2. OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of two different types of group interventions (mindfulness and survivorship education), specifically tailored to the needs of younger female breast cancer survivors, in reducing depressive symptoms, compared to a usual care control group.

2.2 Secondary Objectives

2.2.1 To compare the efficacy of the two interventions relative to a usual care control group on fatigue, sleep disturbance, and vasomotor symptoms.

2.2.2 To examine the efficacy of the two interventions relative to a usual care control group on circulating and genomic markers of inflammation.

2.2.3 To explore potential moderators and mediators of intervention efficacy in the two intervention groups.

3. BACKGROUND

3.1 Younger Breast Cancer Survivors are a Vulnerable Population

Breast cancer is the most common cancer in younger women (< 50 years), with 1 in 53 women in this age group developing breast cancer. Breast cancer is also the most common cause of cancer death for younger women.[1] However, with advances in detection and treatment, the number of women who survive breast cancer has increased significantly, with five-year survival rates approaching 90%, resulting in an estimated 3 million North American women surviving long-term.[2] As survival times increase, addressing the impact of breast cancer and its treatments on long-term outcomes has become increasingly important, especially for younger women who make up approximately 25% of breast cancer cases. These young women can expect several decades of survival after breast cancer treatment ends; however, they are at high risk for adverse psychological and physical problems that can negatively impact the quality and potentially, the length of their survivorship. Indeed, younger women are at elevated risk for breast cancer recurrence and cancer-specific mortality, as well as secondary cancers, premature menopause, osteoporosis, and cognitive declines.

Studies have consistently shown that younger women have greater psychological morbidity after breast cancer than older women and age-matched women with no cancer history, including elevated levels of depressive symptoms, anxiety, and perceived stress.[3,4] Younger breast cancer survivors experience greater impact from cancer, perceive cancer as more threatening[5] and report greater fear of recurrence. They also report feeling more isolated and less satisfied with support groups due to their age.[6] In addition to psychological disturbances, younger women are at increased risk for physical and behavioral side effects of cancer treatment, including fatigue, sleep disturbance, and ongoing vasomotor symptoms associated with long-term endocrine therapy and premature menopause.[3,7-9] Impairments in emotional and physical functioning have been documented up to 10 years after diagnosis, suggesting that effects may not remediate even over time without intervention.[10] Thus, younger breast cancer survivors (BCS) are at risk for negative emotional and physical sequelae that may persist for years after diagnosis and treatment, making them a particularly vulnerable population.

3.2 Potential Interventions to address Behavioral Symptoms in Younger Breast Cancer Survivors

Despite the increased behavioral symptoms reported by younger BCS, few psychosocial interventions have specifically targeted this vulnerable age group.[11-13] In a focus group study with 36 younger BCS conducted by Partridge's group,[14] participating women reported feeling different from older women, especially with regard to relationships, fertility, menopausal symptoms, treatment side effects, and work/financial issues. They also reported facing unique challenges (e.g. partner relationships, dating, infertility, concerns about their young children, work and finances), and noted substantial difficulties transitioning into the survivorship phase of care. Finally, younger BCS reported desiring assistance, including connecting with other young patients, help navigating the healthcare system, tailored educational materials, and referrals to appropriate counselors.[14] These findings document the desire for intervention among younger women and provide some direction with regard to how to address the emotional and physical needs of this group.

In a 2012 systematic review,[3] we identified only three published randomized controlled trials (RCTs) that specifically targeted younger women with breast cancer. The first study by Allen et al.[11] evaluated a problem solving intervention for young breast cancer patients undergoing chemotherapy that led to improvements in quality of life and mental health. The second study, by Scheier et al.[12] was a three group RCT that recruited younger women after chemotherapy completion, and assigned them to a nutrition education or a health education group delivered over 4 monthly sessions and compared them to a concurrent control group. Women in both education groups had significant improvements in physical function and depressive symptoms compared to the control group in the follow-up year. A third study targeted younger survivors who were 5 years post-diagnosis and provided education-based workshops delivered in 3 monthly sessions.[15] This intervention led to improvements in breast-cancer related knowledge and physical activity, though effects on quality of life and symptoms were not assessed. In the broader literature, psychoeducational interventions have been recommended for addressing depressive symptoms and fatigue in cancer patients and survivors.[16,17] These studies provide preliminary evidence that psychoeducational approaches may be helpful to younger BCS during treatment and into the survivorship period. **However, these promising findings have not been translated into the clinical care setting, nor have such interventions been implemented in the post-treatment period, despite considerable need and potential benefit.**

Recently, mindfulness meditation has emerged as a promising intervention for general and cancer populations[18-20] and may be a particularly good option for younger BCS, given their considerable interest in mind-body treatments.[21] Mindfulness involves bringing attention to one's present moment experiences, including thoughts, feelings, and physical sensations, with openness, curiosity, and absence of judgment.[22] Interventions have been developed to cultivate mindfulness through formal meditation and informal practice, and RCTs have documented benefits of mindfulness-based interventions among BCS, including improvements in depressive symptoms, stress, and fatigue.[23-26] We have recently completed a phase II RCT of a 6-week Mindful Awareness Practices (MAPs) group intervention program in younger BCS and have demonstrated its benefit on reduction behavioral symptoms at the immediate post-treatment assessment,[13] suggesting the feasibility and preliminary efficacy of this intervention in the target population of younger BCS (see preliminary data below). Further, we also saw reductions in inflammatory signaling in this trial, which may be due to decreases in physiological arousal. Although trials by our group and others are promising, almost all have been conducted at single institutions and have focused on the short-term effects of mindfulness practice, limiting their translation and potential impact on longer-term health. In the proposed study, we will implement strategies to encourage maintenance of practice beyond the 6-week group intervention, as we hypothesize that this will be important for sustained reduction in behavioral symptoms in this vulnerable population.

an individual's life situations are appraised as stressful.[28] A number of secondary outcomes were also assessed. To determine whether intervention effects extended to cancer-specific distress, cancer-related intrusive thoughts and fear of cancer recurrence were assessed. Intrusive thoughts about cancer were assessed with the 7-item subscale of the *Impact of Events Scale*;[29] this subscale was of interest because it predicts poor quality of life in cancer survivors.[30] *Fear of recurrence* was assessed with a 4-item subscale of the *Quality of Life in Adult Cancer Survivors* (QLACS) questionnaire that assesses concerns about cancer recurrence.[31]

To determine whether the intervention would influence physical symptoms that are common among younger BCS, we assessed fatigue, sleep disturbance, and other physical side effects of cancer treatment. Fatigue was assessed with the *Fatigue Symptom Inventory* (FSI), a 13-item measure that assesses fatigue intensity, duration, and interference with daily functioning.[32,33] Subjective sleep quality was assessed with the *Pittsburgh Sleep Quality Index (PSQI)*, a 19-item scale that assesses sleep quality and disturbances.[34] Side effects of cancer treatment were assessed with 20 items from the *BCPT symptom scales*, which include a variety of physical symptoms relevant to cancer survivors.[35] Effects on positive psychological outcomes were also examined. Meaning and purpose in life were assessed with the 8-item subscale of the *Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being*.[36] Self-reported demographic and disease-related variables were assessed at baseline, and homework was assessed using questionnaires completed each week during the intervention. Participants in the mindfulness group reported on the number of minutes they engaged in formal mindfulness practice each week.

3.3.5 Results

The study took place at the UCLA Medical Center, Los Angeles, CA between March 2011 and October 2012. We screened 151 women for eligibility; 11 (7%) were not eligible, and 69 (46%) were not interested in participating. The primary reasons for ineligibility were breast cancer recurrence or metastasis, or another cancer. We randomized 71 women to either the 6-week MAPs intervention (n = 39) or to a wait-list control condition (n = 32). Thirty-eight women received the allocated intervention, which we defined as attending at least two of the six classes, and complete follow-up data were obtained on 59 participants (83%).

In the MAPs group, the mean number of classes attended was 5.1 (85%) and the median was 5 (83%). The mean number of minutes of mindfulness practice each week, including time spent in the mindfulness classes was 180. At the 3-month post-intervention follow-up, 23 of the 31 women (75%) who attended the mindfulness classes and who completed the 3-month follow-up questionnaire were continuing to use techniques learned in class at least once a week.

The demographic and clinical characteristics of the participants are shown in Table 1 on the next page.

5. REGISTRATION PROCEDURES

5.1 Guidelines for All Participating Institutions

Eligible participants will be entered on study through the RedCAP database that will allow entry and review of study eligibility, followed by random assignment if all eligibility criteria are met. Participants will only be randomized after all of the components of the enrollment visit are completed.

6. Intervention Groups

6.1 Pre-Intervention Preparation

Potential instructors for the mindfulness intervention will be screened by Ms. Winston from the Mindful Awareness Research Center (MARC) at UCLA to ensure that they have had adequate training to deliver this particular intervention. Potential instructors for the survivor education intervention will be identified by site PIs and evaluated for experience in survivorship education, nursing, and oncology. The details of the selection and training of both groups of instructors are found in Appendix B.

6.2 Intervention Programs

6.2.1 Arm A- Mindfulness Meditation (MAPs)

The specific curriculum for this 2 hour/week, 6-week program will be provided to women who are assigned to this group as part of the randomization. Each session will provide structured training and exercises in mindfulness, and women will be given tools to facilitate their practice of these techniques at home through formal meditation practice as well as through guidance in the informal use of mindfulness during daily life. During each session the instructor will assist the participants in learning this practice and will regularly assess how the participants are doing with their mindfulness practice. A general overview of the content for each session is found in Appendix C. A detailed training manual has been developed specifically for use with breast cancer survivors to be used across the clinical sites, and will be used in the instructor training. The sessions will introduce the following topics and associated practices: 1) What is mindfulness? 2) Listening, embodiment, and obstacles; 3) Working with pain; 4) Working with difficult emotions, cultivating positive emotions; 5) Working with thoughts, mindful interactions; 6) Wrap up. This standardized curriculum with delivery by trained clinical providers at each site will be necessary to evaluate the efficacy of the intervention program.

6.2.2 Arm B- Survivorship Education Intervention (SE)

The specific curriculum for this 2 hour/week, 6-week program will be provided to women who are assigned to this group as part of the randomization. The SE intervention is a series of didactic sessions designed specifically for younger breast cancer survivors and to be delivered in a small group format. The seminar series focuses on cancer survivorship issues, but also allows group discussion and support. Lecture topics were selected to address a range of issues that are of high importance to younger breast cancer survivors based on a review of the literature, discussions with younger breast cancer survivors, and input from other experts in breast cancer survivorship. The seminars will be led by an oncology clinician, e.g., nurse, advance practice provider or physician at the clinical site who has expertise in breast cancer survivorship.

The SE sessions will follow a didactic format, with lectures followed by group discussion, as part of a psychoeducational approach. The material presented is based on the empirical literature and on clinical experience with this patient population. The sessions are designed to provide information and include

6.7 Discontinuation of Treatment

Potential reasons for discontinuation of protocol treatment include:

- Breast cancer recurrence. The participant could potentially continue receiving the intervention (if not too disturbing to remaining participants), but outcome data collection would not continue.
- Non-attendance at Arm A or Arm B intervention sessions, e.g., failing to attend after the first session and causing disruption for group as a result of behavior or intermittent participation; the Protocol Chair will determine when non-compliance should lead to removal from study, although participant data will still be included in the intent-to-treat analysis.
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of study outcomes to a significant degree or require discontinuation of study treatment. At participant's own request. Note: The reason for discontinuation from the study must be documented. The participant will be included in the overall evaluation of outcomes (intent-to-treat analysis) if any protocol therapy was administered prior to withdrawal.
- Study is closed for any reason (e.g. new information shows that the trial should be stopped or that administrative factors prevent continuation of the study)
- General or specific changes in the participant's condition render the participant unacceptable for further study involvement in the opinion of the treating investigator.

6.8 Withdrawal from Study

6.8.1 The reasons for withdrawal from the study include:

- Participant withdraws consent.
- Participant is lost to follow-up.
- Study is terminated for any reason.

6.9 Additional Information

Participants will have their parking paid for at the evaluation visits, as well as to attend all of the assigned sessions for Arm A and Arm B. Participants assigned to Arm C will receive the same parking coverage when they receive their chosen intervention after completion of the study.

9. OUTCOME MEASUREMENTS: QUESTIONNAIRES AND ANTHROPOMETRIC MEASURES

We will examine intervention effects on psychological, behavioral, and biological measures. The questionnaires to be used all have good psychometric properties, and many were specifically designed for cancer survivors. The questionnaires will be administered electronically or by paper (consistent method across time points), as preferred by the participant, and will take about 45 minutes to complete at T1 and 30 minutes at T2, T3 and T4.

9.1 Background Variables and Potential Confounds

Demographic information (e.g., age, race, ethnicity, education, relationship status) will be collected via self-report using a standardized form. Clinical information (e.g., data of breast cancer diagnosis, disease stage, previous forms of cancer treatment, dates of previous treatments, endocrine therapy type and duration) will be collected via self-report at baseline, along with concomitant medications. Self-report of this medical information has been found to be reliable in breast cancer patients.[40] Alcohol and tobacco use will be obtained from standardized epidemiologic measures and physical activity using the Godin Leisure-Time Exercise Questionnaire.[41] Height and weight will be measured using standardized anthropometric methods. Comorbid medical conditions will be assessed using a validated self-report instrument developed by Katz and colleagues.[42,43] We will also collect information on concurrent medications at each visit, as well as use of psychosocial support services for cancer-related concerns, both using measures from previous studies with this patient population. Data on current and past use of integrative medicine services will be collected at T1 only. We will also administer the Patient Health Questionnaire-9 (PHQ-9)[44] to evaluate clinically-significant depression at baseline only. Screening PHQ-8 data will be used for stratification purposes in the randomization process, but will not be included as part of this database.

9.2 Self-reported Outcome Variables

The primary trial outcome is depressive symptoms, which will be assessed with the *Center for Epidemiologic Studies-Depression* scale (CES-D), a 20-item self-report scale developed for the general population to assess depressive symptomatology in the last week.[27] Secondary outcomes include cancer-related behavioral symptoms, including fatigue, sleep disturbance, and vasomotor symptoms. Fatigue will be assessed with the *Fatigue Symptom Inventory* (FSI), a 13-item measure that assesses fatigue intensity, duration, and interference with daily functioning.[33] We focus on fatigue severity (assessed with 4 items that capture most fatigue, least fatigue, average fatigue, and current fatigue) and fatigue duration (assessed with 1 item). Subjective sleep quality will be assessed with the *Insomnia Severity Index* (ISI).[45] Side effects of cancer treatment will be assessed with 20 items from the *BCPT Symptom Scale*, which include a variety of physical symptom scales relevant to cancer survivors.[35] In particular, we will focus on the vasomotor symptom scale. The *SF-12 health survey*[46] will be used to capture the broad domains of physical and mental health functioning at each assessment.

Secondary psychological outcomes are as follows: Meaning/purpose in life will be assessed with the *Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being* subscale (FACIT-SP-12), a 12-item scale that measures feelings of meaning/purpose in life and feelings of faith.[36] For this study, we will use 8 items from the meaning/purpose in life subscale. In addition, clinically-significant anxiety will be assessed using the *Generalized Anxiety Disorder-7* questionnaire, a 7-item scale that assesses anxiety symptoms in the past two weeks.[47] Stress will be assessed with the *Perceived Stress Scale* (PSS), a 10-item scale that measures the degree to which an individual's life situations are appraised as stressful.[28] Positive affect will be assessed with the 10-item positive affect subscale of the *Positive and Negative Affect Scale* (PANAS), as well as the Joviality and Serenity subscales of the PANAS-X.[48] Various aspects of the impact of cancer will be measured with three scales (worry, life interference, altruism/empathy scales) from the *Impact of Cancer Version 2* (IOC v.2), [49] and cancer-related distress with the intrusions subscale of the *Impact of*

Events Scale (IES),[29] focused on cancer. Social support will be assessed with the 12-item emotional support subscales of the *2-way Social Support Questionnaire* [50] as well as the 4-item attachment subscale of the *Social Provisions Scale*.[51] Effects of cancer on work and other activities will be assessed with the *6-item Work Productivity and Activity Impairment Questionnaire* (WPAI-GH).[52]

9.3 Potential Moderators of Intervention Efficacy

We will examine several hypothesized moderators of intervention effects, drawing from the empirical literature and our conceptual model. Previous trials have shown that *preparedness for survivorship* and *intervention preference*[53] moderates effects of psychosocial interventions for cancer patients[54] and are conceptually related to our proposed interventions; thus, we will assess this constructs using validated measures. In addition, a growing body of evidence indicates that childhood adversity moderates effects of mindfulness intervention;[55] thus, we will administer the *Risky Families Questionnaire* at baseline to assess this construct.[56]

9.4 Potential Mediators of Intervention Efficacy

Previous research has shown that self-efficacy is a non-specific mediator of behavioral interventions. Thus, we will include a measure to assess *self-efficacy to cope with survivorship* at each assessment.[57] In addition, the following constructs have been found to mediate effects of mindfulness-based interventions: mindfulness, self-kindness, and rumination. These constructs will be assessed at each assessment point with the following measures: the *Mindful Awareness Attention Scale*,[58,59] the self-kindness subscale of the *Self-Compassion Questionnaire*,[60] and the rumination subscale of the *Rumination and Reflection Questionnaire*.[61] Note that these constructs are also relevant to the content of the Health Education program.

Amendment notation 4/10/20: we became aware that the self-efficacy questions were inadvertently omitted from the follow-up questionnaires at T2, T3 and T4. Table of instruments was modified

9.5 Process Related Variables

Shortly after introduction of the assigned intervention, intervention coordinators will administer to all participants a measure of intervention credibility we have used in prior intervention research.[38]* As part of intervention delivery, we will track attendance at intervention group meetings. Participants in the MAPs condition will be asked to record practice of meditation between classes and after the 6-week intervention period. All participants will be asked to report on use of prescription and nonprescription medications, vitamins, supplements, support services (e.g., professional counseling), and mind-body interventions over the course of their participation.

*Note: we became aware that the intervention credibility scale was inadvertently omitted from the baseline assessment in November 2020.

On the next page we provide a summary table of the questionnaires and the timing of their administration.

10.3.1 Gene Expression Profiling

Total RNA will extracted from 2.5 mL of whole blood collected in a PAXgene tube, and subjected to genome-wide transcriptional profiling using RNA sequencing through the UCLA Social Genomics Core following the manufacturer's standard protocol. We will focus on expression of a set of 19 pro-inflammatory cytokine genes that have previously been found to be up-regulated in the context of chronic stress and that were responsive to the MAPs intervention in our pilot study. In addition, to probe molecular underpinnings of alterations in gene expression, we will utilize a novel bioinformatics approach to assess proinflammatory signaling at the molecular level. This approach uses microarray-based genome-wide transcriptional profiling to identify genes that show differential expression in leukocytes from patients randomized to MAPs or SE vs. controls and applies the TELiS transcription factor search engine to identify transcription factor binding motifs that are differentially represented in the promoters of those differentially expressed genes.[68] To identify the primary cellular sources of differentially expressed genes, we will also carry out Transcript Origin Analysis as previously described.[69]

10.3.2 Circulating Pro- and Anti-Inflammatory Markers

Multiplex immunoassays to assess 5 key cytokines (IL1β, IL6, IL8, IL10, TNF-α) will be performed utilizing a Bio-Plex 200 (Luminex) instrument and a high-sensitivity multiplex immunoassay (Performance High Sensitivity Human Cytokine, R& D Systems, Minneapolis, MN) according to the manufacturer's protocol. A high sensitivity ELISA (R&D Systems Quantikine Human CRP) will be utilized to assess CRP.

10.3.3 Genetic/Epigenetic Analysis

Total genomic DNA will be extracted and used to look at individual genetic variation (single nucleotide polymorphisms, genetic sequencing, etc.) and epigenetic DNA modifications (telomere length, DNA methylation, etc.).

11. HANDLING OF SPECIMENS FOR INFLAMMATORY OUTCOMES

All blood draws will be conducted in the morning to control for diurnal variations. Patients will be asked to sit quietly for 15 minutes prior to blood collection. Approximately 15 mL (one tablespoon) of blood will be drawn. Blood samples should be obtained via venipuncture using a blood draw set (butterfly needle and tubing) in the following order:

1. Blood for cytokines and CRP will be collected into two 6 mL EDTA tubes (BD cat. no. 367863, plastic/Hemogard 13x100 mm K2 EDTA). Immediately following collection, EDTA tubes are to be well mixed and then held on wet ice or in the refrigerator until processed.
2. Blood will be collected into one PAXgene Blood RNA Tube (BD cat. no. 762165, 2.5 mL draw, 16-100 mm); tube must be at room temperature prior to blood draw. Be sure to allow sufficient time for the PAXgene tube to complete its filling—although the blood tube is the size of a traditional 10 mL blood draw tube, it will draw only 2.5 mL. After mixing by gentle inversion, PAXgene tube should be placed upright in a rack at room temperature for two hours before further processing/freezing.

Blood samples will be processed by a laboratory at each site, according to study protocols with detailed instructions in a manual that will be provided to each site. EDTA tubes will be processed the same day to plasma aliquots, and frozen at -80°C. PAXgene tubes will be frozen upright in a rack overnight at -20°C, then transferred to -80°C. All samples will be stored at sites and shipped to the UCLA laboratory at the end of the study at which time the planned analyses will be performed.

Samples will be shipped from the collaborating sites to UCLA and are to be shipped frozen via overnight delivery. Ship samples to UCLA no later than Wednesday of any given week. This allows both Thursday and Friday to locate samples if they should go astray. If necessary, samples could be shipped on Thursday, but Wednesday or earlier is preferred. Shipping address is:

UCLA - Cousins Center for PNI
300 Medical Plaza, Room 3160
Los Angeles, CA 90095
Phone: 310-825-0302

The UCLA study team members should be notified by email in advance of when samples will be shipped, and again when they have been shipped; please always include a tracking number. If there are any questions, please contact via email or at the UCLA IBC Lab phone number shown above.

At the UCLA IBC Lab, all samples received will be stored at -80°C. EDTA plasma will be assayed for cytokines and CRP. PAXgene tubes will be stored at -80°C until RNA extraction for gene expression profiling.

(Note: We appreciate the initial specimen management protocol developed by Dr. Elizabeth Breen who is now retired.)

12. SPECIMEN BANKING

Any leftover study blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. Samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

13. STUDY CALENDAR

Procedure	T1[1]	Treatment Period 6 weeks	T2	T3	T4
CLINICAL ASSESSMENTS:					
Study questionnaires	X		X	X	X
Height and Weight	X		X		X
LABORATORY TESTS:					
Blood drawn for inflammatory markers[2]	X		X		X
TREATMENT:					
Arm A		X			
Arm B		X			
Arm C[3]					

1. 1-2 weeks before start of 6-week group intervention for Group 1 and Group 2. 2. Drawn between 8-11AM, specimens sent to UCLA

3. Will receive Arm A or Arm B intervention after 6-month assessment

16. REGULATORY CONSIDERATIONS

16.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center. UCLA will serve as the main institution for the study, and the other clinical sites will be collaborating institutions.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

16.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The participant should read and consider the consent document before signing and dating it, and will be given a copy of the document. No participant will enter the study or have study-specific procedures done before her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

16.3 Ethics and GCP

This study will be carried out in compliance with the protocol as described in:

1. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it.

17. MULTI-CENTER GUIDELINES

17.1 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB

18.3 Stratification and Randomization

Clinical site and severity of clinical depression at screening will be the only stratification factors used, to account for potential variations across sites in the delivery of the interventions, as well as ensure balance of the primary outcome (depressive symptoms) across the three intervention groups. There are 3 clinical sites and there will be two strata for clinical depression severity. We will use the score of the PHQ-8 obtained at screening as a stratification factor and will have two groups: scores 3-7 and 8 and above. This cut point on the PHQ-8 maps to a score on the CES-D that is below or above 16.[74] Randomization at each site will occur in cohorts of size 30 (approximately). When a site has enrolled approximately 30 participants, these participants will be randomized 1:1:1 to the three study conditions, so that there will be about 10 women assigned to each group, to ensure adequate group size for the interventions. Each study site will be expected to enroll four study cohorts during the course of the trial. The randomization sequence will be generated by the UCLA coordinating center using permuted blocks.

18.4 Analysis Plan including Secondary Endpoints

Since all outcome measures are continuous and assessed at multiple time points, the data will be analyzed using linear mixed effects models, with fixed effects for time and condition and random effects for individuals. Analyses will be conducted under the intent-to-treat principle, including all participants in their assigned condition, accomplished by fitting models to all available data for each outcome measure, including data of participants with incomplete follow-up. Linear mixed models provide valid inference under a missing at random assumption.[75] Differences between conditions in change over time will be examined by testing condition-by-time interaction terms. Following recommendations for multicenter trial data analysis,[76] we will also test for center effects and center-by-treatment interactions. Analyses will control for any participant characteristics with baseline imbalance among conditions or that differ between participants retained and those lost to follow-up. For all analyses, we will conduct diagnostics and effects of outliers and influential cases will be assessed by re-analysis with these cases omitted. All tests will be two-sided.

We hypothesize that participants in each intervention will have a greater reduction in CES-D than control participants at post-intervention (T2). Dunnett's procedure, which controls the familywise Type I error when comparing multiple intervention groups to a single control group, will be used to control the familywise error rate at 0.05.[72] We also hypothesize that participants in the two interventions will have improvements in secondary outcomes (fatigue, sleep disturbance, vasomotor symptoms; CES-D at T4) compared to control, and that MAPs participants will have significant reductions in inflammatory markers compared to SE and control. These will be tested using the mixed modeling approach.

Moderator effects will be assessed using condition-by-moderator-by-time interaction terms in mixed models. Since the study is only powered to detect medium to large moderator effects, these analyses are considered exploratory. Mediation analyses will be conducted by estimating the total, direct, and indirect effects of X on Y through mediators, singly and together, using published software procedures (e.g., paramed in Stata), and 95% confidence intervals will be obtained using bootstrap methods.

No interim analyses are planned.

18.5 Statistical Considerations and Analysis Plans for Inflammatory Biomarkers

To test the hypothesis that the mindfulness intervention reduces NF-kB-related transcriptional signaling and increases glucocorticoid- (GR) related transcriptional signaling, we will conduct promoter-based bioinformatics analyses of genes found to be differentially expressed in standard microarray-based transcriptional profiling of peripheral blood leukocytes. In a pilot study of 65 individuals randomized to MAPS vs Control conditions and tested at baseline and post-intervention follow-up, general linear model

analyses of a Group x Time factorial design identified > 60 transcripts showing > 1.2-fold differential change in abundance over time (approximately 30 showing relative up-regulation in MAPS and approximately 30 showing relative down-regulation). TELiS promoter-based bioinformatics analyses (40) identified an average 40% lower prevalence of NF-kB response elements and an average 60% greater prevalence of GR response elements in the promoters of up-regulated genes relative to down-regulated genes (both $p < .02$). Bootstrap analyses of the sampling distribution of differences identified standard errors for both of less than 10%. Based on these estimates, standard power analyses indicate that the proposed sample size will yield > 90% power to detect a similar difference in the proposed study (i.e., yielding >24 up- and down-regulated genes for TELiS analyses following linear model analysis of differential gene expression using the same Group x Time factorial design with differential expression thresholded at 1.2-fold and FDR controlled at < 5%).

For the exploration of the plasma cytokines and CRP, with the proposed sample size of 70 per group at baseline, we will have over 80% power to detect an effect size of 0.5 in difference in change over time between groups at the alpha = 0.05 level.

18.6 **Reporting**

The Steering Committee of the trial will develop policies and procedures early in the course of the study regarding reporting of study results, abstracts and publications.

3.3 **Preliminary Data**

3.3.1 Mindfulness Intervention Program (MAPs)

We have recently completed a phase II randomized trial at UCLA evaluating the efficacy of a mindfulness meditation intervention in younger women who had been diagnosed and treated for premenopausal breast cancer. They were randomly assigned to a 6-week mindfulness meditation intervention designed for breast cancer survivors (n=39) or to a wait-list control group (n=32). At pre- and post-intervention, participants completed questionnaires and provided blood samples for genome-wide transcriptional profiling and bioinformatic analyses as well as circulating inflammatory markers. The primary outcomes of interest were perceived stress and general depressive symptoms, which are commonly reported by younger BCS and are specifically targeted by this treatment. We also examined effects on cancer-specific measures of distress, including intrusive thoughts about cancer and fear of cancer recurrence, and cancer-related physical symptoms, including fatigue and sleep disturbance, as well as vasomotor symptoms. Finally, effects on positive psychological outcomes were assessed. The full study was recently reported.[13]

3.3.2 Assessments

Eligible participants were scheduled for a pre-treatment baseline assessment at UCLA, which was conducted 1-2 weeks before receipt of the intervention program or assignment to the delayed treatment control group. This assessment included completion of self-report questionnaires as well as collection of fasting blood samples and an evaluation of cardiovascular status and autonomic activity. A post-treatment assessment was conducted 1-2 weeks after treatment completion at UCLA to determine acute effects of the intervention. This assessment included completion of self-report questionnaires, collection of fasting blood samples, and an evaluation of cardiovascular and autonomic activity. At three months post-intervention, a follow-up questionnaire packet was mailed to study participants to assess maintenance of treatment effects.

3.3.3 Intervention

The mindfulness meditation-based intervention was based on the Mindful Awareness Practices (MAPs) for Daily Living, a 6-week program developed by Diana Winston and colleagues at the Mindfulness Awareness Research Center (MARC) at UCLA. We tailored the MAPs program for younger breast cancer survivors by including information about enhancing health and preventing breast cancer recurrence. Participants met for 6 weekly, 2 hour, group sessions conducted by an experienced mindfulness instructor that included presentation of information on mindfulness, relaxation, and the mind-body connection; experiential practice of meditation and gentle movement exercises; and a psycho-educational component for cancer survivors. Lecture, discussion, and group process focused on solving problems concerning impediments to effective practice, working with difficult thoughts and emotions, managing pain, and the cultivation of loving kindness. Home practice is a key component of MAP, and participants were instructed to practice mindfulness techniques on a daily basis.

The wait-list condition controlled for naturally occurring changes in stress and other outcomes over the six-week intervention period. After the post-treatment assessments were completed, those assigned to the wait-list control group were offered participation in the MAPs classes.

3.3.4 Outcome Measures

The primary outcomes of interest were depressive symptoms and perceived stress. Depressive symptoms were assessed with the *Center for Epidemiologic Studies-Depression* scale (CES-D), a reliable and valid 20-item measure that assesses depressive symptomatology in the last week.[27] Stress was assessed with the *Perceived Stress Scale (PSS)*, a 10-item scale that measures the degree to which

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).

Scores on the PSS, PSQI, CES-D, and FSI in this group of younger women, who were not screened for evidence of distress, indicate very high levels of stress, depressive symptoms, fatigue, and sleep disturbance, demonstrating the need for clinical intervention.

The main analysis outcomes were post-treatment assessment of **perceived stress (p=0.004)** and **depressive symptoms (p=.09),** which were both lower in the intervention group. We also found that women in the intervention group had higher levels of positive affect (p=.033), meaning & peace (p=.001), and self-compassion (p=.004) at the post-treatment assessment, as well as lower fatigue severity (p=.007), better sleep quality (p=.015), and less severe vasomotor symptoms (p=.015). Although there was no difference between groups in the change in cancer-related distress or fear of recurrence from baseline to post-treatment, there was a significant difference between groups from baseline to the three month follow up time point for both cancer-related distress (p=.049) and fear of recurrence (p=.002), suggesting longer term effects of the intervention on these outcomes. (See Bower et al[13] publication and Appendix A for table with full results of all time points and with all measures.) Further, the intervention group also showed significant down-regulation of pro-inflammatory genes, with accompanying bioinformatic indications of reduced NF-κB and increased glucocorticoid receptor (GR) signaling (all ps < .05); see Figure Panels A and B next page. Transcript origin analysis indicated that these changes were primarily driven by changes in monocytes and dendritic cells (panel C). Unfortunately, by the 3-month post-intervention assessment, both depressive symptoms and perceived stress had returned to the baseline level of severity, suggesting the need for additional support to maintenance of mindfulness practice. There were no significant group effects on plasma inflammatory markers, although post hoc within-group analyses indicated that more minutes of mindfulness practice per week were associated with reductions in the proinflammatory cytokine IL-6 in the intervention group (p = .003). Thus, for the current study, we are also planning to examine the impact of the intervention on inflammatory biology as a secondary aim.

recommendations for "healthy" behaviors in particular areas (e.g., American Cancer Society recommendations for healthy diet and exercise). The overarching goal is to provide current, comprehensive, and engaging coverage of health-related topics that are of central importance to young breast cancer survivors. In addition, the instructor will facilitate group interaction and social support, which has been identified as a key need by young breast cancer survivors. The planned lecture schedule and format are described in Appendix D. An intervention manual will be prepared for delivery of the SE intervention program, along with a slide set for each lecture, power point notes, and information about local community resources that may be helpful to the young survivors to address the health and behavior issues covered in the seminar series.

6.2.3 Arm C- Usual Care/Delayed Treatment Control Group

The participants assigned to this group after randomization will not receive any specific intervention until they have completed their T4 research assessment (6 months after the post-intervention assessments at T2). We will offer the Arm A and Arm B interventions to this group of participants after they have completed their assessments. The Arm C participants will be able to select which program they would like to attend.

6.2.4 Arm A and B Maintenance Activities

To enhance maintenance of treatment effects in both intervention arms, we have developed activities and materials designed to sustain key components of each intervention. For women assigned to the MAPs arm, we will conduct monthly, in person booster sessions led by the mindfulness instructor and attended by other group members for 2 months after the 6-week group intervention (2 booster sessions). These 60 minute sessions will include guided meditation, questions, and discussion of how to maintain a mindfulness practice. Women in the SE arm will receive monthly, electronic newsletters with tailored information about topics of interest to younger survivors, including cancer-related events in the community and tips about following through on recommendations for healthy living (2 newsletters).

6.3 Concomitant Treatments

Participants will be discouraged from engaging in any other psychosocial, educational or behavioral research programs for the duration of the study. Participation in other activities will be monitored through a questionnaire.

6.4 Duration of Therapy and Timing of Assessments

The Arm A and Arm B interventions will last 6 weeks. In-person pre (T1) and post-intervention (T2) assessments will occur, with only a survey 3 months later (T3) and a final in person visit (T4) at 6 months post intervention. These assessments will be done in all study participants.

6.5 Duration of Follow-Up

Participants will be followed through the T4 assessment. As a standard procedure we will include in the consent form an option for the participant to be re-contacted for future research. This will provide the option for longer follow-up by questionnaire or telephone if the study findings indicate a need to do so.

6.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 6.7 applies. All eligible patients who are randomized will be included in the overall evaluation of outcomes (intent-to-treat analysis). All reasons for discontinuation of participation will be documented in the research records.

7. PARTICIPANT RECRUITMENT, ELIGIBILITY SCREENING, AND ENROLLMENT

7.1 Recruitment of Younger Breast Cancer Survivors

Each site will develop local strategies for identification of potentially eligible younger female breast cancer survivors (age 50 years or younger at diagnosis). Institutional tumor registries and clinic lists are excellent initial places to identify potential participants, and with IRB approval they may be invited to participate in the study with an invitation letter and response form (sample letters and response forms will be provided by the UCLA Coordinating Center). Flyers and other announcements should be disseminated to community based support groups, clinical affiliate practices, as well as posted on social media sites (e.g., Young Survival Coalition, Stupid Cancer, Facebook posting/advertisement). We will also do a centralized posting of the study to the Army of Women to recruit breast cancer survivors who live in the geographic areas served by the participating sites. Clinical sites may also choose to do local news or press releases if appropriate for their institution and community. Extra efforts will focus on recruitment of underserved and ethnic minority women to ensure that all members of community are represented in the study sample. Each of the institutions has established community collaborators that will facilitate these outreach activities. Casting a wide net is very important, as each site will likely have to screen twice the number of individuals needed for the site specific enrollment based on recent experience with the mindfulness meditation study.[13]

7.2 Screening for Eligibility

Potentially interested and eligible participants must complete a screening telephone call with the study coordinator at each clinical site. The screening call will review information about the woman's age at diagnosis, her disease stage, when last treatments were completed, if she is disease-free, does not have other serious medical conditions, as well as be screened for level of depressive symptoms with the PHQ-8. For the purposes of study eligibility, we will use a cut point for mild depressive symptoms on the PHQ-8 with a score of 3 or greater. Only women who meet this criterion will be eligible. If the woman is clinically eligible (review of all eligibility inclusion and exclusion criteria), the study will be described in greater detail and she will be asked if she is interested participating and would be able to attend the 6-week group intervention program. If affirmative, then the woman will be invited to attend an enrollment visit. In order to accommodate these young women's busy life schedules, and facilitate their ability to attend the 6 session group intervention programs, we will try to schedule the group interventions at the best time of day/day of week/location to maximize both recruitment and retention. Thus with at least 4 cohorts being recruited at each site, a woman who cannot attend on a week night might be able to attend on a weekend day and join a subsequent cohort. Those women who are either ineligible or not interested will be thanked for their interest and there will be no further contact.

7.3 Formation of Study Cohorts and Preparing for Enrollment

Eligible participants will be enrolled and randomized after the study site has identified up to 15-20 potential participants who will form a cohort for randomization to one of the three groups (the two active interventions and control), so that there will be approximately 6-7 women assigned to each group. Each study site will be expected to enroll 4-6 study cohorts during the course of the trial, with a total target of 70 women randomly assigned to one of the three arms.

Across the three clinical sites, we anticipate achieving the target sample size of 210 randomized participants within a 36-month period of time. Enrollment will be monitored closely to ensure that the target enrollment is achieved in a timely fashion.

9.6 **Summary of Questionnaire Measures**

Table of Measures	**T1**	**T2**	**T3**	**T4**
Background characteristics and potential confounds				
Demographic and clinical characteristics	**x**			
Comorbid conditions	**x**			
Height and weight	**x**	**x**		**x**
Biobehavioral factors (tobacco and alcohol use, physical activity)	**x**	**x**	**x**	**x**
Use of integrative therapies	**x**	**x**	**x**	**x**
Use of psychosocial counseling and support services	**x**	**x**	**x**	**x**
Medications	**x**	**x**	**x**	**x**
Depression (Patient Health Questionnaire-9 [PHQ-9])	**x**			
Outcomes				
Depressive symptoms (Center for Epidemiologic Studies – Depression [CES-D])	**x**	**x**	**x**	**x**
Fatigue (Fatigue Symptom Inventory [FSI])	**x**	**x**	**x**	**x**
Insomnia (Insomnia Severity Index [ISI])	**x**	**x**	**x**	**x**
Menopausal symptoms (BCPT Symptom Checklist)	**x**	**x**	**x**	**x**
Perceived stress (Perceived Stress Scale [PSS])	**x**	**x**	**x**	**x**
Anxiety (Generalized Anxiety Disorder-7)	**x**	**x**	**x**	**x**
Peace and meaning (FACIT- spirituality subscale)	**x**	**x**	**x**	**x**
IOC v.2 scales (worry, life interference, altruism/empathy)	**x**	**x**	**x**	**x**
Cancer-related distress (Impact of Events Scale [IES] – intrusions subscale)	**x**	**x**	**x**	**x**
Positive affect (Positive and Negative Affect Scale [PANAS]- positive affect subscale + items for joviality and serenity subscales)	**x**	**x**	**x**	**x**
Social support (2-way Social Support Questionnaire – emotional support subscales; Social Provisions Scale – attachment subscale)	**x**	**x**	**x**	**x**
Work productivity and activity impairment (WPAI-GH)	**x**	**x**	**x**	**x**
Health Status (SF-12)	**x**	**x**	**x**	**x**
Inflammatory markers	**x**	**x**		**x**
Moderators				
Preparedness for cancer survivorship	**x**			
Intervention preference	**x**			
Childhood adversity (Risky Families Questionnaire)	**x**			
Mediators				
Cancer coping self-efficacy	**x**			
Self-kindness (subscale of Self-Compassion Scale [SCS])	**x**	**x**	**x**	**x**
Mindfulness (Mindful Attention Awareness Scale [MAAS])	**x**	**x**	**x**	**x**
Rumination (subscale of Rumination and Reflection Questionnaire [RRQ])	**x**	**x**	**x**	**x**

14. ADVERSE EVENT REPORTING REQUIREMENTS

14.1 General

Adverse events are rare in behavioral intervention research studies but may occur. First, some participants may become distressed when completing questionnaires that ask about their physical and emotional status. It will be important for the clinical site to have already identified collaborating clinicians or institutional resources where a participant who is severely distressed or depressed can be evaluated and referred for appropriate counseling or other services. In addition, some participants may be disappointed that they are assigned to the delayed intervention group. They should be reassured that they will have an opportunity to participate in the group of their choice at the end of the study.

14.2 Reporting Procedures

Any adverse event should be reported to the Coordinating Center and information related to the event will be disseminated to the participating sites within 5 days of review of the information by the Protocol Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study procedure.

All adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

15. DATA AND SAFETY MONITORING

15.1 Data Management and Reporting

All data management and reporting will be conducted by the UCLA Coordinating Center under the auspices of the trial senior statistician and study data manager. Data from the clinical sites will be submitted via a secure web portal (both participant reported questionnaires and data submitted by the study coordinators) on a regular basis as collected, with queries and delinquency reminders being sent to the sites on a regular basis.

Regular assessment of data quality and any irregularities will be reported to the protocol chair who will discuss specific issues with the clinical site. Data will be summarized and reported to the Data Safety Monitoring Committee (DSMC) annually after protocol activation until the study is completed.

15.2 Meetings

The DSMC will include three faculty members from the UCLA Jonsson Comprehensive Cancer Center who are familiar with the design and implementation of behavioral intervention research in cancer patients. They will meet for the first time just prior to the activation of the study protocol and will have meetings every 12 months after protocol activation. Meetings will also be called should there be major changes in the study protocol that need discussion. This is a minimal risk study and thus we do not expect serious adverse events that would require DSMC attention. In addition, no interim analyses are planned so that the need for study discontinuation for futility or for substantial benefit will be unlikely.

15.3 Monitoring

No auditing is anticipated unless the data manager detects data variances that lead to concerns about reliability and validity.

approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below.

17.2 Records Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

17.3 Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to the Steering Committee and all participating sites prior to submission for publication or presentation.

18. STATISTICAL CONSIDERATIONS

18.1 Study Design/ Endpoints

This is a three group, phase III randomized controlled trial that will evaluate the short-term outcomes of two distinct group interventions designed for younger women with breast cancer in comparison to a delayed intervention control group.

18.1.1 The primary endpoint will be depressive symptoms as measured by the CES-D score at T2.

18.1.2 Secondary endpoints will include:

- CES-D score at T4 (Amendment May 6, 2019 changed this from co-primary to secondary)
- Other behavioral symptoms including hot flashes, fatigue and sleep disturbance, at immediate post-intervention (T2) and 6 months later (T4).
- Examination of changes in measures of inflammation at T2 and T4.
- Exploration of potential moderators and mediators of intervention efficacy.

18.2 Sample Size/ Accrual Rate

The study is designed to provide 80% power to detect effect sizes for change in the primary outcome, CES-D, in the moderate range for both SE and MAPs compared to the control condition. An anticipated effect size of d = 0.50 standard deviation units is based on mean change over time and variability reported in our Phase II mindfulness trial[13] and other studies.[19,20,70,71,12]. Blinded analysis of early study data indicated a change score SD of 9.1 and a correlation between baseline scores and change scores of -0.51. The familywise error rate will be controlled at 0.05 for two hypothesis tests, one comparing SE to control and the other comparing MAPs to control, using Dunnett's procedure. [72,73] Using change score SD of 9.2 and correlation of -0.50, we calculated that 58 participants in each arm at T2 would provide 80% power to detect d = 0.50. We adjusted to 70 per arm to account for attrition of 10-15%.

Total Expected Accrual: 210 from across the three clinical sites (Protocol Amendment, May 6, 2019)

REFERENCES

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians 2014;64:9-29.
2. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA: a cancer journal for clinicians 2014;64:52-62.
3. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. Journal of the National Cancer Institute 2012;104:386-405.
4. Kroenke CH, Rosner B, Chen WY, Kawachi I, Colditz GA, Holmes MD. Functional impact of breast cancer by age at diagnosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004;22:1849-56.
5. Vinokur AD, Threatt BA, Vinokur-Kaplan D, Satariano WA. The process of recovery from breast cancer for younger and older patients. Changes during the first year. Cancer 1990;65:1242-54.
6. Thewes B, Butow P, Girgis A, Pendlebury S. The psychosocial needs of breast cancer survivors; a qualitative study of the shared and unique needs of younger versus older survivors. Psycho-oncology 2004;13:177-89.
7. Ganz PA, Land SR, Geyer CE, Jr., et al. Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:1110-6.
8. Crandall C, Petersen L, Ganz PA, Greendale GA. Association of breast cancer and its therapy with menopause-related symptoms. Menopause 2004;11:519-30.
9. Moinpour CM, Lovato LC, Thompson IM, Jr., et al. Profile of men randomized to the prostate cancer prevention trial: baseline health-related quality of life, urinary and sexual functioning, and health behaviors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2000;18:1942-53.
10. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower JE. Breast cancer in younger women: reproductive and late health effects of treatment. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2003;21:4184-93.
11. Allen SM, Shah AC, Nezu AM, et al. A problem-solving approach to stress reduction among younger women with breast carcinoma: a randomized controlled trial. Cancer 2002;94:3089-100.
12. Scheier MF, Helgeson VS, Schulz R, et al. Interventions to enhance physical and psychological functioning among younger women who are ending nonhormonal adjuvant treatment for early-stage breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:4298-311.
13. Bower JE, Crosswell AD, Stanton AL, et al. Mindfulness meditation for younger breast cancer survivors: a randomized controlled trial. Cancer 2015;121:1231-40.
14. Ruddy KJ, Greaney ML, Sprunck-Harrild K, Meyer ME, Emmons KM, Partridge AH. Young Women with Breast Cancer: A Focus Group Study of Unmet Needs. Journal of adolescent and young adult oncology 2013;2:153-60.
15. Bloom JR, Stewart SL, D'Onofrio CN, Luce J, Banks PJ. Addressing the needs of young breast cancer survivors at the 5 year milestone: can a short-term, low intensity intervention produce change? Journal of cancer survivorship : research and practice 2008;2:190-204.
16. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:1840-50.
17. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2014;32:1605-19.
18. Ledesma D, Kumano H. Mindfulness-based stress reduction and cancer: a meta-analysis. Psycho-oncology 2009;18:571-9.
19. Zainal NZ, Booth S, Huppert FA. The efficacy of mindfulness-based stress reduction on mental health of breast cancer patients: a meta-analysis. Psycho-oncology 2013;22:1457-65.