flow by group.

Randomization and Masking

After women had completed the baseline assessment, the data manager stratified participants by cancer stage (0 *v* I *v* II and IIIA) as well as radiation therapy received or not, and then used an online randomization program to obtain the block randomization sequence (six per block) for assignment to yoga or control within strata. The data manager had no participant contact. Participants were told not to mention their group assignment to study personnel during their post-treatment assessments; questionnaires were administered via computer. The technicians who analyzed blood samples were blind to all other data.

Yoga and Wait-List Control Conditions

Women who were randomly assigned to yoga participated in two 90-minute sessions per week. The protocol outlined poses for the 24 sessions (Appendix Table A1, online only). A senior yoga teacher conducted the initial group, which was videotaped and used to train the subsequent six Yoga Alliance–certified instructors. The 25 yoga groups included 4 to 20 women per group.

To evaluate and limit protocol drift, sessions were audiotaped, and 50% were randomly assessed for omissions from the predetermined poses for the week. Protocol deviations were discussed with teachers.

To maximize adherence, the yoga teacher called any woman who missed a class. Home practice was strongly encouraged, and women recorded their total home plus class practice time in weekly logs.

Participants assigned to the wait-list control were told to continue performing their usual activities, and to refrain from beginning any yoga practice. After their final assessment they were offered the yoga classes.

Measures

The total score on the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) reflected behavioral, cognitive, physical, and affective expressions of fatigue in the last week.[26,27] The energy/fatigue (vitality) scale from the Medical Outcomes Study 36-item short-form health survey (SF-36) measured vitality over the last month.[20,28,29] The Center for Epidemiological Studies Depression Scale (CES-D) assessed depressive symptomatology in the last week.[30] The Pittsburgh Sleep Quality Index (PSQI) evaluated sleep quality and disturbances over a 1-month interval.[31] The increased social interaction provided by the intervention could diminish feelings of fatigue[32]; thus, we measured perceived support by using the Interpersonal Support Evaluation List.[33] The Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire assessed the weekly frequency and duration of various physical activities.[34,35] The Women's Health Initiative Food Frequency Questionnaire (FFQ) provided data on foods and beverages consumed in the past 90 days.[36] All these measures have well-established reliability and validity.

Immunologic Assays

Fasting blood samples were collected between 7:00 and 9:00 AM to control for diurnal variation. Longer-term exercise reduces mononuclear cell production of proinflammatory cytokines[10,11]; thus, lipopolysaccharide-stimulated production of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin-1β (IL-1β) from isolated peripheral blood mononuclear cells was multiplexed and measured by using an electrochemiluminescence method with Meso Scale Discovery kits.[37] Each patient's frozen samples were assayed for all cytokines in one run by using the same controls for all time points for each person.

Sample Size

Sample size was based on detection of meaningful differences in primary end points with 80% power and a two-sided 5% significance level. Effect sizes were based on previously published studies,[15,16] and data we collected from an earlier study of older adults. We estimated expected effect sizes for each of our primary outcomes and based the sample size calculation on the CES-D, which had the smallest estimated effect size and therefore required the largest sample size. The estimated group difference in CES-D was 0.7 (standard deviation, 1.6), requiring 85 patients per group. We expected 15% attrition, so 100 patients per group was required.

Statistical Methods

Baseline demographic and cancer-related characteristics were compared across randomized groups by using *t* tests and χ^2 tests as appropriate. Mixed effect models were used to test the intervention's effect on primary outcomes. Fixed effects included visit, intervention group, and their interaction and baseline outcome levels. Of primary interest were preplanned contrasts comparing group means at each of the two postrandomization time points. Random effects included a patient-specific random intercept that accounted for within-patient correlation (repeated study visits) and a random effect for yoga class assignment that accounted for the partially nested data arising from small clusters being present in the intervention arm but not in the control arm. This explicitly models the within-group correlation among members of the yoga intervention groups while allowing the control patients to remain independent since they were not placed into groups.[38] The intraclass correlation coefficient (ICC) was estimated from the mixed models for each outcome to quantify this within-group correlation. The Kenward-Roger adjustment to the *df* was used to control type I error rates.[39] Lipopolysaccharide-stimulated cytokine responses were natural log (ln) transformed to better approximate normality of residuals. Cohen's *d* as a measure of effect size was calculated for the MFSI-SF fatigue score, SF-36 vitality scale, and CES-D depressive symptoms. Secondary analyses used frequency of continuous yoga practice in place of intervention group to account for differences in frequency of yoga practice in class and at home. For these secondary analyses, all models controlled for age and sagittal abdominal diameter (SAD)[40] as potential confounders. A

Table 1. Demographic and Medical Characteristics of Breast Cancer Survivors Randomly Assigned to Yoga or Wait-List Conditions

Characteristic	Overall (N = 200)				Yoga (n = 100)				Wait-List (n = 100)			
	No.	%	Mean	SD	No.	%	Mean	SD	No.	%	Mean	SD
Age, years			51.6	9.2			51.8	9.8			51.3	8.7
BMI, kg/m^2			27.8	5.7			27.9	5.3			27.6	6.0
SAD, cm			20.8	3.4			20.7	3.3			21.0	3.6
Race/ethnicity												
White	176	88			88	89			88	88		
Black	18	9			8	8			10	10		
Asian	5	3			3	3			2	2		
Current smoker	12	6			4	4			8	8		
Usage of cardiac medication	33	17			17	17			16	16		
CHAMPS activity, total hours/week			6.3	5.7			6.8	6.3			5.8	5.1
MFSI-SF fatigue			15.8	20.1			14.3	19.6			17.3	20.5
SF-36 vitality			46.5	20.6			48.6	20.2			44.4	20.9
CES-D depressive symptoms			10.7	8.2			10.2	8.2			11.2	8.2
Marital status												
Single	26	13			18	18			8	8		
Married	140	70			68	68			72	72		
Separated/divorced	29	14			14	14			15	15		
Widowed	5	3			0	0			5	5		
Education level												
High school or less	12	6			5	5			7	7		
Some college	49	25			27	27			22	22		
College graduate	62	31			29	29			34	34		
Postgraduate	77	38			39	39			38	38		
Employment status												
Employed full or part time	137	68			71	71			66	66		
Unemployed	35	18			15	15			20	20		
Retired	28	14			14	14			14	14		
Income level, $												
< 25,000	10	5			3	3			7	7		
25,000-< 50,000	33	17			18	18			15	15		
50,000-< 75,000	35	18			17	17			18	18		
75,000-< 100,000	46	23			23	23			23	23		
≥ 100,000	59	29			30	30			29	29		
No report	17	8			9	9			8	8		
Type of treatment												
Surgery only	26	13			13	13			13	13		
Surgery plus radiation	52	26			28	28			24	24		
Surgery plus chemotherapy	46	23			23	23			23	23		
Surgery plus radiation plus chemotherapy	76	38			36	36			40	40		

(continued on following page)

Table 1. Demographic and Medical Characteristics of Breast Cancer Survivors Randomly Assigned to Yoga or Wait-List Conditions (continued)

Characteristic	Overall (N = 200)				Yoga (n = 100)				Wait-List (n = 100)			
	No.	%	Mean	SD	No.	%	Mean	SD	No.	%	Mean	SD
Cancer stage												
0	18	9			9	9			9	9		
I	89	45			46	46			43	43		
IIA	52	26			27	27			25	25		
IIB	23	11			10	10			13	13		
IIIA	18	9			8	8			10	10		
HER2 receptor status												
Positive	35	18			18	18			17	17		
Negative	146	73			74	74			72	72		
Unknown	19	9			8	8			11	11		
Progesterone receptor status												
Positive	142	71			73	73			69	69		
Negative	49	25			23	23			26	26		
Unknown	9	4			4	4			5	5		
Estrogen receptor status												
Positive	159	80			81	81			78	78		
Negative	32	16			15	15			17	17		
Unknown	9	4			4	4			5	5		
Tamoxifen/aromatase inhibitors	143	72			72	72			71	71		
Postmenopausal	153	81			76	76			77	77		
Time since diagnosis, months			17.3	8.1			16.3	7.5			18.4	8.5
Time since treatment, months			10.9	7.9			9.9	7.1			11.8	8.5

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiological Studies–Depression; CHAMPS, Community Healthy Activities Model Program for Seniors questionnaire; HER2, human epidermal growth factor receptor 2; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; SAD, sagittal abdominal diameter; SD, standard deviation; SF-36, Short Form-36.

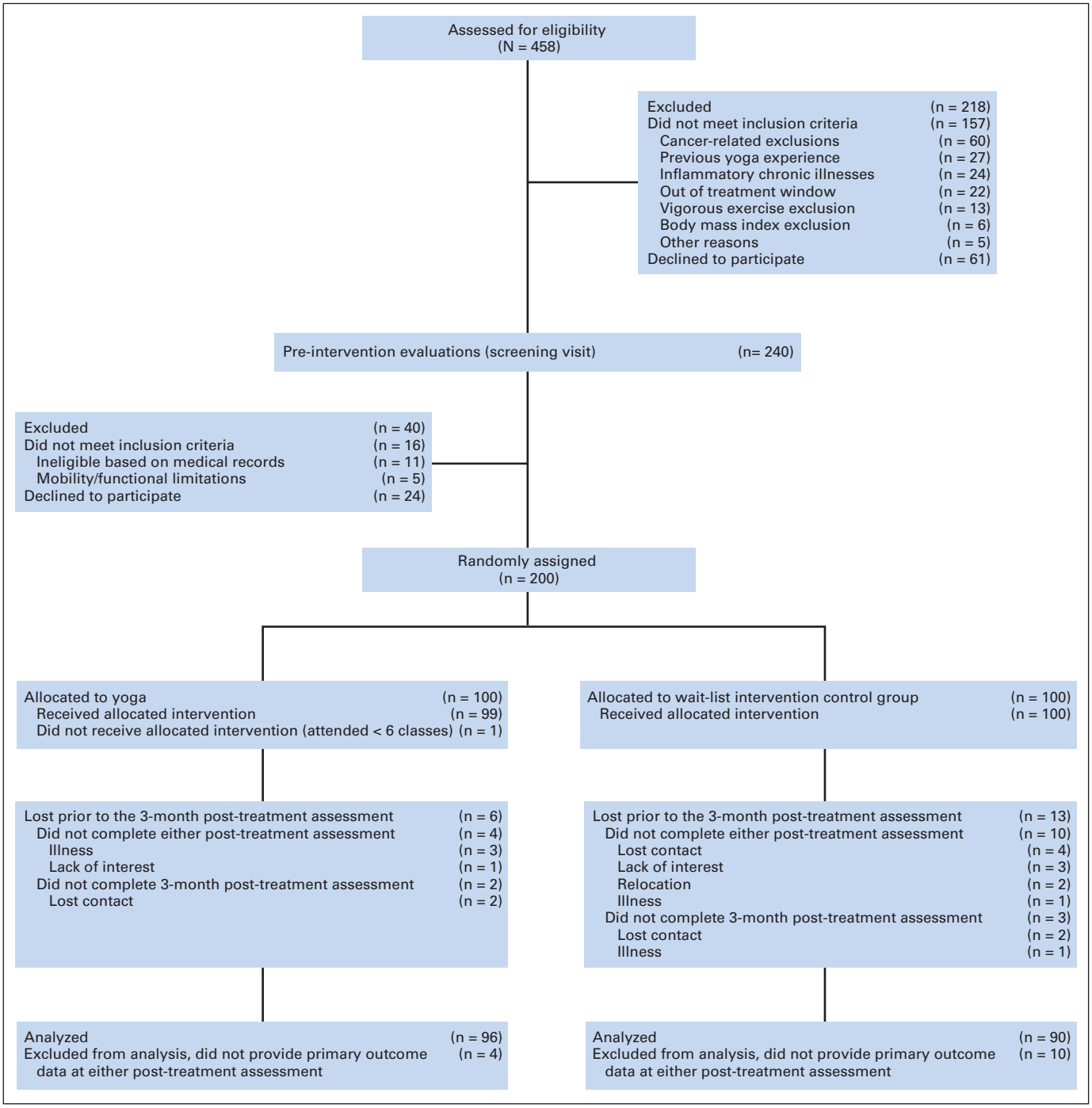

Fig 1. CONSORT diagram showing screening, random assignment, and participant flow by group.

two-sided significance level of $\alpha = .05$ was used for all tests. Analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Study Population, Baseline Data

Table 1 shows baseline characteristics of the study sample. Groups were balanced on demographic and disease-related characteristics at baseline ($P > .1$ for all tests). Importantly, there were no significant differences between groups on activity and fatigue ($P > .25$ for both) or SAD and body mass index ($P > 0.5$ for both).

Protocol Adherence

Of the 200 randomly assigned patients, 186 women received the allocated 12-week intervention and completed the immediate post-treatment assessment, and 3-month post-treatment data were obtained on 181 patients (91%; Fig 1). There were no demographic differences between women who had post-treatment data and women

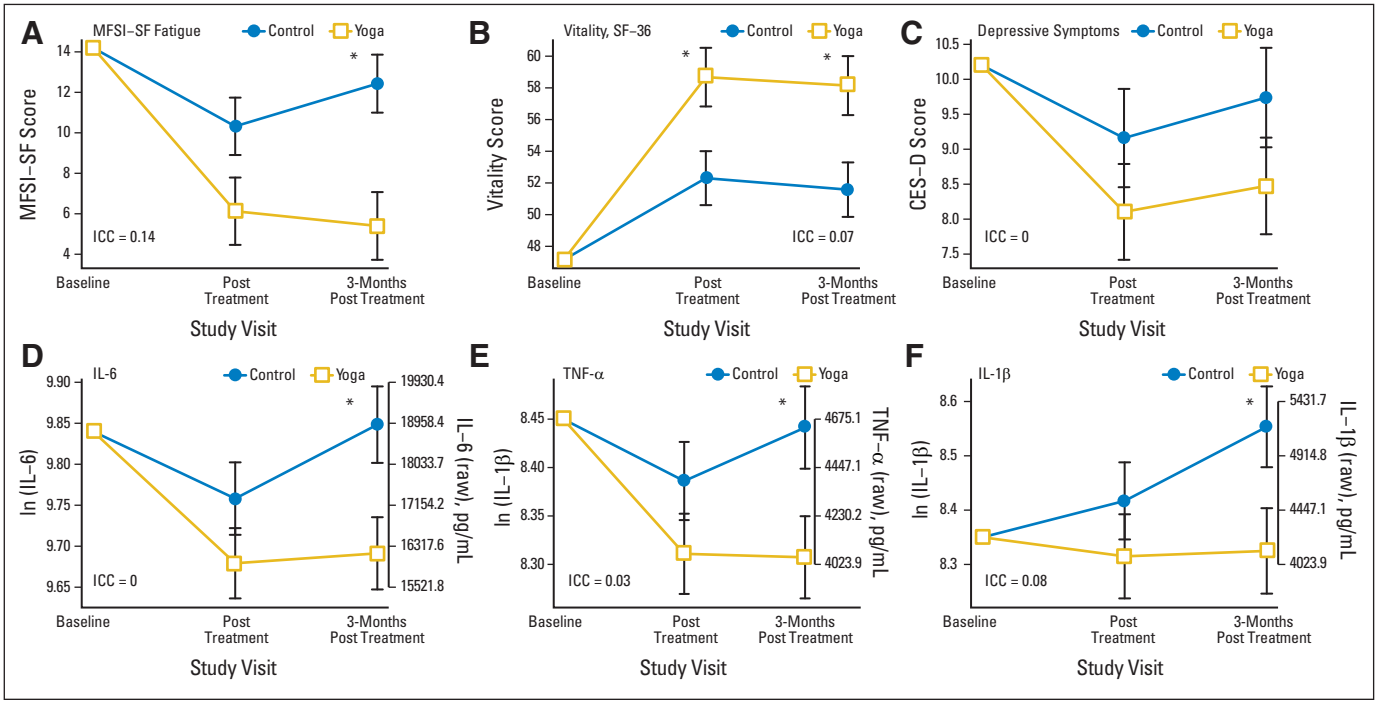

Fig 2. Changes in (A) Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) fatigue scores, (B) vitality scores (36-item short form [SF-36]), (C) depressive symptoms (Center for Epidemiological Studies–Depression [CES-D]), and (D, E, F) lipopolysaccharide-stimulated cytokine production (interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α], and interleukin-1β [IL-1β]) immediately post treatment and 3 months post treatment in the yoga and control groups. Results shown are mean ± SE from mixed models adjusting for baseline levels. All models conditioned on baseline outcome levels as specified a priori in the trial protocol. ICC, intraclass correlation coefficient. (*) $P < .05$ for group comparison. ln, natural log.

who had baseline data only (dropouts). At baseline, the dropouts had significantly higher fatigue than women with post-treatment data (27.4 *v* 14.9; $P = .02$). There were no differences for any other outcomes at baseline (vitality, depression, cytokines). However, dropout appeared to be nondifferential since there were no differences among the dropouts between the yoga and control groups.

In the yoga group, patients attended a mean of 18.1 (75.4%) of 24 classes with a median of 19 (79.1%) of 24 classes and reported an

Table 2. Change in Primary Outcomes for Each 10-Minute Increase in Frequency of Yoga Practice, Adjusting for Baseline Outcome Levels, Age, and SAD

Outcome	No. of Patients	Estimate	SE	95% CI	*P*
MFSI-SF fatigue	186				
Immediately post treatment		−1.7	0.70	−3.1 to −0.28	.019
3 months post treatment		−2.8	0.71	−4.2 to −1.4	< .001
SF-36 vitality	186				
Immediately post treatment		2.1	0.85	0.40 to 3.75	.016
3 months post treatment		2.5	0.85	0.77 to 4.14	.0045
CES-D	186				
Immediately post treatment		−0.66	0.34	−1.3 to 0.0039	.051
3 months post treatment		−0.56	0.34	−1.2 to 0.10	.098
Stimulated TNF-α*	176				
Immediately post treatment		−0.021	0.020	−0.060 to 0.018	.28
3 months post treatment		−0.038	0.020	−0.079 to 0.0021	.063
Stimulated IL-6*	176				
Immediately post treatment		−0.022	0.021	−0.063 to 0.019	.30
3 months post treatment		−0.056	0.022	−0.098 to −0.013	.01
Stimulated IL-1β*	176				
Immediately post treatment		−0.034	0.035	−0.10 to 0.035	.33
3 months post treatment		−0.078	0.036	−0.15 to −0.0074	.030

NOTE. Models used frequency of continuous yoga practice in place of group assignment to predict primary outcomes.
Abbreviations: CES-D, Center for Epidemiological Studies–Depression; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; SAD, sagittal abdominal diameter; SF-36, Short Form-36; TNF-α, tumor necrosis factor alpha.
*Stimulated cytokines are natural log transformed.

average of 24.69 minutes per day of total home plus class practice across 12 weeks. None of the women in the control group reported yoga practice during their wait-list period.

The yoga intervention was administered with high fidelity. In randomly audited sessions, an average of 97% (standard deviation, 5%) of poses were taught as scheduled.

Intervention Effects on Fatigue, Vitality, and Depressive Symptoms

Results for total fatigue, vitality, and depressive symptoms are summarized in Figure 2; unadjusted group means for all outcome variables at each of the three measurement times are available in the Appendix Table A2. After adjusting for baseline levels, mean fatigue was not significantly lower in the yoga group compared with the control group at the immediate post-treatment visit (6.1 *v* 10.3; $P = .058$; Cohen's $d = -0.22$) but was significantly lower at the 3-month post-treatment visit (5.4 *v* 12.4; $P = .002$; Cohen's $d = -0.36$). The average vitality score was higher in the yoga group at the immediate post-treatment visit (58.7 *v* 52.3; $P = .01$; Cohen's $d = 0.31$) and at the 3-month post-treatment visit (58.1 *v* 51.6; $P = .01$; Cohen's $d = 0.32$). Depressive symptoms were not significantly different between groups (immediately post treatment: 8.1 *v* 9.2; $P = .28$; Cohen's $d = -0.13$; 3-month post treatment: 8.5 *v* 9.7; $P = .21$; Cohen's $d = -0.16$).

Table 2 displays the results of preplanned secondary analyses by using yoga practice frequency (minutes per day) during the intervention in place of group assignment, controlling for age and SAD. Overall, frequency of yoga practice showed stronger associations with total fatigue, vitality, and depressive symptoms than simple group assignment, with more frequent yoga practice producing larger changes on all these dimensions (Fig 3). The association with both fatigue and vitality was stronger 3 months post-treatment. A 10-minute-per-day increase in yoga practice was associated with a 1.7-point decrease in MFSI-SF fatigue immediately post-treatment ($P = .019$) and a 2.8-point decrease at 3 months post-treatment ($P < .001$). Similarly, a 10 minute-per-day increase in yoga practice was associated with a 2.1-point increase in vitality immediately post-treatment ($P = .016$) and a 2.5-point increase at 3 months post-treatment ($P = .0045$).

Intervention Effects on Inflammation

Figure 2 shows estimated mean Kenward-Roger adjustment stimulated cytokines post-treatment, after adjusting for baseline levels. For all three cytokines, there were no significant group differences immediately post-treatment, but by 3 months post-treatment, the yoga group had significantly reduced cytokine levels compared with the control group. At 3 months post-treatment, the estimated mean ln TNF-α was 0.13 units lower for the yoga group compared with controls (13% lower TNF-α geometric mean; $P = .027$); the estimated mean ln IL-6 was 0.16 units lower for the yoga group compared with controls (15% lower IL-6 geometric mean; $P = .027$); and the yoga group also had lower mean ln IL-1β, with a group difference of 0.23 units (20% lower IL-1β geometric mean; $P = .037$).

In secondary analyses, the pattern was similar, with significant effects of the frequency of yoga practice on cytokine levels 3 months post-treatment but not immediately post-treatment (controlling for age and SAD). At 3 months post-treatment, a 10-minute-per-day increase in yoga practice was associated with a 5% decrease in the IL-6 geometric mean

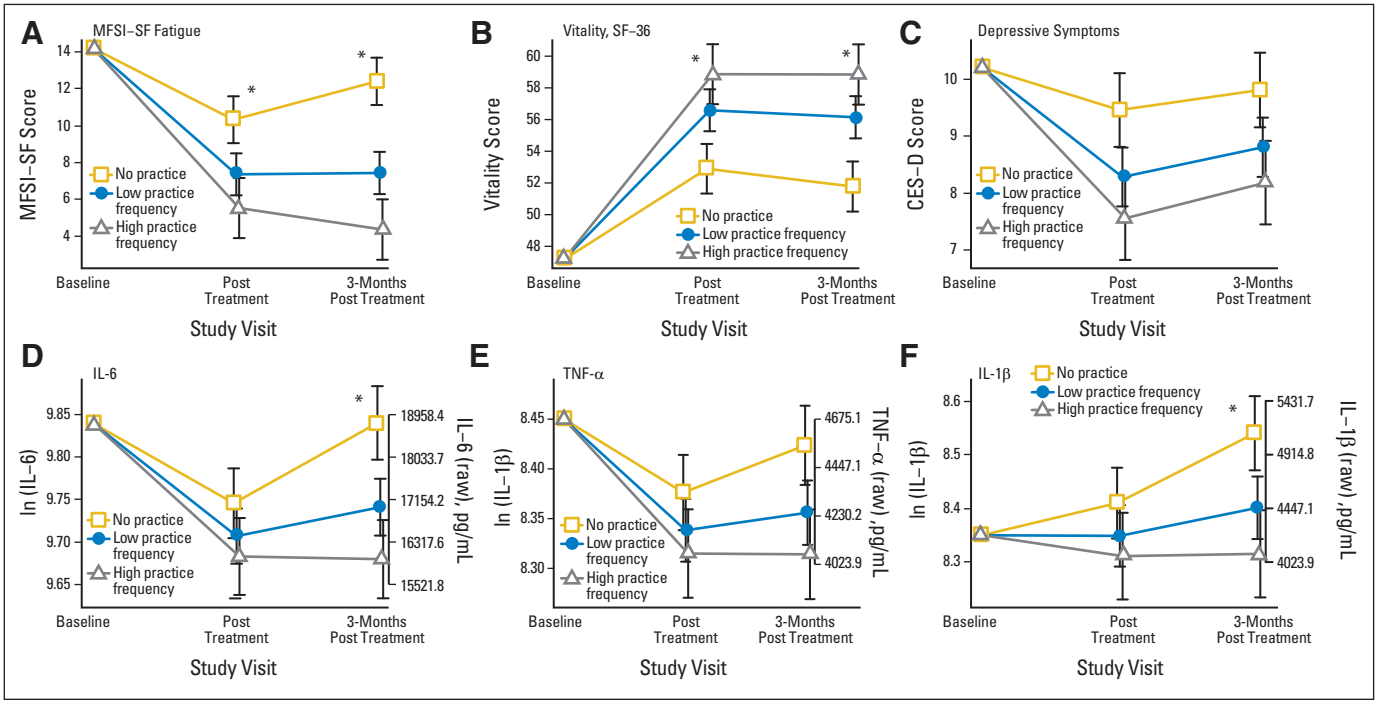

Fig 3. Changes in (A) Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) fatigue scores, (B) vitality scores (36-item short form [SF-36]), (C) depressive symptoms (Center for Epidemiological Studies–Depression [CES-D]), and (D, E, F) lipopolysaccharide-stimulated cytokine production (interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α], and interleukin-1β [IL-1β]) immediately post treatment and 3 months post treatment as a function of yoga practice frequency. Results shown are mean ± SE from mixed models adjusting for baseline levels, age, and sagittal abdominal diameter at yoga practice frequency levels of 0 minutes per day (control, no practice), 18 minutes per day (25th percentile; low practice), and 29 minutes per day (75th percentile; high practice). (*) $P < .05$ for the slope estimate in yoga practice frequency. ln, natural log.

Table 3. Group Difference in Health Behaviors and Support, Adjusted for Baseline Outcome Levels

Outcome	Control		Yoga		Group Difference			
	Least Squares Means	SE	Least Squares Means	SE	Least Squares Means	SE	95% CI	*P*
BMI, kg/m^2	27.8	0.10	27.8	0.11	0.017	0.15	−0.28 to 0.32	.91
Weight, kg	75.2	0.27	75.2	0.29	0.0068	0.40	−0.79 to 0.81	.99
Social support, ISEL total score	93.8	0.98	95.2	1.1	1.5	1.5	−1.0 to 4.5	.34
Pittsburgh Sleep Quality Index	7.0	0.23	6.3	0.22	−0.71	0.32	−1.3 to −0.082	.03
Total physical activity, hours per week	9.1	0.64	11.2	0.78	2.1	1.0	0.10 to 4.1	.04
FFQ dietary data*								
Calories, kcal/kg	25.5	0.71	24.6	0.70	−0.87	1.0	−2.8 to 1.1	.39
Fiber, g/1,000 kcal	12.4	0.33	11.9	0.33	−0.55	0.47	−1.5 to 0.38	.24
Total fat, g/1,000 kcal	36.2	0.79	35.9	0.78	−0.31	1.1	−2.5 to 1.9	.78
Protein, g/1,000 kcal	40.4	0.80	41.1	0.78	0.69	1.1	−1.5 to 2.9	.54
Saturated fat, g/1,000 kcal	12.2	0.32	12.1	0.32	−0.15	0.46	−1.1 to 0.76	.75
Monounsaturated fat, g/1,000 kcal	13.1	0.36	13.1	0.35	0.0002	0.50	1.0 to −1.0	.99
Polyunsaturated fats, g/1,000 kcal	7.6	0.19	7.5	0.18	−0.13	0.26	0.66 to 0.39	.61
Omega-3 fatty acids, g/1,000 kcal	0.87	0.029	0.87	0.029	−0.0003	0.04	−0.082 to 0.081	.99
Linoleic acid, g/1,000 kcal	0.062	0.0025	0.062	0.0024	0.0003	0.0035	−0.0067 to 0.0073	.93

NOTE. Group difference calculated as covariate-adjusted least squares means (SE). Least squares means were adjusted for baseline values, averaged across the two post-treatment visits for outcomes other than Food Frequency Questionnaire (FFQ) data.
Abbreviations: BMI, body mass index; ISEL, International Support Evaluation List.
*FFQ data were measured only once post treatment.

($P = .01$) and an 8% decrease in the IL-1β geometric mean ($P = .03$; Table 2 and Fig 3).

Health Behaviors and Support

Analyses of dietary data, body mass index, and weight did not show differential group changes (Table 3), nor did social support ($P = .34$). However, yoga group participants reported significantly improved sleep (ICC, 0; $P = .03$) compared with the control group.

The yoga group reported 1.65 more total physical activity hours per week immediately post-treatment than at baseline but returned to baseline levels 3 months post-treatment. Control participants reported 1.36 fewer hours per week immediately post-treatment, a decrease that was maintained 3 months post-treatment (ICC, 0.13; $P = .04$ for group effect). The yoga group's increased activity reflected more yoga practice, not additional activities; across the 12-week intervention, yoga participants reported a decrease in non–yoga activity ($P < .001$) from 23.78 to 12.65 minutes per day, consistent with other reports of a downward trend in physical activity among survivors.[41]

Adverse Events

Four recurrent breast cancers (two per group) were not considered intervention related. Two events appeared potentially attributable to the yoga intervention: two women reported the recurrence of chronic back and/or shoulder problems.

DISCUSSION

Yoga practice substantially reduced fatigue and inflammation. Immediately post-treatment, vitality was higher in the yoga group compared with the control group. At 3 months post-treatment, the yoga group's fatigue was lower, vitality was higher, and IL-6, TNF-α, and IL-1β were lower for yoga participants compared with controls. More frequent practice produced greater benefits in fatigue, vitality, and inflammation.

This is the first physical activity trial with breast cancer survivors to show significant inflammatory changes. Indeed, although observational studies reliably show that people who report more frequent and more intense physical activity have lower inflammation than their sedentary counterparts,[7,10] RCT data demonstrating that exercise training reduces inflammation are sparse and inconsistent.[42,43] The discrepancies are a function of underpowered trials, differences in how much the interventions altered body fat, disparities in intensity and duration, participants' variable levels of baseline inflammation, and absent or inappropriate control groups.[43] In fact, two recent reviews concluded that exercise RCTs produce little or no change in inflammatory markers in healthy people who do not lose weight.[42,43]

Despite the fact that our participants' weight did not change and our trial did not include aerobic or resistance exercise, cytokine production decreased significantly in yoga participants compared with the wait-list group. Blood mononuclear cells provide a direct source for data on whole body inflammation, and their function may provide a proxy for inflammatory responses of macrophages in adipose tissue.[10] Leukocyte cytokine production increases with age,[7] and persistent subclinical inflammation appears to increase risk for chronic disease and disability among older adults.[5-7,44-47] In related work, reductions in leukocyte nuclear factor kappa B activity followed participation in a yogic meditation intervention[48]; those data suggest one possible mechanism for the inflammatory changes we observed that persisted through 3 months post-treatment.

Among the many cancer-related fatigue treatments, exercise has been the most consistently beneficial. Our effect sizes for fatigue and depressive symptoms are comparable to those reported in meta-analyses for aerobic and/or resistance exercise,[49,50] suggesting that yoga confers similar benefits on these dimensions. These meta-analyses show that

better adherence is associated with greater improvement, paralleling our yoga practice frequency results.

Up to 60% of cancer survivors report sleep problems during survivorship, a rate that is two or three times as high as that in similar adults without a cancer history.[51,52] Disturbed sleep elevates inflammation as well as fatigue,[52,53] and thus the improved sleep reported by yoga group participants likely contributed to the positive changes on these dimensions, as well as their continuance through the 3-month post-treatment visit.

Strengths of this study include excellent adherence with minimal attrition; only 9% failed to complete the full trial. Randomization produced groups that were well-balanced on all key dimensions. Adverse effects were infrequent.

We did not compare the yoga group to an active control group, and it is possible that increased attention or group support produced nonspecific treatment benefits,[20] a limitation. However, yoga participants did not report the changes in social support that would be expected if support were a key mechanism. In addition, women who practiced yoga more frequently showed greater improvements in inflammation, mood, and fatigue than those who practiced less frequently, and these dose-response effects support yoga's efficacy rather than nonspecific treatment benefits.

Fatigue and depressive symptoms were not used as part of the inclusion criteria, and thus women who were less fatigued and less depressed had less room to show positive change,[20] another limitation. Accordingly, our data may underestimate yoga's potential benefit.

Persistent subclinical inflammation appears to enhance risk for chronic disease and disability among older adults.[5-7,44-47] Cancer survivors have a greater risk for secondary cancers as well as several chronic diseases, including cardiovascular disease, diabetes, and osteoporosis compared with individuals without a cancer history.[54,55] Chronic inflammation has been linked to a spectrum of health problems including cancer, cardiovascular disease, diabetes, and osteoporosis.[46,56] In fact, more globally, chronic inflammation has been suggested as one key biologic mechanism that may fuel fatigue as well as declines in physical function leading to frailty and disability.[5-9,16] If yoga dampens or limits fatigue and inflammation, then regular practice could have substantial health benefits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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GLOSSARY TERMS

cytokines: Cell communication molecules that are secreted in response to external stimuli.

interleukin-6 (IL-6): Produced predominantly by activated immune cells such as microglia. IL-6 is involved in the amplification of inflammatory reactions.

TNF-α (tumor necrosis factor alpha): A cytokine with pleiotropic activities. TNF-α (originally called cachexin) is secreted by several types of cells (eg, macrophages, monocytes, neutrophils, T cells) and in response to a variety of stimuli (eg, interferons, interleukin-2, platelet-activating factor). It acts as a cytolytic and cytostatic agent on several cell types. In addition, by promoting thrombotic processes, TNF-α is significantly involved in pathologic processes, including venous thromboses and arteriosclerosis. It is also a potent activator of angiogenesis in vivo.

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Appendix

Table A1. Yoga Poses and Timing Across the Intervention

Pose	Benefits	Week 1/2	3/4	5/6	7/8	9/10	11/12	Total Classes
On the floor								
Pavana Muktasana (releasing of the winds pose)		X	X	X	X	X	X	24
Pavana Muktasana with arms reaching overhead	U		X	X	X	X	X	20
Supta Padangusthasana (reclined big toe pose)		X	X	X	X	X	X	24
Active Setu Bandha Sarvangasana (bridge pose)	U, D, F,			X		X		8
Jathara Parivartanasana (abdomen turning pose)	U, I		X		X		X	12
Balasana (child's pose)	F		X	X	X	X		16
Vajrasana (puppy pose)	U	X		X		X		12
Marjarasana (cat-cow pose)	I	X		X				8
Bhujangasana (cobra pose)	D	X		X			X	12
Adho Mukha Svanasana (downward facing dog pose)	I		X	X	X	X		16
Standing								
Mukha Svanasana (dog pose) standing	U, D, I	X	X		X			12
Chaturanga Dandasana (four-limb staff pose) at wall	U					X	X	8
Arm(s) up wall, side to wall, or facing wall	U	X	X	X	X		X	20
Chest stretch	U		X	X	X	X		16
Prasarita Padottanasana (wide-leg forward extension)	U, D, I			X		X		8
Tadasana (mountain pose)	D, U	X	X	X	X	X	X	24
Seated (in chair or on blankets on floor)								
Seated twist with legs in Sukhasana (simple pose)	I	X		X		X		12
Janushirasana (head-to-knee pose)	D, I		X		X		X	12
Paschimottanasana (full forward bend)	I		X		X		X	12
Restorative								
Savanasana (corpse pose)	D, F, I	X	X	X	X	X	X	24
Supta Baddha Konasana (reclined bound angle pose)	D, F, I		X		X		X	12
Viparita karani (restful inversion)	D, F, I	X	X	X	X	X	X	24
Supported Setu Bandha Sarvangasana (bridge pose)	U, D, F, I	X		X		X		12
Breathing practices								
Deerga Swasam (3-part breath)	D, I		X	X	X	X	X	20
Ujjayi (extreme conquering) breathing	D, F, I			X		X		8
Nodi Sodhana (alternate nostril) breathing	D, I				X		X	8
Prana Sukha (breath of joy)	D, I		X	X	X	X	X	20

Abbreviations: D, depression; F, fatigue; I, immune function; U, upper body.

Table A2. Unadjusted Group Means at Each Time Point for Each Primary Outcome

Outcome	No. of Patients	Group Effects on Primary Outcomes								
		Control		Yoga		Group Difference				
		Unadjusted Least Squares Mean	SE	Unadjusted Least Squares Mean	SE	Unadjusted Least Squares Mean	SE	95% CI	*P**	ICC
MFSI-SF fatigue	200									0
Baseline		17.3	2.0	14.3	2.0	−3.0	2.8	−8.6 to 2.5	.28	
Immediate post treatment		12.7	2.0	6.3	2.0	−6.3	2.9	−12.0 to −0.68	.028	
3 months post treatment		14.7	2.0	5.8	2.0	−9.0	2.9	−14.7 to −3.3	.002	
Energy scale (SF-36; vitality)	200									0.1
Baseline		44.4	2.0	48.1	2.4	3.7	3.2	−2.6 to 10.1	.24	
Immediate post treatment		50.7	2.1	58.9	2.4	8.3	3.2	1.8 to 14.7	.01	
3 months post treatment		49.9	2.1	58.3	2.5	8.3	3.2	1.8 to 14.8	.01	
CES-D	200									0.01
Baseline		11.2	0.083	10.3	0.87	−0.94	1.2	−3.3 to 1.4	.44	
Immediate post treatment		9.8	0.86	8.1	0.88	−1.7	1.2	−4.1 to 0.75	.17	
3 months post treatment		10.4	0.87	8.5	0.88	−1.8	1.2	−4.3 to 0.64	.15	
TNF-α†	199									0.06
Baseline		8.44	0.043	8.45	0.048	0.012	0.065	−0.12 to 0.14	.85	
Immediate post treatment		8.38	0.046	8.30	0.049	−0.077	0.067	−0.21 to 0.056	.25	
3 months post treatment		8.43	0.048	8.30	0.050	−0.13	0.069	−0.26 to 0.0097	.068	
IL-6†	200									0
Baseline		9.84	0.047	9.83	0.047	−0.0042	0.067	−0.14 to 0.13	.95	
Immediate post treatment		9.76	0.050	9.67	0.049	−0.088	0.070	−0.23 to 0.049	.21	
3 months post treatment		9.83	0.052	9.69	0.050	−0.14	0.072	−0.28 to 0.0033	.056	
IL-1β†	200									0.09
Baseline		8.25	0.071	8.39	0.083	0.14	0.11	−0.072 to 0.36	.19	
Immediate post treatment		8.37	0.076	8.33	0.085	−0.048	0.11	−0.27 to 0.18	.67	
3 months post treatment		8.49	0.079	8.34	0.086	−0.16	0.12	−0.39 to 0.077	.19	

Abbreviations: CES-D, Center for Epidemiological Studies–Depression; ICC, intraclass correlation coefficient; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MFSI-SF, Multidimensional Fatigue Symptom Inventory–Short Form; SF-36, Short Form-36; TNF-α, tumor necrosis factor alpha.

*P value for group by visit interaction: MFSI-SF fatigue, $P = .014$; SF-36 vitality scale, $P = .10$; CES-D depressive symptoms, $P = .66$; TNF-α, $P = .087$; IL-6, $P = .18$; IL-1β, $P = .03$.

†Stimulated cytokines are natural log-transformed.