Original Article

Mindfulness-Based Cancer Recovery and Supportive-Expressive Therapy Maintain Telomere Length Relative to Controls in Distressed Breast Cancer Survivors

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BACKGROUND: Group psychosocial interventions including mindfulness-based cancer recovery (MBCR) and supportive-expressive group therapy (SET) can help breast cancer survivors decrease distress and influence cortisol levels. Although telomere length (TL) has been associated with breast cancer prognosis, the impact of these two interventions on TL has not been studied to date. **METHODS:** The objective of the current study was to compare the effects of MBCR and SET with a minimal intervention control condition (a 1-day stress management seminar) on TL in distressed breast cancer survivors in a randomized controlled trial. MBCR focused on training in mindfulness meditation and gentle Hatha yoga whereas SET focused on emotional expression and group support. The primary outcome measure was relative TL, the telomere/single-copy gene ratio, assessed before and after each intervention. Secondary outcomes were self-reported mood and stress symptoms. **RESULTS:** Eighty-eight distressed breast cancer survivors with a diagnosis of stage I to III cancer (using the American Joint Committee on Cancer (AJCC) TNM staging system) who had completed treatment at least 3 months prior participated. Using analyses of covariance on a per-protocol sample, there were no differences noted between the MBCR and SET groups with regard to the telomere/single-copy gene ratio, but a trend effect was observed between the combined intervention group and controls (F [1,84], 3.82; $P = .054$; $\eta^2 = .043$); TL in the intervention group was maintained whereas it was found to decrease for control participants. There were no associations noted between changes in TL and changes in mood or stress scores over time. **CONCLUSIONS:** Psychosocial interventions providing stress reduction and emotional support resulted in trends toward TL maintenance in distressed breast cancer survivors, compared with decreases in usual care. ***Cancer* 2014;000:000-000.**

KEYWORDS: psychosocial interventions, mindfulness-based stress reduction, supportive-expressive therapy, telomere length, clinical trial.

INTRODUCTION

Given the growing cohort of breast cancer survivors resulting from a combination of early detection and better survival outcomes,[1,2] coupled with ongoing psychosocial issues for many including fears of disease recurrence, depression, anxiety, and fatigue,[3] interventions to support the survivorship phase have increased in importance and urgency.[2] We recently reported primary outcomes of the MINDSET trial, which compared 2 empirically supported psychosocial group interventions, mindfulness-based cancer recovery (MBCR) and supportive-expressive group therapy (SET), with a minimal-intervention control condition on mood, stress symptoms, quality of life, social support, and diurnal salivary cortisol in distressed breast cancer survivors.[4] Although MBCR participation resulted in the most psychosocial benefit, including improvements across a range of psychosocial outcomes, both MBCR and SET resulted in healthier cortisol profiles over time compared with the control condition.

In this secondary analysis of MINDSET trial data, we collected and stored blood samples taken from a subset of women to further investigate the effects of these interventions on potentially important biomarkers. Telomeres are specialized nucleoprotein complexes that form the protective ends of linear chromosomes[5] and provide genomic stability

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through several mechanisms. Telomere dysfunction and the loss of telomere integrity may result in DNA damage or cell death; when a critically short telomere length (TL) is reached, cells enter senescence and have reduced viability, and chromosomal fusions appear.[6] Shorter TL has been implicated in several disease states, including cardiovascular disease, diabetes, dyskeritosis congenita, aplastic anemia, and idiopathic pulmonary fibrosis.[7] Shorter TL also was found to be predictive of earlier mortality in patients with chronic lymphocytic leukemia,[8] promyelocytic leukemia,[9] and breast cancer.[10-12] However, the relationships between TL and the clinical or pathological features of tumors are still not clearly understood.[13]

Recent emerging research has suggested that TL and its enzyme telomerase may be susceptible to psychosocial influences, particularly stress.[14] Telomerase is the specialized cellular reverse transcriptase that elongates telomeric DNA, thereby counteracting the telomere shortening that occurs with successive rounds of cell division.[5] The earliest studies demonstrated associations between naturally occurring stressors and telomere biology in noncancer samples, in which stress was associated with shorter TL and lower telomerase activity.[15,16]

Although stress plays a role in the etiology and progression of many diseases,[17-19] the role of stress in cancer remains suggestive.[20,21] Nonetheless, several biobehavioral pathways between psychosocial stress and mechanisms of cancer development have been indentified.[20,22] Telomere biology represents another provocative potential pathway that may link psychosocial influences with cancer progression.[23] One report of associations between decreases in distress levels and increased TL over a 4-month period in survivors of cervical cancer is to our knowledge the only current evidence of associations between TL and stress in individuals with cancer.[23]

Intervention studies have now examined the effects of psychosocial programs on telomerase activity and TL. An uncontrolled study by Ornish et al reported lifestyle changes including a low-fat diet, exercise, and stress reduction in patients with low-risk prostate cancer were significantly associated with increases in telomerase activity, which was significantly associated with decreases in low-density lipoprotein, cholesterol, and psychological distress.[24] However, there was no control group and TL was not measured. More recently, 3 small trails of meditation intervention studies measured telomerase activity in healthy volunteers,[25] individuals with obesity,[26] and caregivers of patients with Alzheimer disease.[27] One study also measured TL in healthy meditators.[28] Although each of these trials demonstrated promising results, they had small sample sizes (ranging from 37-60 participants) and only postassessment measurements,[25] and the one study that measured TL (as opposed to telomerase)[28] lacked randomization. Assessing TL before and after psychosocial interventions would allow for the development of an understanding of the potential short-term effects of psychosocial support and mind-body practices on TL. We expected different results in TL between MBCR and SET. This is because TL is susceptible to psychological influences[14] and MBCR was found to be superior to SET in improving mood and stress symptoms in our previous study.[4]

The objectives of the current study were to: 1) compare the effects of 2 psychosocial interventions for distressed breast cancer survivors with a control condition on TL, and 2) assess the relationships between changes in TL and changes in stress and mood. Because the TL data were available for only a subset of participants, the current study aimed to demonstrate preliminary evidence of the effect of psychooncological interventions on TL so that future research may target TL as a primary outcome with greater sample sizes.

MATERIALS AND METHODS

Study Design

The current study used a longitudinal randomized controlled design with 3 groups: MBCR, SET, and a minimal treatment control group (6-hour stress management seminar [SMS]). Participants were randomized in cohorts between October 2007 and December 2010. The study was approved by the Institutional Review Board of the Faculty of Medicine at the University of Calgary. The study was registered on clinicaltrials.gov (number NCT00390169).

Participants

Participants were breast cancer survivors who had completed all medical treatments at least 3 months previously, with the exception of hormonal or trastuzumab therapy. Women were included if they: 1) were diagnosed with AJCC stage I to III breast cancer; 2) were aged >18 years; and 3) scored ≥ 4 on the National Comprehensive Cancer Network Distress Thermometer,[29] thereby indicating clinically significant distress.[30] We included only those women who exhibited significant distress because they would likely benefit most from these interventions.

Exclusion criteria included: 1) a diagnosis of a concurrent disorder of either psychosis, substance abuse, bipolar disorder, or active suicidality (according to the 4th edition of the *Diagnostic and Statistical Manual of Mental*

Disorders [DSM-IV]; 2) current use of psychotropic medications (antipsychotics or anxiolytics; the use of antidepressants was not an exclusionary factor due to their high prevalence); 3) a diagnosis of a concurrent autoimmune disorder; and 4) past participation in an MBCR or SET group.

A total of 271 women participated in the larger study from both Calgary, Alberta and Vancouver, British Columbia. Due to the availability of resources, blood samples were only collected in Calgary. Of the 128 women in Calgary, 5 declined to donate their blood. Thirty-one women provided their blood only at the preintervention time period; therefore, the current study included 92 women who donated a blood sample before and after the intervention.

Procedures

Participants were self-referred through advertising or direct mailing of personalized study invitation letters through cancer registries. If patients were eligible and provided informed consent, before and after the intervention, they completed questionnaires and donated a blood sample at the cancer center laboratory. Women in the control group provided their blood samples before and 10 weeks after the SMS. Participants did not receive any incentives for their participation.

Randomization and Blinding

Randomization was conducted once a group of participants was assembled for a cohort. The biostatistician randomized participants into one of the MBCR, SET, or control programs with a 2:2:1 ratio using the Research Randomizer (randomizer.org/). The intervention commenced within 2 weeks of randomization. Both participants and Research Assistants were blind to the condition at the time of baseline assessment.

Interventions

Mindfulness-based cancer recovery

MBCR was modeled on the mindfulness-based stress reduction program originally developed at the Massachusetts Medical Center.[31] The program cultivates mindfulness, awareness of the present moment in an open and nonjudgemental manner.[31] Two of us (L.E.C. and M.S.) developed and manualized MBCR[32] specifically to meet the needs of oncology populations, and its efficiency has been validated in previous studies.[33-39] Facilitators were clinical psychologists and a nurse who were fully trained in mindfulness-based stress reduction and had led groups in previous MBCR trials. Participants attended 8 weekly group sessions of 90 minutes in duration, and a six-hour retreat between weeks 6 and 7. Participants were provided with a course booklet and practice compact discs for guided meditation and mindful body movement at home.

Supportive-expressive group therapy

SET is also a manualized, well-validated psychosocial intervention for oncology populations.[40] Participants met in a group for 90 minutes weekly for 12 weeks with clinical psychologist(s) and/or clinical social worker(s) who were highly experienced in SET. The SET program encourages openness and emotional expression, with an aim toward developing a mutual support system among members as well as improving interactions with family and treating physicians. Through group discussion, SET also aims to facilitate coping skills and to detoxify negative emotions surrounding mortality.

MBCR and SET were different in content; however, both programs were similar in nonspecific components, including structure, group size, group environment, and total contact time (18 hours).

Control Condition

Stress management seminar

Women in the control condition participated in a 1-day (6-hour) didactic SMS led by an experienced clinical social worker. The seminar was the same control condition used by the University of Miami Center for Psycho-Oncology Research.[41] The SMS was used to minimize the likelihood of demoralization for those randomized to the control condition and hence to maximize accrual and retention.

Measures

Demographics

Age, marital status, employment status, education history, medical and psychiatric history, current medications, and previous experience with yoga or meditation were obtained.

Disease parameters

Information regarding the stage of disease at the time of study enrollment, first diagnosis date, and types and frequency of medical treatment were obtained through the Alberta Cancer Registry.

Health behavior

Daily physical activity level, alcohol and nicotine intake, and quality of diet and sleep were assessed.

Mood

The Profile of Mood States (POMS)[42] assesses 6 dimensions of mood.[43] A total score was used to indicate the overall level of mood disturbances.

Stress

The short form of the Symptoms of Stress Inventory (SOSI),[44] the Calgary SOSI (C-SOSI),[45] consists of 56 items and 8 subscales. It assesses physical and psychological symptoms and behavioral responses to stressful situations. A total score was used to indicate the level of subjective stress.

Preparation of blood samples

Two 6-mL ethylenediamine tetraacetic acid tubes of blood collected from participants before and after the intervention were refrigerated and processed within 24 hours of collection. The ethylenediamine tetraacetic acid tubes were mixed well, allowed to sit for 30 minutes, and then centrifuged at 1500g for 10 minutes at 4°C. A total of 0.25 mL of buffy coat was aliquoted into each of 4 cryovials and frozen at −80°C. Total genomic DNA was extracted from 250 μL of buffy coat using the DNeasy Blood and Tissue Kit (Qiagen, Germantown, Md), as per the manufacturer's instructions.

Telomere length

We used a high-throughput analysis to measure relative TL using quantitative real-time polymerase chain reaction (qPCR). Sample reactions were set up in triplicate using 10 ng of template DNA and qPCR was run using Power SYBR Green PCR Master Mix (Life Technologies, Grand Island, NY) for both TL and the single-copy gene, ribosomal acidic protein 36B4. Fluorescent signal detection was monitored and quantified as per the manufacturer's directions on an ABI7900 Real Time PCR System (Applied Biosystems, Foster City, Calif). A reference sample was run on each reaction plate to calculate interplate variation. The ratio of the telomere PCR signal to the single-copy gene (ribosomal acidic protein 36B4) signal (the T/S ratio) is proportional to the average TL of all the cells in a sample and was based on the calculation of the ΔCt ($Ct^{(telomere)}/Ct(^{single\ gene})$), normalized to the average T/S ratio of a pooled reference standard. The reference sample is the average T/S ratio of all samples run, which by definition relative to itself is 1.00. T/S values, therefore, represent relative TLs, expressed relative to the T/S ratio value of the reference standard DNA sample. Samples with a T/S >1.0 have an average TL that is greater than the standard DNA; samples with a T/S <1.0 have an average TL that is shorter than the standard DNA.

Data Analyses

Potential baseline differences with regard to demographic and medical variables between conditions were assessed. T/S ratio values were determined as outliers and excluded if they were either greater or lower than 4 standard deviations from the mean. Two T/S ratio values were excluded, from each of the pre and post-assessment time points, resulting in a total of 88 survivors with complete data. The T/S ratios were positively skewed. To correct this, $\log_{10}$ transformations were applied to the pretreatment and posttreatment T/S ratios. To identify potential confounders, either correlations (for continuous variables) or analyses of variance (for categorical variables) were conducted among TL, age, time since diagnosis, alcohol and nicotine intake, cancer severity, quality of sleep and diet, marital status (single, married/cohabitating, or separated/divorced/widowed), and employment status (full-time work, part-time work, or retired/unemployed).

Objective 1

Our primary analysis compared the $\log_{10}$ T/S ratios of the MBCR and SET psychosocial interventions (the treatment group) with the control group in an analysis of covariance (ANCOVA). We used an orthogonal contrast to make this comparison and used preintervention $\log_{10}$ T/S ratios as a covariate. Within the same ANCOVA, we first used another orthogonal contrast to test the comparability of postintervention T/S ratios in the 2 intervention arms (MBCR vs SET).

Objective 2

Residual change scores were calculated by obtaining residual scores from linear least-squares models using pretreatment values to predict posttreatment values for the posttreatment $\log_{10}$ T/S ratio, POMS total score, and the C-SOSI scores, using pretreatment scores on the same variable as predictors. Using residualized change scores is hence a much more conservative analysis than using raw pre to post values. We then calculated Pearson product-moment correlations among residual change scores both within each treatment group and for all subjects (ignoring treatment group). In all analyses, 2-sided alpha values of 5% were used. All statistical analyses were conducted using IBM SPSS software (version 20; SPSS Inc, IBM Corporation, Armonk, NY).

RESULTS

Participants

Figure 1 shows the flow of participants. Table 1 summarizes demographic and medical characteristics for all groups. The 3 groups were well balanced with regard to their baseline characteristics, with no group differences found.

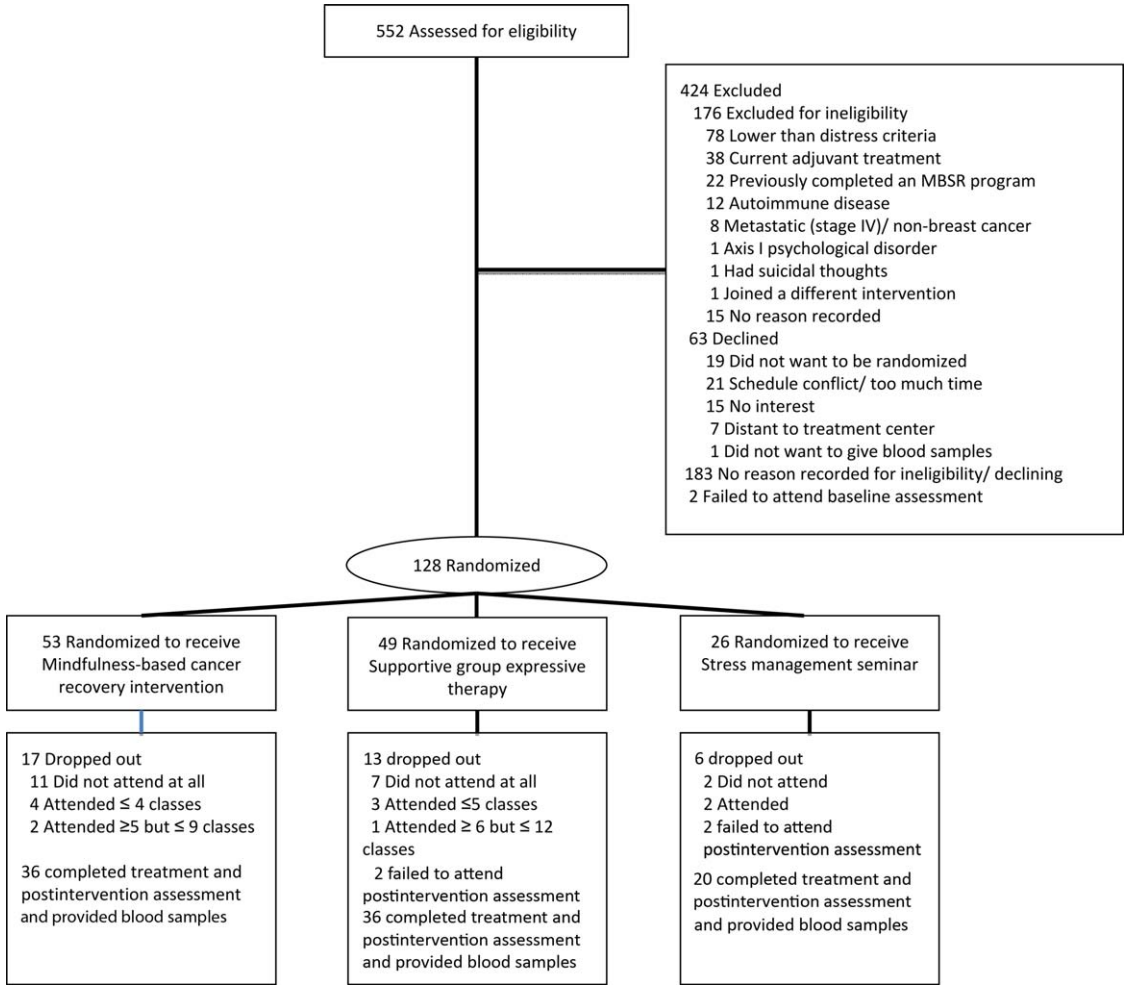

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart is shown.

Confounding Variables

There were no associations noted between baseline TL and any of the medical, demographic, and health behavioral factors (all $P > .19$). Hence, only baseline TL was included as a covariate in the subsequent analyses.

Objective 1: Changes in TL Between MBCR Versus SET

Table 2 shows TL at both preintervention and postintervention across groups and the results of significance testing. Figure 2 represents distributions of preintervention and postintervention T/S ratios across groups. The results of ANCOVA demonstrated no statistical evidence of differences in postintervention TL between the MBCR and SET interventions after adjusting the impact of the preintervention $\log_{10}$ T/S ratios. The mean difference was −0.12 (95% confidence interval [95% CI], −0.74 to 0.50). Because the 2 interventions shared similar nonspecific components and no significant differences emerged in their baseline-adjusted postintervention T/S ratios, the 2 intervention groups were subsequently combined to allow greater power for detecting any effects on TL related to participation in a psychosocial intervention compared with the control condition.

Changes in TL Between Intervention Versus Control

After adjustment for the baseline $\log_{10}$ T/S ratio, there was a statistical trend toward a difference in posttreatment $\log_{10}$ T/S ratios between treatment and control subjects (statistics shown in Table 2). The adjusted mean difference was 0.67 (95% CI, −0.01 to 1.35). The effect size of η^2 was 0.043 (small to medium). T/S ratios in the control group demonstrated a trend toward a decrease

TABLE 1. Baseline Demographic and Medical Characteristics of Participants Across 3 Conditions

Characteristics	MBCR n = 34	SET n = 36	Control n = 18
Mean age (SD), y	54.43 (9.00)	54.05 (9.50)	56.01 (10.20)
Mean no. of y of education (SD)[a]	14.81 (2.44)	15.27 (3.09)	13.78 (1.90)
Mean time since diagnosis (SD), mo	25.56 (24.33)	27.74 (35.94)	21.16 (14.49)
Marital status, no. (%)[a]			
Single	2 (5.9)	2 (5.6)	1 (5.6)
Cohabiting/married	28 (82.4)	24 (66.7)	14 (77.8)
Divorced/separated/widowed	4 (11.8)	9 (25.0)	3 (16.7)
Employment, no. (%)			
Unemployed/retired/disabled	14 (41.2)	14 (38.9)	8 (44.4)
Part time	8 (23.5)	8 (22.2)	2 (11.1)
Full time	12 (35.3)	13 (36.1)	8 (44.4)
Cancer stage, no. (%)[b]			
0	1 (2.9)	1 (2.8)	2 (11.1)
I	14 (41.2)	18 (50.0)	7 (38.9)
II	13 (38.2)	11 (30.6)	7 (38.9)
III	4 (11.8)	3 (8.3)	2 (11.1)
Medical treatment received, no. (%)			
Surgery only	0 (0)	3 (8.3)	0 (0)
Surgery and radiation	2 (5.9)	6 (16.7)	1 (5.6)
Surgery and multimodal	32 (94.1)	27 (75.0)	17 (94.4)

Abbreviations: MBCR, mindfulness-based cancer recovery; SET, supportive-expressive group therapy; SD, standard deviation.
[a] Data were missing for 1 participant.
[b] Data were missing for 5 participants.

relative to those in the intervention group, which remained relatively stable.

Based on these results, we calculated a sample size to detect a significant group difference with 80% power. Although the exact size of the change in T/S ratios needed for clinical significance is unknown, to detect a 0.5 difference in T/S ratios between the intervention and the SMS, a new trial would require 106 survivors in each group (total of 212 survivors) with a 1:1 randomization ratio.

Objective 2: Associations Between TL and Psychosocial Measures

There was no statistical evidence of correlations between residual changes in TL and POMS or C-SOSI in the intervention ($r = -.03$ [$P = .804$] and $r = .14$ [$P = .244$]) or control ($r = -.27$ [$P = .277$] and $r = -.11$ [$P = .669$]) groups, or across the 2 combined conditions ($r = -.11$ [$P = .307$] and $r = .07$ [$P = .546$]).

DISCUSSION

To our knowledge, the current study is the first report to demonstrate a potential effect of these psychosocial interventions on TL among distressed breast cancer survivors. There was little discernment between MBCR and SET. Both maintained TL over the 3-month intervention period, whereas women in the control condition demonstrated a trend toward decreases in relative TL. Similarly, in our previous report of the larger parent trial, both the MBCR and SET groups maintained the steepness of salivary cortisol slopes compared with those in the control group, whose slopes became flatter, largely due to elevations in evening cortisol levels.[4] Together, these changes suggest an effect of the interventions on potentially important biomarkers of psychosocial stress. Given the increasingly well-documented association between TL and cancer initiation[46] and survival,[47] this finding adds to the literature supporting the potential for stress-reducing interventions to impact important disease-regulating processes and ultimately disease outcome.[48]

Inconsistent with other findings,[23,28] we did not observe any associations between changes in stress or mood scores over the course of the interventions and concomitant changes in TL. This could be due to the short time span of the interventions, and the use of different measures of stress and mood than previous researchers, in a different population (patients with breast cancer vs cervical cancer[23] and healthy individuals[28]).

Although the current study is strengthened by randomization and the inclusion of only distressed survivors, it does have several limitations. Chief among these is missing data, which precluded the feasibility of conducting intent-to-treat analyses. The control condition was also therefore small (18 individuals), because twice as many women were randomized to the active intervention groups as to the control condition. Hence, the study would

TABLE 2. Preintervention and Postintervention T/S Ratio Values Across Groups and Results of Significance Testing

T/S Ratio Measures (Log^{10} Values)	MBCR n = 34	MBCR Versus SET F (1,84), P	SET n = 36	MBCR and SET n = 70	Intervention Versus Control F (1,84), P	Control n = 18
Preintervention, mean (95% CI)	0.14 (−0.27 to 0.54)		−0.02 (−0.48 to 0.45)	0.06 (−0.25 to 0.36)		0.12 (−0.46 to 0.71)
Postintervention, mean (95% CI)	−0.04 (−0.51 to 0.43)		0.04 (−0.39 to 0.48)	0.001 (−0.31 to 0.31)		−0.65 (−1.34 to 0.04)
Postintervention adjusting for baseline T/S ratios, mean (SD)	−0.07 (−0.50 to 0.36)	.15 .702	0.07 (−0.35 to 0.48)	0.01 (−0.30 to 0.31)	3.82 .054	−0.67 (−1.27 to −0.06)

Abbreviations: 95% CI, 95% confidence interval; MBCR, mindfulness-based cancer recovery; SET, supportive-expressive group therapy; SD, standard deviation; T/S ratio, telomere/single-copy gene ratio.

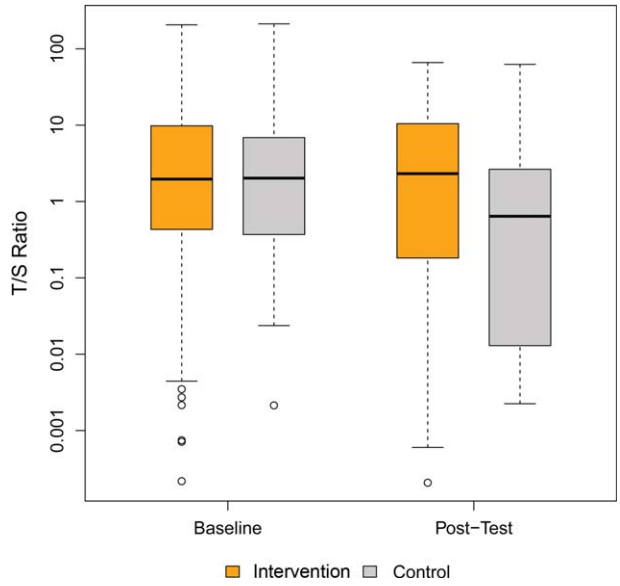

Figure 2. Preintervention and postintervention untransformed telomere lengths are shown. For each group, the top and bottom of the box represents the 75th and 25th percentiles of the data, respectively. The horizontal line through the box is the median. The top and bottom of the error bars are the maximum and minimum values, respectively, that are not outliers (the top and bottom 25% of scores). Circles outside of the lines represent individual outliers. T/S ratio indicates the telomere/single-copy gene ratio.

require approximately twice as many participants in each group to detect a change in the T/S ratio of 0.5.

There have also been reports that TL varies with breast cancer subtype, such that women with more aggressive types, including luminal B, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative tumors, had shorter TL.[49] Unfortunately we did not have subtyping data available. TL also may be affected by chemotherapy among patients with breast cancer, but effects varied across participants in previous research. Some demonstrated increased leukocyte TL after chemotherapy, and some showed decreases, such that no overall group changes were noted.[50] This is consistent with the current study finding of no differences in TL across treatment groups.

We also are not aware of the long-term effects of these interventions on TL. Future investigators should power studies of intervention effects on TL and telomerase as primary outcomes, and follow participants over time to better understand the clinical implications of group differences. The interpretation of any changes in TL in patients with breast cancer is difficult. One study that analyzed TL in breast tumor tissue found no relations between TL and any clinical or pathological features or

disease or survival outcomes,[13] whereas other studies have shown that TL was related to breast cancer risk[46,51] and survival.[10,46,47] Although interpretation remains difficult, the results of the current study nonetheless provide provocative new data that suggest it is possible to influence TL in cancer survivors through the use of psychosocial interventions involving group support, emotional expression, stress reduction, and mindfulness meditation.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Carlson holds the Enbridge Research Chair in Psychosocial Oncology, which is cofunded by the Canadian Cancer Society Alberta/NWT Division and the Alberta Cancer Foundation. She is also an Alberta Innovates-Health Solutions Health Scholar. She has received operating grants from the Alberta Cancer Foundation and the Canadian Breast Cancer Research Alliance for work performed as part of the current study. In addition, she and Dr. Speca have received royalties from New Harbinger Publications for a book on mindfulness-based cancer recovery, which is one of the programs in the research, for work performed outside of the current study. Dr. Beattie is a scholar of the Alberta Cancer Foundation and Dr. Degelman is the recipient of a Canadian Institutes of Health Research doctoral scholarship. Dr. Tamagawa is supported by an Alberta Innovates-Health Solutions postdoctoral fellowship and Canadian Psychosocial Oncology Research Training fellowship for work performed as part of the current study. Dr. Speca has received a grant from the Canadian Breast Cancer Research Alliance for work performed as part of the current study.

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