Original Article

Mindfulness Meditation for Younger Breast Cancer Survivors: A Randomized Controlled Trial

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BACKGROUND: Premenopausal women diagnosed with breast cancer are at risk for psychological and behavioral disturbances after cancer treatment. Targeted interventions are needed to address the needs of this vulnerable group. **METHODS:** This randomized trial provided the first evaluation of a brief, mindfulness-based intervention for younger breast cancer survivors designed to reduce stress, depression, and inflammatory activity. Women diagnosed with early stage breast cancer at or before age 50 who had completed cancer treatment were randomly assigned to a 6-week Mindful Awareness Practices (MAPS) intervention group (n = 39) or to a wait-list control group (n = 32). Participants completed questionnaires before and after the intervention to assess stress and depressive symptoms (primary outcomes) as well as physical symptoms, cancer-related distress, and positive outcomes. Blood samples were collected to examine genomic and circulating markers of inflammation. Participants also completed questionnaires at a 3-month follow-up assessment. **RESULTS:** In linear mixed models, the MAPS intervention led to significant reductions in perceived stress ($P = .004$) and marginal reductions in depressive symptoms ($P = .094$), as well as significant reductions in proinflammatory gene expression ($P = .009$) and inflammatory signaling ($P = .001$) at postintervention. Improvements in secondary outcomes included reduced fatigue, sleep disturbance, and vasomotor symptoms and increased peace and meaning and positive affect ($P < .05$ for all). Intervention effects on psychological and behavioral measures were not maintained at the 3-month follow-up assessment, although reductions in cancer-related distress were observed at that assessment. **CONCLUSIONS:** A brief, mindfulness-based intervention demonstrated preliminary short-term efficacy in reducing stress, behavioral symptoms, and proinflammatory signaling in younger breast cancer survivors. ***Cancer*** **2015;121:1231-40.** © *2014 American Cancer Society.*

KEYWORDS: mindfulness, breast cancer, inflammation, premenopausal, stress.

INTRODUCTION

Breast cancer is the most common cancer in women and the leading cause of death in women aged <55 years. Approximately 25% of breast cancer cases occur premenopausally.[1] The management of younger women presents many challenges, because the diagnosis often comes at a time when women are in the midst of child-rearing and career development and believe they are "too young" to be confronting a life-threatening illness. In empirical studies, younger women report increased psychological stress and depression, fatigue, sleep disturbance, and vasomotor symptoms after cancer diagnosis relative to older women.[2-5] Furthermore, younger women perceive cancer as more threatening[6] and report greater fear of recurrence.[7]

Despite their high levels of distress, very few interventions have been developed for younger breast cancer survivors. Indeed, we identified only 2 nonpharmacologic, randomized controlled trials focusing on younger women.[8,9] Thus, interventions are required that specifically address the emotional and physical needs of this vulnerable group. This is particularly important, as younger survivors report feeling more isolated and less satisfied with traditional support groups because of their age.[10] Mindfulness meditation has emerged as a promising intervention for cancer populations[11-13] and may be a particularly good option for younger survivors given their interest in mind-body treatments.[14] Mindfulness involves bringing attention to an individual's present moment experiences, including thoughts, feelings, and physical sensations, with openness, curiosity, and acceptance.[15] Interventions have been developed to cultivate mindfulness through formal meditation and informal practice, and randomized controlled trials have documented the benefits of mindfulness-based interventions among breast cancer survivors, including improvements in depressive symptoms, stress, and fatigue.[16-20]

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However, to our knowledge, the feasibility and efficacy of mindfulness interventions specifically for younger women have not been examined.

In addition, the effects of mindfulness on key biologic and psychological processes relevant for breast cancer survivorship are unclear. These include inflammation, which is involved in cancer growth and progression[21] and may also contribute to behavioral problems in breast cancer survivors.[22] Inflammatory processes are regulated in part by signals from the central nervous system, including stress hormones,[23] and individuals who report higher levels of stress and depression also exhibit elevations in inflammatory activity.[24,25] Thus, interventions that reduce stress could potentially lead to reductions in inflammation. There is preliminary evidence from nonrandomized trials that mindfulness may have beneficial effects on proinflammatory cytokine production in cancer patients.[26] However, these effects have not been evaluated in a randomized trial, nor have the effects of mindfulness on the molecular processes that regulate cytokine production been examined. Furthermore, very few trials have examined the effects of mindfulness on positive psychological outcomes, such as positive affect and meaning/purpose in life, although these are increasingly recognized as important dimensions of quality of life in cancer survivorship.[27]

The current randomized controlled trial was designed to evaluate the feasibility and efficacy of a mindfulness-based intervention for women who had been diagnosed with breast cancer at or before age 50 years. The primary outcomes were perceived stress and depressive symptoms, which are elevated in younger breast cancer survivors and are targeted by this treatment. Effects on inflammatory activity also were assessed, focusing on proinflammatory gene expression and associated transcription factors. We also explored the effects on secondary outcomes that are known to be concerns for younger survivors and are relevant for quality of life, including behavioral symptoms, cancer-related distress, and positive psychological processes.

MATERIALS AND METHODS

Design

This was a single-center, 2-armed randomized controlled trial that took place at the University of California-Los Angeles (UCLA) Medical Center (Los Angeles, Calif) between March 2011 and October 2012. The UCLA Institutional Review Board approved study procedures, and written informed consent was obtained from participants. The ClinicalTrials.gov Identifier for this trial is NCT01558258.

Participants

Participants were recruited through invitations to women who had enrolled in an earlier study,[28] physician referrals, and Internet recruitment. Interested women completed a telephone screening to determine eligibility. Inclusion criteria were: 1) diagnosis with stage 0, I, II, or III breast cancer at or before age 50 years; and 2) completed local and/or adjuvant cancer therapy (except hormone therapy) at least 3 months previously. We included women up to 10 years after cancer treatment, because the need for and benefits from stress management are not time-limited. Exclusion criteria were: 1) breast cancer recurrence, metastasis, or another cancer diagnosis (excluding nonmelanoma skin cancer); 2) active, uncontrolled medical illness that could impact inflammation; and 3) inability to commit to the intervention schedule.

Randomization

Given class scheduling considerations, participants were randomized in blocks. Once a sufficient number of participants to comprise the mindfulness and control groups (8-14 women) had been screened as eligible and had completed the baseline assessment, they were randomized (4:3) to the intervention group or the wait-list control group, with slightly more women allocated to the intervention group to maintain adequate group size. Randomized condition assignments were kept in sealed envelopes in the research office, according to Consolidated Standards of Reporting Trials guidelines.

Assessments

In-person assessments were conducted before and within 1 or 2 weeks after the intervention. At each assessment, participants completed questionnaires and provided fasting blood samples at morning appointments. The posttreatment assessment was the primary endpoint of the trial. A follow-up questionnaire packet was mailed to participants 3 months after the intervention to assess the persistence of treatment effects.

Intervention

The intervention was based on the Mindful Awareness Practices (MAPs) program at UCLA (http://marc.ucla.edu; accessed November 10, 2014) and was tailored for younger survivors by including information about maintaining health and preventing breast cancer recurrence. Participants met for 6 weekly, 2-hour group sessions that included presentations of theoretical materials on mindfulness,

relaxation, and the mind-body connection; experiential practice of meditation and gentle movement exercises (eg, mindful walking); and a psychoeducational component for cancer survivors. Lectures, discussions, and group processes focused on solving problems concerning impediments to effective practice, working with difficult thoughts and emotions, managing pain, and cultivation of loving kindness. Home practice is a key component of MAPs, and the participants were instructed to practice mindfulness techniques on a daily basis, beginning with 5 minutes daily and increasing to 20 minutes daily. In the final class, participants were encouraged to continue practicing, both formally and informally, and were given instructions for doing so.

The wait-list condition controlled for naturally occurring changes in stress and other outcomes over the assessment period. After the 3-month follow-up assessments were completed, those assigned to the control group were offered participation in the MAPs classes.

Psychological and Behavioral Outcomes

The primary psychological outcomes were perceived stress[29] and depressive symptoms.[30] Secondary outcomes included fatigue,[31] sleep quality,[32] musculoskeletal pain,[33] and menopausal symptoms (ie, hot flashes and night sweats).[33] Cancer-specific distress was assessed using measures of fear of cancer recurrence[34] and cancer-related intrusive thoughts.[35] Positive psychological outcomes included positive affect[36] and meaning and purpose in life.[37] All were assessed at baseline, postintervention, and at the 3-month follow-up.

Self-reported demographic and disease-related variables were assessed at baseline. To assess home practice, participants in the mindfulness condition completed daily reports of the number of minutes they engaged in formal mindfulness practice each day over the 6-week intervention period. At the 3-month follow-up assessment, they were asked to indicate how many days they had meditated for at least 5 minutes in the past week.

Inflammatory Outcomes

The primary biologic outcomes were functional genomic markers of inflammation, which may be more sensitive to intervention effects than "noisier" circulating markers.[38] Genomic outcomes were: 1) expression of a set of 19 proinflammatory gene transcripts previously identified as up-regulated in the context of chronic stress,[23] and 2) promoter-based bioinformatics measures of the activity of the proinflammatory transcription factor nuclear factor κB (NF-κB), a key regulator of proinflammatory cytokine production. Secondary bioinformatics analyses also assessed the activity of 3 other a priori-selected, inflammation-related transcription factors: the anti-inflammatory glucocorticoid receptor (GR), cyclic adenosine monophosphate response element-binding (CREB) family factors, and type I interferon response factors. RNA was extracted (RNEasy; Qiagen, Hilden, Germany) from peripheral blood mononuclear cells, which were isolated from 10-mL venipuncture samples collected into sodium heparin Vacutainers, then was tested for suitable mass (Nanodrop ND1000; Thermo Scientific, Wilmington, Del) and integrity (Agilent Bioanalyzer; Agilent Technologies, Santa Clara, Calif) and subjected to genome-wide transcriptional profiling using Illumina HT-12 v4 BeadArrays in the UCLA Neuroscience Genomics Core according to the manufacturer's standard protocol (Illumina Inc., San Diego, Calif). Quantile-normalized gene expression values were log2-tranformed before analysis.

Circulating markers of inflammation were also assessed, including interleukin 6 (IL-6), C-reactive protein (CRP), and soluble tumor necrosis factor (TNF) receptor type II (sTNF-RII) (a marker of TNF activity), which have been linked to the psychological and behavioral outcomes of interest[39] and to breast cancer progression[40] and may be influenced by mind-body interventions.[38,41] Blood samples for circulating markers were collected by venipuncture into ethylene diamine tetra-acetic acid tubes, placed on ice, centrifuged for acquisition of plasma, and stored at -80°C for subsequent batch testing. Plasma levels of IL-6 and CRP were determined by using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minn, for IL-6; Immun Diagnostik, American Laboratory Products Company [ALPCO], Salem, NH, for CRP), and levels of sTNF-RII were determined using a regular ELISA (R&D Systems), as previously described.[42] All samples were run in duplicate, and samples for an individual participant were run in parallel to avoid interassay variability. Inflammatory markers were log-transformed before analysis to normalize distributions, and 1 outlier for CRP was removed from the analysis (CRP = 50 μg/L).

Statistical Analyses

Specifying an α value of .05 and assuming 85% retention, we estimated that sample sizes of 40 and 30 in the intervention and control arms, respectively, would provide 80% power to detect a standardized effect size of .6, which was the expected effect size based on results from other mindfulness-based trials in cancer populations.[11] Primary intent-to-treat analyses were conducted using linear mixed

effects models to allow the inclusion of all available data. The model included group assignment (mindfulness, wait list), time (baseline, postintervention, and 3-month follow-up for questionnaire-based outcomes) with control covariates as fixed effects and a random intercept for participants. Genomic analyses also included standard RNA indicators of major leukocyte subset prevalence (*CD3D*, *CD3E*, *CD4*, *CD8A*, *CD19*, *NCAM1*/CD56, *FCGR3A*/CD16, and *CD14*) as covariates. The *group* × *time* interaction at postintervention was the primary effect of interest. Analyses were conducted using the SAS 9.1 (SAS Institute, Inc., Cary, NC) and Stata 12 (StataCorp, College Station, Tex) software packages.

Group differences in transcription factor activity were assessed using Transcription Element Listening System (TELiS) promoter-based bioinformatics analyses, in which the ratio of response element frequencies in the promoters of up-regulated genes versus down-regulated genes was taken as a measure of differential activity of transcription control pathways, and (log) ratios were averaged over 9 different parametric combinations of promoter length (−300, −600, and −1000 to +200 base pairs upstream of RefSeq-designated transcription start site) and motif detection stringency (TRANSFAC [Transcription Factor Database, Biobase, Wolfenbuttel, Germany] mat_sim values of .80, .90, and .95) to ensure robust results.[43] To identify the primary cellular sources of differentially expressed genes, we conducted Transcript Origin Analysis.[44] Both TELiS and Transcript Origin Analysis were based on genes that exhibited >1.2-fold differential change in expression over time in the mindfulness group versus the control group.

Exploratory analyses evaluated the dose-response relation between mindfulness practice and changes in the primary psychological outcomes and circulating inflammatory markers among intervention group participants. Linear regression models tested whether number of minutes practiced (including class time and home practice) was associated with postintervention values on the outcome of interest, controlling for baseline levels of that outcome.

RESULTS

We screened 151 women for eligibility and randomized 71 to either the intervention group (n = 39) or a wait-list control group (n = 32) (see Fig. 1). All women completed baseline questionnaires, although blood samples were not obtained from 6 women at baseline because of difficulties with venipuncture. Sixty-five participants completed the post-treatment questionnaire, yielding a follow-up rate of 92% at the primary endpoint. Fifty-nine participants (83%) completed the 3-month follow-up questionnaire. Groups were comparable at baseline on most demographic and disease-related variables (Table 1). Women in the intervention group were less likely to be married and were more likely to have received radiation and/or to have a history of smoking than women in the control group ($P \leq .10$). Women in the control group also reported higher depressive symptoms (see Table 2). These variables were included as covariates in all analyses, with the exception of analyses with the Center for Epidemiologic Studies Depression Scale (CES-D) score as the outcome variable, which already included all CES-D measurements as dependent variables. Across groups, the percentage of women who endorsed clinically significant depressive symptoms (as indicated by scores greater than or equal to 16 on the CES-D) was 48%.

Among the 38 women who received the mindfulness intervention (defined as attending 2 or more classes), the mean number of classes attended was 5.24 (range, 2-6 classes), and the total number of minutes of mindfulness practice during the 6-week intervention period (including time spent in the mindfulness classes and home practice) was 897 minutes (range, 305-1527 minutes). At the 3-month follow-up assessment, 8 of the 31 respondents (25%) indicated that they had not meditated, 7 (23%) indicated that they had meditated on 1 or 2 days, 9 (29%) indicated that they had meditated on 3 or 4 days, and 7 (23%) indicated that they had meditated on 5 to 7 days in the past week.

Intervention Effects at Postintervention

Adjusted means for psychological and behavioral outcomes are listed in Table 2. The mindfulness intervention led to significant reductions in perceived stress from preintervention to postintervention relative to the wait-list control group ($P = .004$ for group × time interaction) (see Fig. 2). A similar trend was observed for depressive symptoms ($P = .095$). The effect sizes for changes in perceived stress and depression were .67 and .54, respectively. Similar *P* values emerged from analyses that were adjusted for multiplicity using the Hommel procedure ($P = .008$ for perceived stress; $P = .095$ for depression). In terms of secondary outcomes, mindfulness led to significant improvements in fatigue ($P = .007$), subjective sleep disturbance ($P = .015$), and hot flashes/night sweats ($P = .015$) from preintervention to postintervention relative to controls. Mindfulness also led to significant increases in positive affect ($P = .03$) and peace and meaning ($P = .001$). Effects on other self-reported outcomes

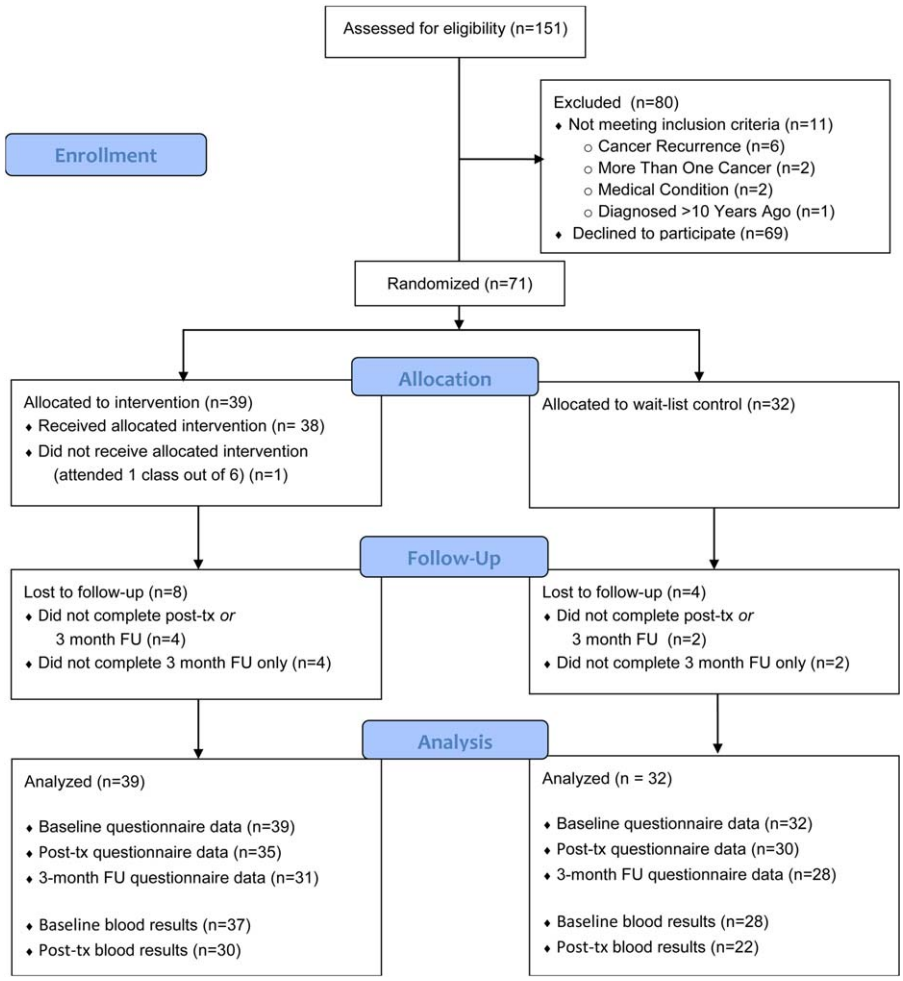

Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram of the current trial. FU indicates follow-up; tx, treatment.

were not significant. Analyses controlling for additional covariates, including time since diagnosis, chemotherapy, and endocrine therapy, yielded comparable results.

In genome-wide transcriptional profiling of peripheral blood mononuclear cell samples, primary analyses of a 19-transcript composite of proinflammatory genes revealed a significantly greater decline from baseline to postintervention in the mindfulness group versus the control group ($P = .009$ for group $\times$ time interaction) (see Fig. 3A). Across all transcripts assayed, 24 genes exhibited >1.2-fold greater up-regulation over time in the mindfulness group versus the control group, and 42 genes exhibited >1.2-fold greater down-regulation (individual genes are listed in Table 3). TELiS promoter-based bioinformatics analyses implicated reduced activity of the proinflammatory transcription factor NF-κB ($P = .0016$) and increased activity of anti-inflammatory GR ($P = .018$) in structuring these empirical differences in gene expression (Fig. 3B). The results also indicated increased activity of transcription factors involved in type I interferon signaling ($P = .007$) and a nonsignificant reduction in the activity of CREB family transcription factors ($P = .143$). Parallel transcript origin analyses identified monocytes and plasmacytoid dendritic cells as the primary cellular context for down-regulated genes and B lymphocytes as the primary cellular context for up-regulated genes ($P < .01$ for all) (Fig. 3C). Similar results emerged in analyses that also controlled for age, body mass index, chemotherapy, endocrine therapy, white/non-white race, and years postdiagnosis. The sole exception was the indicated reduction in GR signaling activity, which failed to reach statistical significance in the additionally adjusted analyses ($P = .766$).

TABLE 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	MAPS Group, n = 39	Control Group, n = 32
Age: Mean (range), y	46.1 (28.4-60)	47.7 (31.1-59.6)
Time since diagnosis: Mean ± SD, y	4.0 ± 2.4	4.1 ± 2.3
Ethnicity, no. of patients		
White	29	25
African American	1	1
Asian	3	5
Other	6	1
Married, %[a]	56	75
Education, %		
<College	13	22
College graduate	23	25
>College	64	53
Employed full- or part-time, %	80	63
Income >$100K, %	62	58
Received chemotherapy, %	77	69
Received herceptin, %	21	31
Received radiation, %[a]	77	56
Currently on endocrine therapy, %	62	66
Smoking history, %		
Ever smoked[a]	28	53
Currently smoke	5	13

Abbreviations: MAPS, Mindful Awareness Practices; SD, standard deviation.
[a] For this variable, there was a chance imbalance between groups, as indicated by $P < .10$ (chi-square test or 2-sample t test).

There were no significant intervention effects for CRP, IL-6, or sTNF-RII ($P > .20$ for all). Adjusted means for circulating inflammatory markers are listed in Table 4.

Intervention Effects at the 3-Month Follow-Up Assessment

Secondary analyses examined intervention effects at the 3-month follow-up (Table 2). There were no group differences in change from the baseline assessment to the 3-month follow-up assessment for perceived stress or depressive symptoms (see Fig. 2). Similarly, there were no group differences in change from baseline to 3-month follow-up for physical symptoms or positive affect. However, there was a significant group difference for fear of recurrence ($P = .048$ for group × time interaction) and cancer-related intrusive thoughts ($P = .002$): women in the mindfulness group exhibited significantly greater decreases in these outcomes at the 3-month follow-up assessment than controls. The mindfulness group also had marginally greater increases in peace and meaning at the 3-month follow-up ($P = .069$).

Mindfulness Practice as a Predictor of Primary Outcomes

Exploratory analyses revealed that intervention group participants who practiced mindfulness more frequently (including attending classes and home practice) had lower levels of IL-6 at the postintervention assessment, controlling for baseline IL-6 levels ($P = .025$). Minutes of practice were not associated with stress, depressive symptoms, or other inflammatory markers ($P > .05$ for all).

TABLE 2. Adjusted Means and Results for Psychological and Behavioral Outcomes[a]

	Baseline, n = 71		Postintervention, n = 65			3-Month Follow-Up, n = 59		
	Mean Score ± SD		Mean Score ± SD			Mean Score ± SD		
Outcome	MAPS Group	Control Group	MAPS Group	Control Group	P[b]	MAPS Group	Control Group	P[c]
Primary outcomes								
Perceived stress: PSS	18.05 ± 0.99	18.42 ± 1.12	14.25 ± 1.04	19.15 ± 1.14	**.004**	17.42 ± 1.09	18.21 ± 1.16	.796
Depressive symptoms: CES-D	14.50 ± 1.58	19.25 ± 1.75	9.99 ± 1.64	18.47 ± 1.80	.095	14.17 ± 1.70	17.92 ± 1.82	.664
Secondary outcomes								
Fatigue: FSI	4.18 ± 0.24	3.56 ± 0.26	3.61 ± 0.25	4.08 ± 0.27	**.007**	4.15 ± 0.26	3.30 ± 0.27	.572
Sleep quality: PSQI	8.13 ± 0.62	8.39 ± 0.70	6.48 ± 0.65	8.70 ± 0.71	**.015**	7.27 ±0.67	7.86 ± 0.72	.647
Pain: BCPT	1.31 ± 0.17	1.56 ± 0.19	1.27 ± 0.17	1.37 ± 0.19	.444	1.17 ±0.18	1.38 ± 0.19	.881
Hot flashes/night sweats: BCPT	1.24 ± 0.19	1.31 ± 0.22	0.94 ± 0.20	1.53 ± 0.22	**.015**	1.20 ±0.20	1.22 ± 0.22	.827
Fear of recurrence: QLACS	11.61 ± 0.86	10.68 ± 0.94	9.67 ± 0.88	10.42 ± 0.96	.128	8.94 ±0.91	10.26 ± 0.97	**.048**
Intrusive thoughts: IES	1.59 ± 0.17	1.39 ± 0.19	1.34 ± 0.18	1.34 ± 0.20	.385	1.12 ± 0.18	1.67 ± 0.20	**.002**
Positive affect: PANAS-PA	29.60 ± 1.03	31.65 ± 1.15	31.99 ± 1.08	30.50 ± 1.18	**.033**	29.94 ± 1.13	31.99 ± 1.20	.996
Meaning and peace: FACIT	16.86 ± 0.60	17.95 ± 0.67	18.43 ± 0.63	16.53 ± 0.69	**.001**	18.26 ± 0.65	17.65 ± 0.70	.069

Abbreviations: BCPT, Breast Cancer Prevention Trial Symptom Checklist; CES-D, Center for Epidemiologic Studies Depression Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FSI, Fatigue Symptom Inventory; IES, Impact of Events Scale; MAPS, Mindful Awareness Practices; PANAS-PA, Positive and Negative Affect Schedule-Positive Affect; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; QLACS, Quality of Life in Adult Cancer Survivors; SD, standard deviation.
[a] The models were adjusted for marital status, radiation therapy (yes/no), history of smoking (yes/no), and baseline CES-D scores.
[b] These are P values for group × time interactions testing group differences in baseline to postintervention means. Values in boldface indicate a statistically significant difference.
[c] These are P values for group × time interactions testing group differences in baseline to 3 month follow-up means. Values in boldface indicate a statistically significant difference.

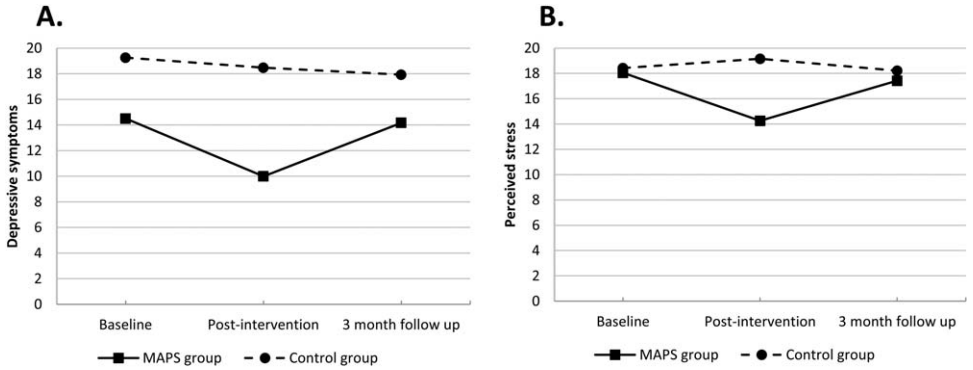

Figure 2. Adjusted means for (A) perceived stress and (B) depressive symptoms are illustrated in the intervention group and the control group. Linear mixed effects models revealed significant reductions in stress and marginally significant reductions in depressive symptoms in the Mindful Awareness Practices (MAPS) group versus the control group from baseline to postintervention. These effects were not maintained at the 3-month follow-up.

DISCUSSION

The objective of this trial was to determine the feasibility and efficacy of a brief mindfulness intervention on psychological, behavioral, and biologic outcomes among breast cancer survivors who were diagnosed at or before age 50 years. There was excellent adherence to the intervention, with a class attendance rate of 87%. Relative to wait-list controls, the 6-week intervention led to significant improvements in perceived stress and a trend toward improvement in depressive symptoms, both of which were high in this sample. In addition, the intervention led to improvements in fatigue, sleep disturbance, menopausal symptoms, and positive psychological processes. Mindfulness also led to significant reductions in proinflammatory gene expression and bioinformatic indications of proinflammatory signaling. Although the intervention did not result in changes in plasma markers of inflammation, women in the mindfulness group who practiced more frequently did evidence lower levels of IL-6 at the post-treatment assessment.

Previous randomized controlled trials of mindfulness for breast cancer survivors have demonstrated improvements in stress,[18] depression,[16-18,20] and physical symptoms.[45] Our current results add to this growing literature and demonstrate that mindfulness also has beneficial effects on psychological and behavioral outcomes in younger breast cancer survivors. Furthermore, our trial indicates that the benefits of mindfulness may extend to

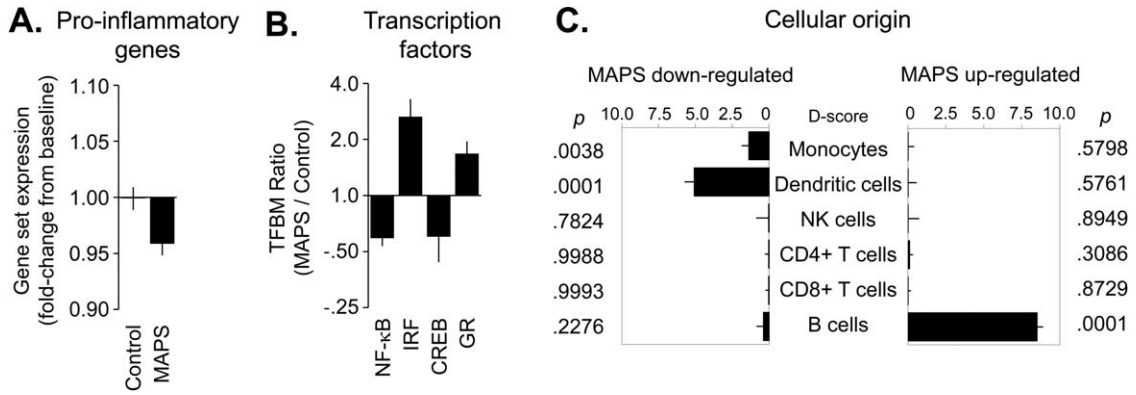

Figure 3. (A) Transcriptional profiling of peripheral blood mononuclear cell samples demonstrated a significantly greater decline in a 19-transcript composite of proinflammatory genes in the Mindful Awareness Practices (MAPS) group versus the control group. (B) Bioinformatics analysis of transcription factor activity indicated reduced activity of the proinflammatory transcription factor nuclear factor κB (NF-κB) and increased activity of the anti-inflammatory glucocorticoid receptor (GR) in the MAPS group versus the control group. Analyses also indicated increased activity of interferon-related transcription factors (IRF) but no significant difference in cyclic adenosine monophosphate response element-binding (CREB) activity. TFBM indicates transcription-factor binding motif. (C) Transcript origin analyses identified genes that were down-regulated in the intervention participants as originating primarily from monocytes and dendritic cells and genes that were up-regulated as originating predominately from B lymphocytes. NK indicates natural killer.

TABLE 3. Up-Regulated and Down-Regulated Genes in the Mindful Awareness Practices Group Versus the Control Group

Gene	Group × Time	Fold-Difference[a]
Up-regulated genes		
HBM	0.483	1.398
EPB42	0.449	1.365
ALAS2	0.434	1.351
AHSP	0.393	1.313
SLC4A1	0.390	1.310
CA1	0.384	1.305
CHURC1	0.379	1.300
HBD	0.369	1.292
DEFA1	0.356	1.280
LOC100008589	0.352	1.276
WDR40A	0.344	1.270
DEFA3	0.329	1.256
LOC100132394	0.321	1.249
LOC100131164	0.320	1.249
SELENBP1	0.320	1.248
DEFA1B	0.314	1.243
ALPL	0.300	1.231
LOC731682	0.295	1.227
C5ORF53	0.290	1.222
FRAT2	0.289	1.222
IFIT1L	0.286	1.219
LOC389599	0.284	1.217
LILRA3	0.267	1.203
LOC100133875	0.264	1.201
Down-regulated genes		
IGJ	−0.924	0.527
HLA-DRB5	−0.858	0.552
LOC652493	−0.717	0.608
LOC647450	−0.686	0.621
LOC642113	−0.664	0.631
TNFRSF17	−0.658	0.634
TXNDC5	−0.640	0.642
LOC649923	−0.637	0.643
MGC29506	−0.625	0.648
LOC647506	−0.557	0.680
LOC651751	−0.539	0.688
IGLL1	−0.522	0.697
LOC652102	−0.520	0.697
HIST1H4H	−0.496	0.709
CD38	−0.484	0.715
EGR1	−0.480	0.717
LOC652694	−0.454	0.730
TYMS	−0.381	0.768
GLDC	−0.378	0.770
LGALS2	−0.377	0.770
HLA-DRB1	−0.375	0.771
CDC20	−0.372	0.773
ISG15	−0.365	0.777
IFITM3	−0.364	0.777
MGC13057	−0.357	0.781
TNFRSF13B	−0.342	0.789
CLEC1B	−0.341	0.789
DUSP2	−0.326	0.798
ITM2C	−0.322	0.800
PF4V1	−0.310	0.806
TMEM176A	−0.307	0.808
IL8	−0.304	0.810
AQP10	−0.303	0.810
IFI44L	−0.296	0.814
LOC652775	−0.296	0.815
DUSP5	−0.287	0.819
LOC645128	−0.281	0.823
NAT8B	−0.279	0.824
SLC7A5	−0.276	0.826
CA2	−0.274	0.827
ABCB9	−0.273	0.828
RBPMS2	−0.268	0.831

Abbreviations: ATP, adenosine triphosphate; GCN5, a histone acetyltransferase; Ig, immunoglobulin; TNF, tumor necrosis factor.
[a] Analyses were adjusted for marital status, radiation therapy, history of smoking, baseline Center for Epidemiologic Studies Depression Scale score, and RNA indicators of leukocyte subsets.
[b] The fold difference is a ratio that reflects the change from baseline to post-intervention in the Mindful Awareness Practices group versus the control group.

genomic markers of inflammation, including reductions in proinflammatory gene expression and activity of the proinflammatory transcription factor NF-κB. To our knowledge, this is the first trial to demonstrate the effects of mindfulness on inflammatory gene expression in cancer patients. The effects of mindfulness on circulating markers of inflammation may be more difficult to detect; indeed, previous trials in noncancer populations have observed only marginally significant decreases in these markers[38,46] or have observed effects only among individuals who practiced more frequently,[47] similar to our findings.

Although acute effects of mindfulness on stress, depressive symptoms, and other outcomes have been demonstrated in cancer populations, the persistence of these effects in the weeks and months postintervention is less clear. Several trials of mindfulness-based stress reduction for cancer survivors have reported significant effects on depressive symptoms at postintervention assessments but *not* at follow-up assessments conducted between 1 and 24 months after the intervention,[19,20,48] consistent with our results. One recent trial conducted in a relatively large sample of 336 breast cancer survivors did report beneficial effects of mindfulness-based stress reduction on depressive symptoms that persisted over a 12-month follow-up period.[16] Sustained effects have also been observed on other outcomes, including spirituality.[19] It is unclear why participants in our study did not sustain the improvements in stress, depression, and other symptoms observed at post-treatment, although they did report improvements in cancer-specific distress at the follow-up assessment. It is possible that these women may require more support to continue their mindfulness practice and maintain its benefits, particularly given their high baseline levels of stress and depression. In general, the impact of mindfulness on different dimensions of well being and the persistence of those effects is an important topic for future research. The

TABLE 4. Adjusted Means and Results for Circulating Inflammatory Markers[a]

	Baseline, n = 65		Postintervention, n = 52		
	Mean Score ± SD		Mean Score ± SD		
Outcome	MAPS Group	Control Group	MAPS Group	Control Group	P^b
CRP, μg/L	1.24 ± 1.70	1.45 ± 1.81	1.22 ± 1.66	1.32 ± 1.75	.415
IL-6, pg/mL	1.24 ± 0.87	1.16 ± 0.58	1.19 ± 0.67	1.32 ± 0.63	.158
sTNF-RII, pg/mL	2342.8 ± 503	2335.5 ± 1244	2209.3 ± 461	2211.2 ± 1042	.857

Abbreviations: CRP, C-reactive protein; IL-6, interleukin 6; MAPS, Mindful Awareness Practices; sTNF-RII, soluble tumor necrosis factor receptor II.
[a] The model was adjusted for marital status, radiation therapy (yes/no), history of smoking (yes/no), baseline Center for Epidemiologic Studies Depression Scale score, body mass index, and age. Note that log-transformed values were used in the analyses.
[b] These are *P* values for group × time interactions testing group differences in baseline to postintervention means.

maintenance of intervention effects is particularly relevant for younger women with early stage breast cancer, because they can expect to survive for several decades after diagnosis and cancer treatment.

Limitations of this study include the relatively small sample, which limits statistical power to discover statistically significant associations between the intervention and the expression of any given gene transcript. The sets of differentially expressed genes reported here serve only as inputs into higher order gene set-based bioinformatics analyses testing a limited number of a priori hypotheses regarding shared transcription factor promoter motifs (ie, inflammation-related NF-κB, GR, and CREB) and shared cellular origin (ie, proinflammatory monocytes), as documented in previous gene expression reference studies. It will be important to replicate these findings in a larger trial and to determine whether the effects are generalizable to diverse groups of younger breast cancer survivors. In addition, the use of a wait-list control group does not control for nonspecific effects of the intervention, and it is possible that intervention effects may simply have been caused by attention. Future studies should compare mindfulness with an active control condition and should include a longer term follow-up to determine the persistence of effects on psychological and biologic outcomes.

Women diagnosed with premenopausal breast cancer are in need of strategies to help them manage elevated levels of stress, distress, and physical symptoms over a potentially long survivorship period. Results from the current trial suggest that a brief mindfulness intervention may offer short-term benefit for these women and lead to improvements in psychological, behavioral, and biologic outcomes. If these effects can be maintained over time, then there is potential benefit for improving cancer survivorship.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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