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Bower, Julienne E
Partridge, Ann H
Wolff, Antonio C
et al.

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Improving biobehavioral health in younger breast cancer survivors: Pathways to Wellness trial secondary outcomes

Julienne E. Bower, PhD,[1,2,3,4,*] Ann H. Partridge, MD,[5,6] Antonio C. Wolff, MD,[7] Steve W. Cole, PhD,[2,3,4,8] Michael R. Irwin, MD,[1,2,3,4] Elissa D. Thorner, MHS,[7] Hadine Joffe, MD, MSc,[9,10,11] Laura Petersen, MA,[4] Catherine M. Crespi, PhD,[4,12] Patricia A. Ganz, MD[4,8,13]

[1]Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA
[2]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[3]Cousins Center for Psychoneuroimmunology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA, USA
[4]Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA, USA
[5]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
[6]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[7]The Johns Hopkins University School of Medicine and Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA
[8]Department of Medicine (Hematology-Oncology), David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[9]Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[10]Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[11]Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute, Boston, MA, USA
[12]Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA
[13]Department of Health Policy and Management, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA

*Correspondence to: Julienne E. Bower, PhD, 1285 Psychology Building, Los Angeles, CA 90095-1563, USA (e-mail: jbower@ucla.edu).

Abstract

Background: The Pathways to Wellness trial tested the efficacy of 2 interventions for younger breast cancer survivors: mindful awareness practices (MAPs) and survivorship education (SE). This planned secondary analysis examines intervention effects on stress, positive psychological outcomes, and inflammation (Clincaltrials.gov NCT03025139).

Methods: Women diagnosed with breast cancer at or before age 50 years who had completed treatment and had elevated depressive symptoms were randomly assigned to 6 weeks of MAPs, SE, or wait-list control (WLC). Assessments conducted at pre- and postintervention and at 3- and 6-month follow-up measured general stress perceptions, cancer-related intrusive thoughts and worry, positive affect, meaning and peace in life, altruism and empathy, and markers of inflammation. Analyses compared change in outcomes over time in each intervention group relative to WLC using linear mixed models.

Results: A total 247 women were randomly assigned to MAPs (n = 85), SE (n = 81), or WLC (n = 81). MAPs statistically significantly decreased intrusive thoughts and worry at postintervention and 3-month follow-up relative to WLC ($P < .027$) and statistically significantly increased positive affect and meaning and peace at postintervention, with positive affect persisting at 3-month follow-up ($P < .027$). SE statistically significantly decreased intrusive thoughts at 3-month follow-up and statistically significantly increased positive affect at 6-month follow-up relative to WLC ($P < .01$). Proinflammatory gene expression increased in WLC relative to MAPs ($P = .016$) but did not differ from SE. There were no intervention effects on other outcomes.

Conclusion: MAPs had beneficial effects on psychological and immune outcomes in younger breast cancer survivors and is a promising approach for enhancing biobehavioral health.

Breast cancer is the most common cancer in younger women (<50 years at time of diagnosis), who comprise approximately 19% of incident breast cancer cases (1). The breast cancer experience is particularly stressful and disruptive for younger women not only because they are generally at higher risk of recurrence than older women (2), often necessitating more aggressive therapy, but also because the disease is occurring at a time in life when they are focusing on completing their education, developing their careers, and/or raising a family (3). Younger women perceive cancer as more threatening (4), have higher levels of illness intrusiveness (5), and report greater fear of recurrence (6) than older survivors. Younger breast cancer survivors (BCS) also report lower levels of positive psychological factors that may help buffer the negative impact of diagnosis and treatment, including a sense of peace and meaning in life (5).

Interventions are needed for this vulnerable group that target biobehavioral factors contributing to poor quality of life and the potential for shorter survival. However, few interventions have been specifically designed for younger BCS beyond the acute phase of treatment (7). In the broader literature, psychoeducation (8) and mindfulness meditation (9,10) have emerged as promising approaches for reducing distress and improving quality of life in

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cancer patients and survivors. These approaches may be particularly relevant for younger women, who often report unmet informational needs (targeted by education) as well as high levels of stress (targeted by mindfulness) (11,12).

The Pathways to Wellness (PTW) trial was designed to test the efficacy of both educational and mindfulness-based interventions developed specifically for younger BCS. As previously reported, both interventions led to reductions in depressive symptoms, the primary trial outcome; mindfulness also led to reductions in physical symptoms (fatigue, insomnia, vasomotor symptoms) relative to wait list control (13). Here, we report on intervention effects on additional psychological and biological outcomes relevant for long-term health and well-being in BCS. These were predefined outcomes designed to assess cancer-specific and general measures of stress (14) as well as measures of well-being (positive affect, meaning and peace in life, altruism and empathy) (15). In addition, we examined intervention effects on inflammation, which is known to play a role in tumor growth and spread (16-18), contribute to cancer-related physical symptoms (19), and promote medical conditions that are prevalent in cancer survivors (eg, cardiovascular disease) (20). Inflammation is regulated by physiological stress systems (21), and interventions that reduce stress signaling have the potential to influence inflammatory biology. Indeed, psychosocial and mind-body interventions have been shown to reduce markers of inflammation, particularly proinflammatory gene expression (22,23).

Methods

Overview of trial design

PTW is a randomized, 3-arm, phase III trial designed to evaluate the efficacy of 2 distinct group interventions, mindful awareness practices (MAPs) and survivorship education (SE), for younger BCS with elevated depressive symptoms (13,24). The trial compared each program with a wait-list control (WLC) condition in an efficient design given that both are credible interventions. The trial was conducted at 3 sites: University of California Jonsson Comprehensive Cancer Center in Los Angeles, CA; Dana-Farber Cancer Institute in Boston, MA; and Johns Hopkins Kimmel Comprehensive Cancer Center in Baltimore, MD. The study was approved by the institutional review boards at each site and registered at Clincaltrials.gov (NCT03025139); the PTW trial protocol is provided in the Supplementary Materials (available online). All participants provided informed consent.

Participants

Women were eligible if they met the following criteria: 1) breast cancer diagnosis (stage 0, I, II, or III) at or before age 50 years; 2) within 5 years of diagnosis; 3) completion of surgery, radiation, and/or chemotherapy at least 6 months previously; 4) ability to complete questionnaires in English; 5) ability to participate in the intervention; and 6) presence of at least mild depressive symptoms as indicated by score of at least 5 on the Patient Health Questionnaire-8 (PHQ-8) (25). This PHQ-8 score was used through May 2019 and then liberalized to a score of at least 3 to enhance recruitment. Exclusion criteria were 1) recurrent or metastatic breast cancer, 2) another interval cancer diagnosis following breast cancer diagnosis (excluding nonmelanoma skin cancer), 3) current mindfulness practice, 4) pregnancy, and 5) serious chronic medical or psychiatric condition that could detract from intervention participation or measurement of outcomes.

Procedure

Recruitment was conducted from February 2017 to September 2019 using institutional and community resources, including regional cancer registries. After determination of eligibility, participants completed baseline assessments and were randomly assigned to MAPs, SE, or WLC (1:1:1 ratio) after stratifying on study site and PHQ-8 score ($\leq$7, $\geq$8) using permuted blocks. Postintervention assessments were conducted within 2 weeks after intervention completion, and follow-up assessments were conducted 3 and 6 months after intervention completion. All assessments included questionnaires; blood collection was conducted at baseline, postintervention, and 6-month follow-up (with exception of 6-month follow-up for the final cohort, which was questionnaire only due to COVID-19).

Interventions

MAPs and SE are both 6-week, standardized group interventions that met in-person for weekly 2-hour sessions. MAPs involved presentation of theoretical material on mindfulness and experiential practice of mindfulness meditations, including attention to breath and body sensations and approaches for dealing with pain, difficult thoughts and feelings, and enhancing loving kindness. SE involved presentation of information on topics relevant for younger BCS, including quality of life, medical management, relationships, sexuality and fertility, and energy balance. After completion of the 6-week programs, 2 booster sessions were conducted for women assigned to MAPs, and 2 newsletters were provided for women assigned to SE. See Bower et al. (13) for details on intervention content and fidelity.

Study outcomes

Questionnaires were electronically administered using REDCap to assess demographic and clinical characteristics and study outcomes. The primary outcome was depressive symptoms; this report focuses on secondary psychological and biological outcomes.

Psychological outcomes

General stress perceptions were assessed with the Perceived Stress Scale (26). Intrusive thoughts about cancer, a measure of cancer-related stress, were assessed with the intrusions subscale of the Impact of Events Scale (IES) (27). Worry about cancer, which includes items assessing fear of recurrence, was assessed with the worry subscale of the Impact of Cancer scale version 2 (IOCv2) (28). Positive affect was assessed with the positive affect subscale of the Positive and Negative Affect Scale (29). Meaning and peace in life was assessed with meaning and peace subscale of the FACIT-Spiritual scale (30), and cancer-related altruism and empathy was assessed with the relevant subscale of the IOCv2 (28). All are validated subscales used in previous research with cancer patients and selected a priori to assess the constructs of interest.

Immune outcomes

The primary immune outcome was inflammatory gene expression measured through a prespecified composite score of standardized proinflammatory gene transcripts. This composite has been shown to be upregulated in the context of chronic stress (31) and downregulated in the context of well-being (32,33) and in response to the MAPs intervention (11,34). RNA was extracted (QiagenRNEasy) from peripheral blood mononuclear cells isolated from 10-mL venipuncture samples collected into sodium

heparin Vacutainers, tested for suitable mass (Nanodrop ND1000) and integrity (Agilent Bioanalyzer) and subject to genome-wide transcriptional profiling using a high-efficiency mRNA-sequencing assay (LexogenQuantSeq 3' FWD) in University of California, Los Angeles Neuroscience Genomics Core following the manufacturer's standard protocol.

Plasma markers of inflammation, interleukin-6 and C reactive protein (CRP), were also assessed; these have been linked to cancer-related symptoms (35) and breast cancer progression (18) and may be influenced by behavioral interventions (22). Details of collection and assay procedures are provided in the Supplementary Methods (available online). Inflammatory markers were log transformed before analysis to normalize distributions.

Sample size

Sample size calculations were based on the primary outcome, CES-D depressive symptoms at postintervention. The study was designed to provide 80% power to detect medium effect sizes of $d = 0.50$ for change in CES-D from pre- to postintervention for MAPs and SE compared with WLC (11), yielding a target sample size of 70 per arm. The study was not powered to test differences between the 2 active interventions or to test effects on secondary outcomes.

Statistical methods

Baseline differences across study arms were assessed using χ^2 square, Kruskal-Wallis, and analysis of variance tests. Outcome analyses were conducted under the intent-to-treat principle, including all participants in their assigned condition, using linear mixed models fitted to all available data for each outcome variable, including data of participants with incomplete follow-up. Models included fixed effects for time and condition and random effects for individuals and controlled for study site and demographic and clinical variables with baseline imbalance or that differed between participants retained and lost to follow-up.

Primary analyses examined differences from baseline to postintervention in the MAPs and SE groups relative to WLC, as indicated by statistically significant group × time interaction terms. For psychosocial outcomes, we also examined differences in change over time from baseline to 3-month and 6-month follow-up for MAPs and SE compared with WLC. Linear mixed models were conducted with random effects for participant and controlling for site, race (White vs non-White), and partnered status (partnered vs not), which differed across groups. *P* values are for difference in change over time between each intervention group and WLC. Dunnett's method was used to adjust for multiple comparisons within each outcome (MAPs vs WLC and SE vs WLC), which is equivalent to using a *P* value threshold of .027 rather than .05 (36,37). We did not adjust for multiple comparisons across outcomes. Sensitivity analyses were conducted for outcomes with a statistically significant baseline imbalance across groups using an analysis of covariance (ANCOVA) approach, controlling for baseline levels of the outcome. All tests were 2-sided. Analyses were conducted using Stata/SE 15.1.

In analyses of RNA data, raw transcript abundance counts were normalized to transcripts per million mapped reads (TPM), log2-transformed, and screened to omit samples with insufficient read depth (<5 million) or assay precision (average Pearson correlation with other samples <.7) and transcripts with minimal level or variation in expression (SD > .5 log2 transcripts per million mapped reads). This resulted in the omission of 5 gene transcripts, leaving a final set of 14 proinflammatory indicator genes that were analyzed by linear mixed models with random effects for participant and controlling for gene (*FOS*, *FOSL2*, *IL1B*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *PTGS1*, *PTGS2*, *REL*, *RELA*, *RELB*, *TNF*), site, race (White vs non-White), partnered status (partnered vs not), and body mass index (38) using SAS PROC MIXED. Given the reduced sample size for inflammatory markers at the 6-month follow-up (due to COVID-19–related restrictions in our ability to collect blood samples at this assessment for our final cohort of participants), analyses for inflammatory outcomes focused only on changes from pre- to postintervention.

Results

Characteristics of study participants

Over 2.5 years of recruitment, 1525 women expressed interest in the study, 1216 were screened for eligibility, and 247 were eligible and included in the study sample (see Supplementary Figure 1 [available online] for CONSORT diagram and allocation of patients). Table 1 provides demographic and clinical characteristics as well as means for the psychological and immune outcome variables at baseline. Race and partner status were statistically significantly different across study arms and were included as covariates in analyses. Comparison of completers vs noncompleters revealed statistically significant differences across sites, and site was included as a covariate in all analyses. There was also a chance imbalance on IES scores at baseline ($P < .03$), and sensitivity analyses for this outcome were conducted controlling for baseline IES scores. No group differences in other psychological or biological outcomes were observed at baseline.

Intervention characteristics and attendance

Both MAPs and SE were reasonably well-attended; the mean number of classes attended was 4.5 of 6 total classes for MAPs (SD = 1.9, range = 0-6) and 3.8 for SE (SD = 2.1, range = 0-6).

Psychological outcomes

Linear mixed models were fit to compare each intervention group to WLC on change in psychological outcomes, controlling for study site, race, and marital status. Table 2 reports differences in change scores for MAPs vs WLC and SE vs WLC as well as standardized effect sizes and *P* values for these differences. Mean scores at each assessment are reported in Supplementary Tables 1 (available online) (unadjusted means) and 2 (adjusted means). Trajectories of adjusted means in each condition are depicted in Figures 1 and 2.

MAPs led to statistically significant reductions in cancer-related intrusive thoughts and cancer-related worry from pre- to postintervention and 3-month follow-up relative to WLC. Sensitivity analyses controlling for baseline IES levels yielded the same pattern of results. With respect to positive psychological outcomes, MAPs led to statistically significant increases in positive affect from pre- to postintervention and 3-month follow-up. MAPs also led to a statistically significant increase in peace and meaning in life from pre- to postintervention. There was no evidence for statistically significant effects of MAPs on general perceived stress or altruism and empathy.

SE led to a reduction in cancer-related intrusive thoughts that was statistically significant at 3-month follow-up relative to WLC. Analyses controlling for baseline IES scores yielded the same results. There was a delayed effect of SE on positive affect, with a statistically significant increase from baseline emerging at 6-month follow-up relative to WLC. There was no evidence for statistically significant effects of SE on cancer-related worry,

Table 1. Baseline characteristics by intervention group[a]

Characteristics	Mindful awareness practices n = 85	Survivor education n = 81	Waitlist control n = 81	Total n = 247
Demographics				
Age at baseline, y				
Mean (SD)	44.5 (7.7)	45.8 (5.6)	45.9 (5.6)	45.4 (6.4)
Median (min, max)	46.2 (23.2, 54.5)	46.3 (30.1, 55.4)	47.8 (33.0, 53.7)	46.7 (23.2, 55.4)
Age at diagnosis, y				
Mean (SD)	41.9 (7.5)	43.4 (5.2)	43.2 (5.5)	42.8 (6.2)
Median (min, max)	43.7 (20.9, 50.8)	43.7 (29.1, 50.8)	44.4 (29.3, 50.8)	43.9 (20.9, 50.8)
Years since diagnosis				
Mean (SD)	2.6 (1.1)	2.4 (1.0)	2.7 (1.2)	2.6 (1.1)
Median (min, max)	2.4 (0.9, 5.2)	2.4 (0.8, 4.7)	2.6 (0.4, 5.7)	2.4 (0.4, 5.7)
Months from last cancer treatment				
Mean (SD)	23.7 (13.2)	22.5 (12.0)	25.6 (14.4)	23.9 (13.2)
Median (min, max)	21.7 (3.9, 55.1)	22.4 (4.8, 52.4)	21.7 (4.5, 61.2)	21.8 (3.9, 61.2)
Race (missing n = 2), No. (%)				
Asian	5 (6)	9 (11)	6 (8)	20 (8)
Black	3 (4)	11 (14)	5 (6)	19 (8)
Other	2 (2)	2 (3)	1 (1)	5 (2)
White	75 (88)	58 (73)	68 (85)	201 (82)
Hispanic, No. (%)				
Yes	10 (12)	5 (6)	9 (11)	24 (10)
No	75 (88)	76 (94)	72 (89)	223 (90)
Marital status, No. (%)				
Married or living as married	58 (68)	41 (51)	61 (75)	160 (65)
Not married (divorced, widowed, single)	27 (32)	40 (49)	20 (25)	87 (35)
Education, No. (%)				
No college degree	13 (15)	16 (20)	18 (22)	47 (19)
College	38 (45)	32 (40)	38 (47)	108 (44)
Postgraduate degree	34 (40)	33 (41)	25 (31)	92 (37)
Employment status, No. (%)				
Full-time	54 (64)	60 (74)	54 (67)	168 (68)
Part-time	14 (16)	10 (12)	11 (14)	35 (14)
Not employed	17 (20)	11 (14)	16 (20)	44 (18)
Annual household income (missing n = 19), No. (%)				
<$60K	14 (18)	18 (24)	16 (21)	48 (21)
$60K-$100K	19 (24)	19 (26)	15 (20)	54 (23)
>$100K	46 (58)	37 (50)	44 (49)	127 (56)
Clinical characteristics				
BMI, mean (SD)	26.2 (5.5)	27.1 (6.2)	28.0 (6.5)	27.1 (6.1)
Had chemotherapy, No. (%)	61 (72)	46 (57)	46 (57)	153 (62)
Had radiation, No. (%)	57 (67)	52 (64)	53 (65)	162 (66)
Took trastuzumab (missing n = 5), No. (%)	26 (31)	16 (20)	21 (27)	63 (26)
Endocrine therapy, current, No. (%)	54 (64)	53 (65)	55 (68)	162 (66)
Endocrine therapy, past (missing n = 6), No. (%)	13 (15)	12 (15)	13 (17)	38 (16)
Ovarian suppression, current, No. (%)	11 (13)	8 (10)	15 (19)	34 (14)
Outcome variables at baseline, mean (SD)				
General stress perceptions (PSS)	19.2 (7.0)	18.6 (5.9)	19.0 (6.7)	19.0 (6.5)
Cancer-related intrusive thoughts (IES)	14.0 (9.0)	13.4 (8.8)	10.6 (8.5)	12.7 (8.9)
Cancer-related worry (IOCv2)	4.0 (0.7)	3.9 (0.9)	3.7 (0.9)	3.9 (0.8)
Positive affect (PANAS)	29.6 (7.6)	30.6 (7.0)	29.7 (7.1)	30.0 (7.2)
Meaning/purpose in life (FACIT-Sp)	16.0 (4.1)	16.5 (3.7)	16.3 (4.8)	16.3 (4.2)
Cancer-related altruism/empathy (IOCv2)	4.2 (0.6)	4.1 (0.7)	4.1 (0.7)	4.1 (0.7)
IL-6, pg/mL	1.04 (1.75) (n = 83)	0.82 (0.54) (n = 76)	0.80 (0.60) (n = 72)	0.89 (1.15) (n = 231)
CRP, mg/L	3.56 (4.93) (n = 83)	3.81 (5.31) (n = 76)	4.00 (5.72) (n = 72)	3.78 (5.29) (n = 231)

[a] BMI = body mass index; CRP = C reactive protein; FACIT-Sp = Functional Assessment of Chronic Illness Therapy-Spiritual; IES = Impact of Events Scale; IL = interleukin; IOCv2 = Impact of Cancer Scale version 2; PANAS = Positive and Negative Affect Scale; PSS = Perceived Stress Scale.

general perceived stress, peace and meaning in life, or altruism and empathy.

Immune outcomes

Analyses of a prespecified set of proinflammatory gene transcripts showed a statistically significant group × time interaction for MAPs vs WLC at postintervention (difference: $P = .016$). As shown in Figure 3, the WLC group showed increased expression of proinflammatory genes from pre- to postintervention relative to MAPs [WLC change: +.125 log2 RNA ± .043 SE, t(7003) = 2.89, $P = .004$; MAPs change: −.017 ± .040 t(7003) = −0.43, $P = .66$]. In contrast, there was no statistically significant difference between SE and WLC; the SE group paralleled the WLC group in showing increased expression of proinflammatory genes from baseline to postintervention [SE change: +.211 ± .044, t(7003) = 4.82, $P < .001$; difference from WLC: $P = .16$]. There were no effects of either intervention on circulating concentrations of interleukin-6 or CRP ($P > .15$).

Table 2. Difference in change scores and standardized effect sizes (95% CIs) for outcome variables[a]

	Postintervention			3-Mo follow-up			6-Mo follow-up		
Outcome variable	Difference in change scores	P[b]	Standardized effect size	Difference in change scores	P[b]	Standardized effect size	Difference in change scores	P[b]	Standardized effect size
Perceived stress (PSS)									
MAPs vs WLC	−1.8 (−3.5 to −0.0)	.048	−0.27 (−0.54 to 0.0)	−1.8 (−3.7 to 0.06)	.058	−0.28 (−0.56 to 0.0)	−1.5 (−3.4 to 0.3)	.101	−0.23 (−0.51 to 0.05)
SE vs WLC	−1.2 (−3.0 to 0.7)	.211	−0.18 (−0.45 to 0.1)	−0.4 (−2.3 to 1.5)	.666	−0.06 (−0.36 to 0.23)	−0.4 (−2.3 to 1.5)	.658	−0.07 (−0.35 to 0.22)
Intrusive thoughts (IES)									
MAPs vs WLC	−3.9 (−6.1 to −1.7)	.001	−0.44 (−0.69 to −0.19)	−6.2 (−8.5 to −3.8)	< .001	−0.70 (−0.96 to −0.43)	−2.2 (−4.5 to 0.1)	.063	−0.25 (−0.51 to 0.01)
SE vs WLC	−2.0 (−4.3 to 0.3)	.083	−0.23 (−0.48 to 0.03)	−4.2 (−6.7 to −1.8)	.001	−0.48 (−0.75 to −0.21)	−2.4 (−4.8 to −0.1)	.045	−0.27 (−0.54 to −0.01)
Cancer-related worry (IOCv2)									
MAPs vs WLC	−0.3 (−0.4 to −0.1)	.001	−0.32 (−0.52 to −0.13)	−0.3 (−0.4 to −0.1)	.004	−0.31 (−0.53 to −0.1)	−0.2 (−0.3 to 0.0)	.091	−0.18 (−0.39 to 0.29)
SE vs WLC	−0.2 (−0.3 to 0.0)	.062	−0.20 (−0.40 to 0.01)	−01 (−0.3 to −0.1)	.219	−0.14 (−0.35 to 0.08)	−0.1 (−0.3 to 0.1)	.395	−0.09 (−0.31 to 0.12)
Positive affect (PANAS)									
MAPs vs WLC	2.5 (0.3 to 4.7)	.025	0.35 (0.04 to 0.66)	2.9 (0.5 to 5.2)	.017	0.40 (0.07 to 0.72)	2.4 (0.1 to 4.7)	.041	0.33 (0.01 to 0.65)
SE vs WLC	1.0 (−1.3 to 3.3)	.392	0.14 (−0.18 to 0.45)	1.8 (−0.6 to 4.3)	.134	0.26 (−0.08 to 0.59)	3.3 (0.9 to 5.7)	.007	0.46 (0.13 to 0.79)
Meaning/peace (FACIT-Sp)									
MAPs vs WLC	1.7 (0.5 to 2.9)	.007	0.40 (0.11 to 0.68)	0.5 (−0.8 to 1.8)	.466	0.11 (−0.19 to 0.42)	1.3 (0.1 to 2.6)	.042	0.31 (0.01 to 0.61)
SE vs WLC	1.1 (−0.2 to 2.3)	.108	0.24 (−0.05 to 0.54)	0.3 (−1.0 to 1.6)	.630	0.08 (−0.24 to 0.39)	0.8 (−0.5 to 2.1)	.220	0.19 (−0.12 to 0.5)
Altruism/empathy (IOCv2)									
MAPs vs WLC	0.0 (−0.1 to 0.2)	.698	0.05 (−0.21 to 0.31)	0.1 (−0.0 to 0.3)	.099	0.23 (−0.04 to 0.5)	0.2 (0.0 to 0.4)	.047	0.27 (0.0 to 0.54)
SE vs WLC	0.1 (−0.1 to 0.2)	.415	0.11 (−0.15 to 0.37)	0.1 (−0.1 to 0.2)	.494	0.10 (−0.18 to 0.38)	0.1 (−0.0 to 0.3)	.119	0.22 (−0.06 to 0.5)
CRP[c] (log)									
MAPs vs WLC	−0.05 (−0.35 to 0.25)	.753	−0.03 (−0.25 to 0.18)	—	—	—	—	—	—
SE vs WLC	−0.06 (−0.37 to 0.25)	.689	−0.05 (−0.27 to 0.18)	—	—	—	—	—	—
IL-6[c] (log)									
MAPs vs WLC	0.06 (−0.14 to 0.19)	.760	0.04 (−0.20 to 0.28)	—	—	—	—	—	—
SE vs WLC	−0.05 (−0.22 to 0.12)	.568	−0.07 (−0.32 to 0.18)	—	—	—	—	—	—

[a] Change scores are for change from baseline. Change scores and effect sizes are adjusted for study site, race, and marital status. CI = confidence interval; CRP = C reactive protein; FACIT-Sp = Functional Assessment of Chronic Illness Therapy-Spiritual; IES = Impact of Events Scale; IL = interleukin; IOCv2 = Impact of Cancer Scale version 2; MAPs = Mindful Awareness Practices; PANAS = Positive and Negative Affect Scale; PSS = Perceived Stress Scale; SE = Survivorship Education; WLC = wait list control.

[b] *P* values are from comparison of change scores in each intervention group to change score in WLC group. *P* values less than .027 are considered statistically significant after Dunnett multiple comparison method is applied.

[c] For CRP and IL-6, results are presented for the postintervention assessment only, because blood samples were not collected for any participants at 3-month follow-up and were collected for only a subset of participants at 6-month follow-up due to COVID-19 restrictions.

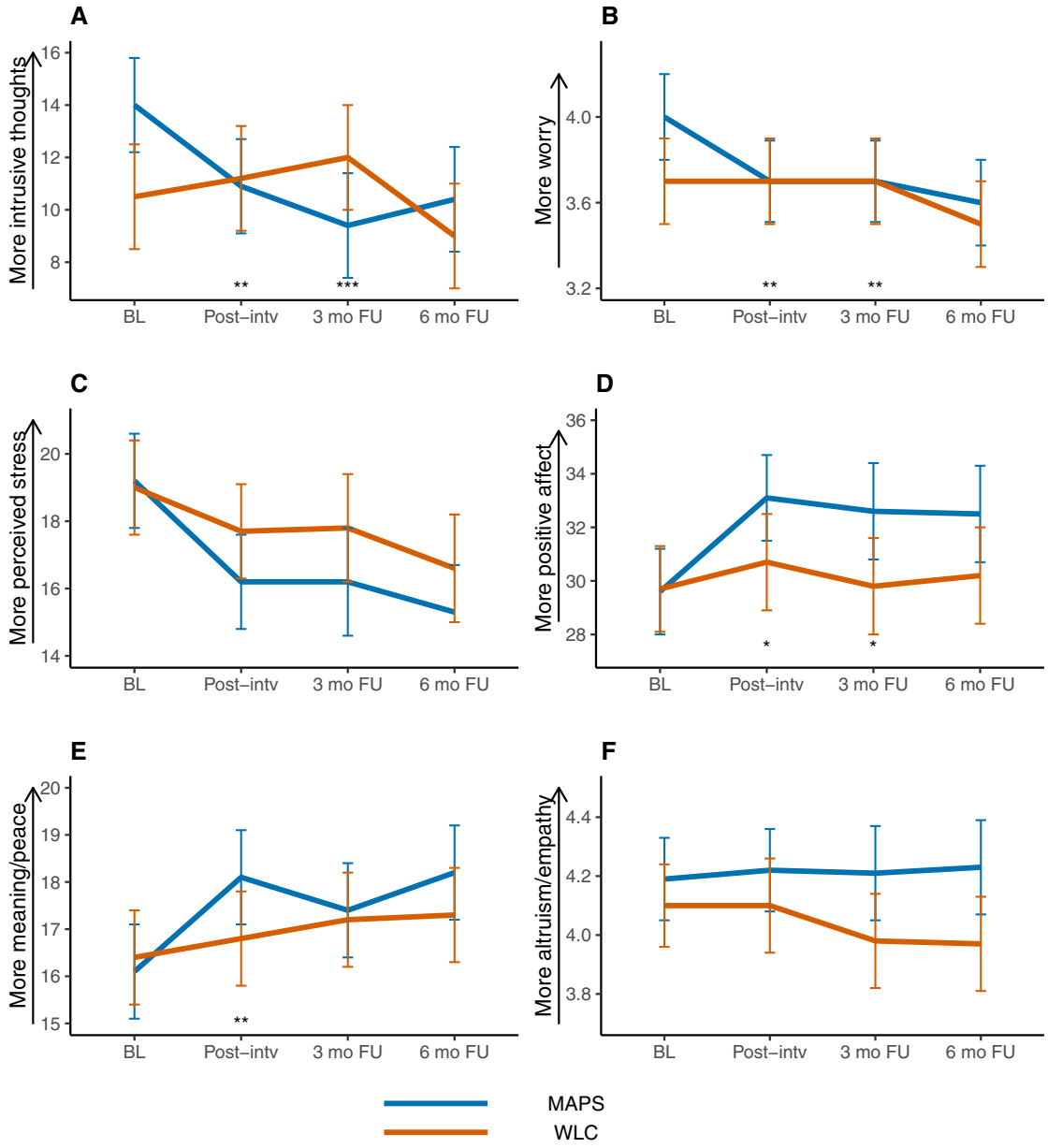

Figure 1. Adjusted mean scores for psychological outcomes at each assessment in mindful awareness practices (MAPs) and wait list control (WLC). Outcomes include cancer-related intrusive thoughts (**A**), cancer-related worry (**B**), perceived stress (**C**), positive affect (**D**), meaning and peace (**E**), and cancer-related altruism and empathy (**F**). Means are from linear mixed models and are adjusted for study site, race, and marital status. Difference in change from BL: *$P < .027$ (Dunnett multiplicity threshold); **$P < .01$; ***$P < .001$. The **error bars** represent 95% confidence intervals. BL = baseline; Post-intv = postintervention; 3 mo FU = 3-month follow-up; 6 mo FU = 6-month follow-up.

Discussion

The PTW trial evaluated the efficacy of 2 behavioral interventions—MAPs and SE—for younger BCS and showed beneficial effects of both interventions on depressive symptoms (13). In this report, we examined key psychological and inflammatory outcomes relevant for health and well-being in cancer survivorship. MAPs led to statistically significant decreases in cancer-related worry and intrusive thoughts and statistically significant increases in positive affect and meaning and peace in life, with small effect sizes relative to WLC. Effects of SE were more limited, with effects on specific outcomes (intrusive thoughts, positive affect) apparent only at certain assessments. MAPs also appeared to buffer the increase in proinflammatory gene expression observed in the WLC group from pre- to postintervention, whereas there were no differences between SE and WLC on this outcome.

Previous behavioral intervention trials in cancer survivors have primarily focused on depression, anxiety, quality of life, and physical symptoms. However, younger women also struggle with troublesome thoughts and feelings that are more proximal to the cancer experience, including fear of recurrence and intrusive thoughts about cancer. This is the first well-powered trial, to our knowledge, to demonstrate beneficial effects of mindfulness on these important outcomes in younger BCS. Results are consistent

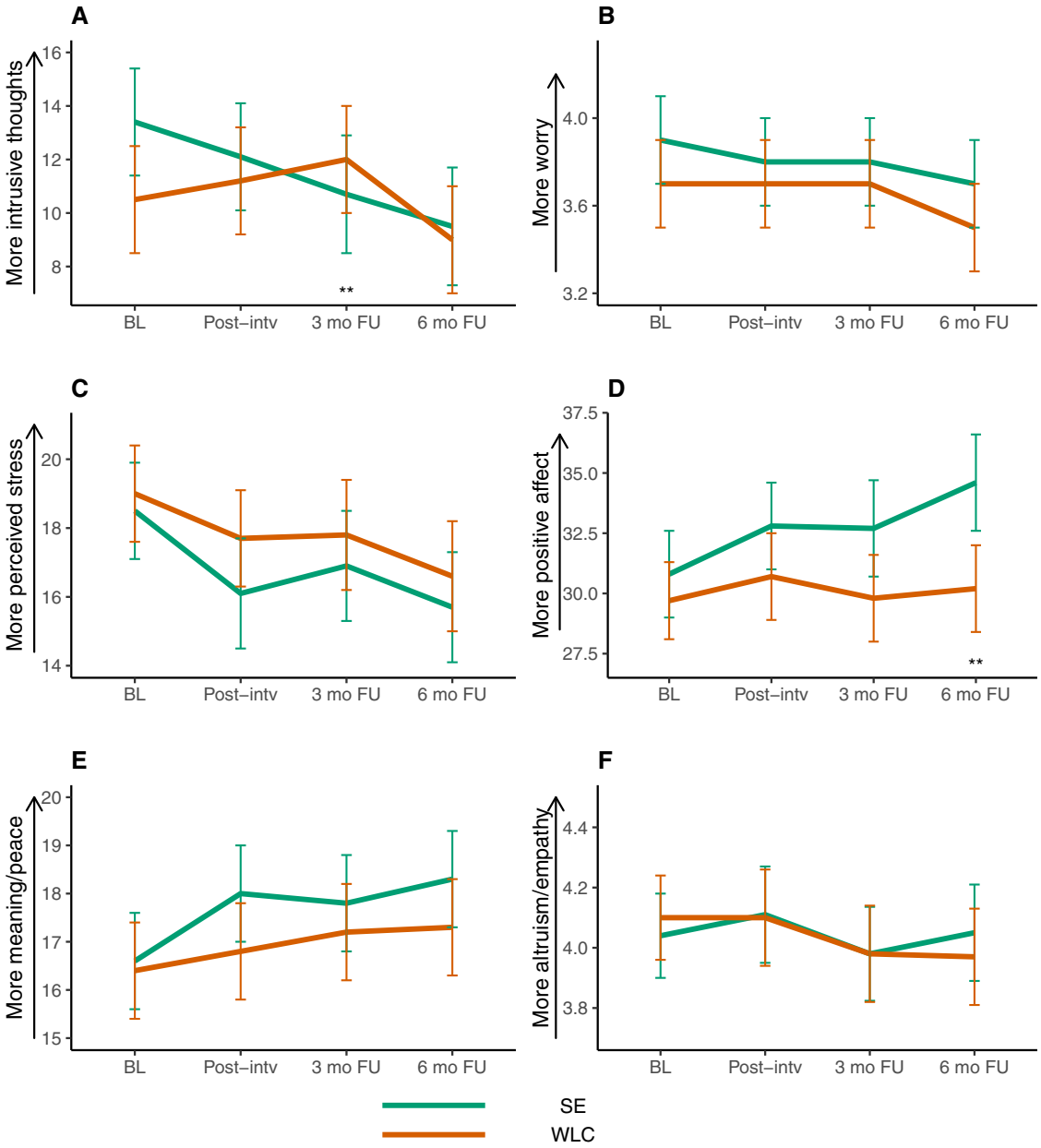

Figure 2. Adjusted mean scores for psychological outcomes at each assessment in survivorship education (SE) and wait list control (WLC). Outcomes include cancer-related intrusive thoughts (**A**), cancer-related worry (**B**), perceived stress (**C**), positive affect (**D**), meaning and peace (**E**), and cancer-related altruism and empathy (**F**). Means are from linear mixed models and are adjusted for study site, race and marital status. Difference in change from BL: *$P < .027$ (Dunnett multiplicity threshold); **$P < .01$. The **error bars** represent 95% confidence intervals. BL = baseline; Post-intv = postintervention; 3 mo FU = 3-month follow-up; 6 mo FU = 6-month follow-up.

with our smaller phase II trial with younger BCS (13) and a trial with BCS of mixed ages (39). Further, the current trial demonstrated persistence of effects for months after intervention completion. Interestingly, MAPs intervention effects on a general measure of stress were more modest; although the MAPs group did show reductions in stress from pre- to postintervention and over the follow-up period, the control group also showed declines on this measure, and differences between groups were not statistically significant controlling for multiple comparisons. Previous mindfulness studies with BCS have shown mixed effects on perceived stress (9,10), suggesting that mindfulness may be more effective in reducing negative thoughts and feelings about cancer than general feelings of being stressed and overwhelmed with life.

MAPs also improved positive psychological outcomes, including positive affect and feelings of meaning and peace in life. These outcomes have received less attention in intervention research, although earlier reports have shown beneficial effects of mindfulness on these and related outcomes (eg, posttraumatic growth, meaning in the face of adversity) in BCS (11,40,41). Indeed, increases in positive psychological states are thought to be a key pathway through which mindfulness can enhance resilience and overall well-being (42).

SE also had some beneficial effects, including decreases in intrusive thoughts (at 3 months postintervention) and increases in positive affect (at 6 months postintervention), with small effect sizes. Psychoeducational interventions can be effective in reducing depressive symptoms in cancer patients and survivors (8,43),

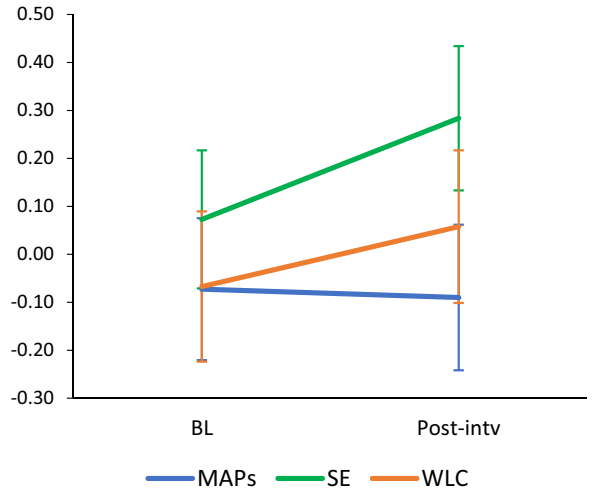

Figure 3. Adjusted mean scores for proinflammatory gene transcripts at baseline and posttreatment in mindful awareness practices (MAPs), survivorship education (SE), and wait list control (WLC). The proinflammatory gene set included the following genes: *FOS*, *FOSL2*, *IL1B*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *PTGS1*, *PTGS2*, *REL*, *RELA*, *RELB*, and *TNF*. The **error bars** represent 95% confidence intervals. BL = baseline; Post-intv = postintervention.

although effects on other aspects of psychological function have not been as well studied. In general, the overall pattern of findings suggests that mindfulness has broader efficacy across a range of outcomes relevant for cancer survivorship.

Paralleling results for the psychological outcomes, results for proinflammatory gene expression supported beneficial effects of the MAPs intervention. Women assigned to MAPs showed no statistically significant change in proinflammatory gene expression from pre- to postintervention, whereas those in WLC (and those in SE) showed a statistically significant increase over this period, suggesting a buffering effect of mindfulness. In our phase II trial, we also found beneficial effects of MAPs on inflammation-related gene expression in young BCS (11). Of note, no changes in circulating inflammatory markers were observed in this study, consistent with our earlier trial and with other mindfulness interventions in cancer survivors (44). Mindfulness and mind-body interventions have generally shown more reliable effects on inflammatory gene expression than circulating inflammatory markers, perhaps because immune cell gene expression is more directly modulated by stress signaling pathways and thus more sensitive to behavioral interventions, particularly in the short term (22). Inflammation is known to contribute to behavioral symptoms and clinical outcomes in BCS (20), and programs that can reduce inflammation have the potential to improve both quality and potentially length of life in cancer survivorship.

Attendance at the in-person interventions ranged from 63% (for SE) to 75% (for MAPs). Given that each class session provides unique content, it is possible that attending more classes would lead to greater and more sustained benefits. Regular practice is particularly important for mindfulness and can be difficult to sustain on one's own. This may explain why intervention effects often wane after treatment completion (11) and why offering booster sessions likely helped to sustain effects in the current trial. Of course, attending in-person sessions is challenging, particularly for younger survivors who may also be juggling work and family responsibilities. We are currently developing digital versions of MAPs that can be disseminated more broadly and will make intervention content more readily accessible, both during the 6-week program and in the months and years after intervention completion.

This trial was conducted at comprehensive cancer centers rather than community clinics and excluded non-English speakers, limiting generalizability of results. The MAPs intervention has shown efficacy when delivered in Spanish (45) and should be tested in more diverse groups of BCS, including Spanish speakers. The study was not specifically powered for the secondary outcomes described in this report, and there was no control for multiple comparisons across these outcomes. Thus, results of these secondary analyses should be considered hypothesis generating and require confirmation in a larger trial. Finally, the 6-month follow-up for the final cohort of 90 patients was conducted during the initial phase of the COVID-19 pandemic, which may have attenuated effects at this assessment.

Younger women who have undergone diagnosis and treatment for breast cancer are at risk for persistent worries and distress about the cancer experience, lower levels of peace and meaning in life, and inflammation-related physical conditions, including cancer recurrence and mortality. Here, we show that a brief mindfulness intervention is effective in improving these important psychological and inflammatory outcomes, with relevance for enhancing survivorship in this vulnerable group.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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