Examining Mediators and Moderators of Yoga for Women With Breast Cancer Undergoing Radiotherapy

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Abstract

Hypothesis. This study examines moderators and mediators of a yoga intervention targeting quality-of-life (QOL) outcomes in women with breast cancer receiving radiotherapy. *Methods.* Women undergoing 6 weeks of radiotherapy were randomized to a yoga (YG; n = 53) or stretching (ST; n = 56) intervention or a waitlist control group (WL; n = 54). Depressive symptoms and sleep disturbances were measured at baseline. Mediator (posttraumatic stress symptoms, benefit finding, and cortisol slope) and outcome (36-item Short Form [SF]-36 mental and physical component scales [MCS and PCS]) variables were assessed at baseline, end-of-treatment, and 1-, 3-, and 6-months posttreatment. *Results.* Baseline depressive symptoms (*P* = .03) and sleep disturbances (*P* < .01) moderated the Group × Time effect on MCS, but not PCS. Women with high baseline depressive symptoms in YG reported marginally higher 3-month MCS than their counterparts in WL (*P* = .11). Women with high baseline sleep disturbances in YG reported higher 3-months MCS than their counterparts in WL (*P* < .01) and higher 6-month MCS than their counterparts in ST (*P* = .01). YG led to greater benefit finding than ST and WL across the follow-up (*P* = .01). Three-month benefit finding partially mediated the effect of YG on 6-month PCS. Posttraumatic stress symptoms and cortisol slope did not mediate treatment effect on QOL. *Conclusion.* Yoga may provide the greatest mental-health–related QOL benefits for those experiencing pre-radiotherapy sleep disturbance and depressive symptoms. Yoga may improve physical-health–related QOL by increasing ability to find benefit in the cancer experience.

Keywords

breast cancer, QOL, yoga, moderation, mediation

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Introduction

Moderators of Mind-Body Interventions

Despite the large number of behavioral intervention studies for individuals diagnosed with cancer, the overall efficacy of these treatments in addressing patient symptom burden has been heavily debated.[1-5] Though an estimated 20%-40% of cancer patients experience depression, the typical cancer patient enrolled in psychosocial trials tends to be not depressed.[4,6] Thus, the frequently used "all-comers" approach to patient recruitment may result in negligible treatment gains for quality of life (QOL) indicators such as depression. In fact, a recent meta-analysis of 61 trials demonstrated that

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psychological distress moderated the efficacy of psychosocial treatments regarding mood management for cancer patients.[7] Furthermore, a meta-analysis of trials targeting depressed cancer patients indicated that psychotherapeutic and pharmacological interventions are effective in reducing depressive symptoms with sustained effects.[8]

Although these meta-analyses have been instrumental in identifying the importance of examining moderators of treatment efficacy, they have rarely included trials of complementary medicine interventions such as yoga and meditation. Such exclusion is surprising in light of the rapid proliferation of Eastern-influenced behavioral interventions in oncology research and practice.[9-17] Yoga in particular has gained popularity in the cancer setting, and several systematic reviews and meta-analyses have examined the QOL benefits associated with cancer patients' and survivors' yoga practice.[14-17] For instance, a meta-analysis of 13 randomized controlled trials (RCTs) of yoga in cancer patients and survivors revealed large effects for psychological health; medium effects for fatigue, general QOL, and psychosocial well-being; and small effects for sleep disturbances and physical function.[17] It is important to note that the reviewed trials did not select for elevated symptom burden (ie, used an "all-comer" approach). Thus, yoga may lead to even greater grains in at-risk participants. However, with the exception of some limited evidence,[18] it is largely unknown if patients with elevated distress derive greater QOL benefit from a yoga intervention compared with their less-distressed counterparts.

The benefits of yoga are multifaceted, targeting not only psychological but also physical and spiritual dimensions of QOL.[17] Thus, participant characteristics beyond psychological distress may moderate the efficacy of a yoga intervention. Sleep disturbances, potentially caused by the cancer process itself or cancer treatments, are commonly experienced among women with breast cancer[19-21] and are associated with impaired QOL in cancer patients even when controlling for depression and fatigue.[20,22,23] Because yoga is an effective treatment to improve sleep in cancer patients and survivors,[9,24,25] it may be particularly efficacious for patients reporting high levels of sleep disturbances. In fact, a multicenter RCT involving 410 survivors with moderate to high sleep disturbances demonstrated that an 8-session yoga intervention improved self-reported and actigraphy-assessed sleep relative to standard care.[9] However, to the best of our knowledge, sleep disturbances have not yet been examined as a yoga intervention moderator.

Mediators of Mind-Body Interventions

In addition to lacking a clear understanding of for whom mind-body interventions are most helpful, no cohesive theoretical framework has been proposed to explain how and why yoga interventions produce change.[26,27] A recent systematic review reports that few potential mechanisms of yoga have been explored to date, and no mechanisms of yoga have been tested in cancer populations.[28,29] The exception is one study on mindfulness-based stress reduction for cancer patients, which includes some yoga. This study found that increasing mindfulness partially mediated the intervention's beneficial effects on stress and posttraumatic avoidance.[30] However, in light of the growing RCTs examining yoga in cancer and the limited exploration of mediators of this intervention, further examination of yoga mediators guided by a conceptual model is needed.

We propose a stress response model as a way to understand how yoga produces change in cancer patients. A diagnosis of cancer and its treatment are typically experienced as stressful, or even traumatic, events, and yoga interventions are generally conceptualized within the framework of a stress reduction program. Thus, practicing yoga may improve health outcomes in cancer patients via modulating the stress response.[28] Put another way, yoga may affect posttraumatic stress symptoms, such as cognitive interference and avoidance, while also increasing posttraumatic growth or benefit finding. Importantly, both constructs of trauma response (ie, posttraumatic stress symptoms and benefit finding) have been consistently and prospectively associated with psychological and physical QOL outcomes in various cancer samples.[31-39]

With this model in mind, we previously examined the effects of yoga versus usual care on intrusive thoughts/avoidance behaviors and benefit finding in a small pilot trial in women with breast cancer undergoing radiotherapy.[10] Differences between groups in benefit finding did not emerge until the last 3-month assessment time point, precluding the examination of benefit finding as an intervention mediator. Surprisingly, the yoga group reported increased intrusive thoughts 1 month after the end of radiotherapy compared with the women in the usual care group, with subsequent reduction at the 3-month time point, and nonsignificant reductions in avoidance behaviors. Interestingly, intrusive thoughts at 1 month were positively associated with benefit finding at 3 months. There is some evidence to suggest that heightened levels of intrusive thoughts experienced during the aftermath of a traumatic event may help individuals more effectively adjust to the stressor and ultimately to find benefit in the traumatic experience.[40] Thus, the increase in intrusive thoughts associated with yoga may have led to better, more mindful processing of the cancer experience, ultimately fostering finding meaning in the cancer experience.

Moreover, within a trauma response model, cortisol rhythmicity may represent one biological pathway by which mind-body interventions improve health and well-being. Both types of trauma response (posttraumatic stress symptoms and benefit finding) are associated with hypothalamic-pituitary-adrenal axis function in cancer patients, which in turn is associated with behavioral symptoms (eg, fatigue,

sleep disturbance, and depression), making changes to cortisol rhythmicity a potential mechanism of yoga.[41-44] Although previous studies have shown group main effects of a yoga intervention on diurnal cortisol and speculated a mediating effect, no empirical evidence exists to date.[28]

The Present Study

The goal of the current study was to examine moderators and mediators of a previously reported 3-arm yoga RCT for women diagnosed with breast cancer undergoing radiotherapy.[45] We focused only on mediators and moderators of the primary outcome variable: health-related QOL. First, we hypothesized that, compared with active and waitlist control groups, the yoga program would be especially beneficial at improving posttreatment QOL for women with elevated pretreatment depressive symptoms and sleep disturbance. Second, we hypothesized that the beneficial QOL effects of the intervention would be mediated by improved trauma responses (ie, short-term increases in intrusive thoughts and reduction in avoidance behaviors and increased benefit finding) as well as better stress hormone regulation (ie, a steeper cortisol slope).

Method

Participants

Women were recruited prior to radiotherapy treatment (XRT), with inclusion criteria being the following: ≥18 years old; ability to read, write, and speak English; diagnosed with stage 0 to III breast cancer; and scheduled to undergo daily adjuvant XRT for 6 weeks at MD Anderson Cancer Center. Patients with lymphedema, metastatic bone disease, deep-vein thrombosis, documented diagnosis of a formal thought disorder, and extreme mobility problems or those who had practiced yoga in the year before diagnosis were excluded. The protocol was approved by the institutional review board.

Procedures

Details of the study procedures have been reported elsewhere.[45] Briefly, after receiving written informed consent, self-report and saliva samples (for cortisol data) were collected from participants at baseline before randomization, during the last week of XRT, and 1, 3, and 6 months later.

Participants were randomly assigned to 1 of 3 groups: (1) yoga (YG); (2) stretching control (ST); or waitlist control (WL) using a form of adaptive randomization,[46] according to age, stage of disease, time since diagnosis, type of surgery, and chemotherapy (neoadjuvant or adjuvant). Participants in the WL group received usual care, completed all assessments on the same timeline as the active groups,

and were offered yoga classes at the end of their study participation. All participants were asked to refrain from participating in any other yoga classes while on study. Participants in the YG and ST groups attended up to three 60-minute classes per week during their 6 weeks of XRT. Each participant received an audio CD and a written manual of the program to encourage at-home practice.

The integrated yoga program, described previously,[10] included the following: (1) preparatory warm-up synchronized with breathing; (2) selected postures, or *asanas* (forward-, backward-, and side-bending asanas in sitting and standing positions, cobra posture, crocodile, and half-shoulder-stand with support); (3) deep relaxation (supine posture); (4) alternate-nostril breathing or *pranayama*; and (5) meditation. The program was taught by Vivekananda Yoga Anusandhana Samsthana–trained teachers with specific oncology training.

The stretching program included exercises recommended specifically for women undergoing or recovering from breast cancer treatment.[47,48] The exercises approximated the gross movements of the yoga exercises and were taught by cancer center physiotherapists.

Measures

Primary Intervention Outcome: Health-Related QOL. Overall QOL was assessed by the Medical Outcomes Study 36-item Short Form survey (SF-36) and was the primary outcome of the clinical trial published previously.[45] The SF-36 assesses physical functioning, physical impediments to role functioning, bodily pain, general health perceptions, vitality, social functioning, emotional impediments to role functioning, and mental health and includes an overall physical and mental component scale (PCS and MCS).[49,50] To reduce the number of analyses, only the component scales are included in outcome analyses. Higher scores reflect better QOL.

Proposed Moderators. Depressive symptoms were assessed using the Centers for Epidemiological Studies–Depression measures (CES-D),[51] a well-validated measure focusing on affective components of depression. Lower scores reflect fewer depressive symptoms. In this study sample, the internal reliability was high (Cronbach's α = .89).

Sleep disturbances were assessed using the Pittsburgh Sleep Quality Index (PSQI),[52] a questionnaire that assesses sleep disturbances over a 1-month period. We report on the total score, with lower scores reflecting fewer sleep disturbances. Acceptable internal reliability was found in this study sample (Cronbach's α = .70).

Proposed Mediators: Posttraumatic Responses. Posttraumatic stress symptoms were measured by the Impact of Event Scale (IES), a scale that assesses the 2 most common categories of responses to traumatic events: intrusion (intrusively

experienced ideas, images, feelings, or bad dreams) and avoidance behaviors (conscious efforts to avoid certain ideas, feelings, or situations).[53] We report on the intrusive thoughts and avoidance behaviors subscales and the total score. Lower scores reflect fewer symptoms. Adequate internal reliability was found for the total scale (Cronbach's α = .85) as well as intrusive (Cronbach's α = .85) and avoidance (Cronbach's α = .79) subscales.

Participants' ability to find benefit was measured by the Benefit Finding Scale (BFS),[54,55] a scale assessing acceptance of life's imperfections, change in priorities, and development of a sense of purpose in life as a result of having been diagnosed with cancer. Higher scores reflect greater benefit finding. In this study sample, the internal reliability was high (Cronbach's α = .94).

Cortisol Rhythmicity. Cortisol was obtained via 5 saliva samples (waking, 45 minutes later, approximately 8 and 12 hours after waking, and at bedtime) for 3 consecutive days at each assessment. Participants chewed on a cotton swab (Salivette) and placed it in a plastic tube (Sarstedt), which was then frozen at −80°C for later time-resolved immunoassay with fluorescence detection performed at the University of Dresden. Values <0.0001 and >70 nmol/L were classified as missing. If patients missed a collection point, they were told to leave the tube empty. Reliability for each collection time point within a day across the 3 days and the 5 assessment time points ranged from 0.20 to 0.87, with only 6 out of 25 α values (5 samples a day at 5 time points) dropping below 0.50. Reliability was directly related to the sample size, which dropped off by the 6-month follow-up. A steeper, more-negative cortisol slope indicates better cortisol regulation.

Covariates. Patients also completed basic demographic information (eg, age, marital status, education). Medical information was obtained from electronic medical records.

Data Analyses

Hypothesis 1: To evaluate whether the intervention was more effective in regard to health-related QOL (SF-36 MCS and PCS) for participants with high depressive symptoms (Hypothesis 1A) or greater sleep disturbance (Hypothesis 1B) at baseline, we used an ANCOVA framework to first examine the Group × Baseline moderator effect using PROC MIXED in SAS v9.2. This was followed by a Group × Time × Baseline moderator ANCOVA to see if the moderator effect varied by time. We controlled for the respective baseline outcome as well as randomization factors (age, stage of disease, time since diagnosis, type of surgery, and chemotherapy type). We also controlled for baseline SF-36 general health scores in all analyses as a result of imbalances across groups. We treated

time as a categorical variable and the intercept as a random effect. We specified an unstructured covariance structure. For significant 3-way interactions, we decomposed the interaction according to high and low (mean ± ½SD) baseline depressive symptoms or sleep disturbance and compared the least-squared means (LSM) for each group at each time point using a general linear model analysis, controlling for baseline levels of the outcome variable and illustrating the interaction by plotting the LSM.

Hypothesis 2: We were interested in determining mediators of significant group effects on health-related QOL. The original trial[45] demonstrated group differences in SF-36 PCS at 1 and 3 months, and a subscale of the SF-36 PCS (physical functioning) at those time points and 6 months. We chose to examine mediators of SF-36 PCS at 1, 3, and 6 months, rather than the physical functioning subscale because the SF-36 PCS is a more comprehensive index of physical health–related QOL.

To determine the mediator variables, we regressed each proposed mediator (ie, IES, BFS, and cortisol slope) on group, time, and the Group × Time interaction using the model and covariates described above. Where there was a group or Group × Time effect on the proposed mediator variable, we chose the time point associated with the largest group or Group × Time effect as the mediator. If a proposed mediator variable did not significantly differ by group, it was not further examined. Only primary outcome variables assessed after our chosen mediators were included as dependent variables in the mediation models to enable a predictive relationship between the mediator and the dependent variable to be established.[56]

To test for mediation, we calculated indirect effects using Hayes and Preacher's bias-corrected bootstrap procedure via the MEDIATE macro for SPSS, which is designed to estimate indirect effects of multicategorical independent variables.[57] Indicator coding of the grouping variable was used, with WL functioning as the reference group. $D1$ codes the effect of YG compared with WL controlling for ST, and $D2$ codes the effect of ST compared with WL controlling for YG. Indirect effects were determined significant when the mean of the indirect effect across all 5000 bootstrap samples was associated with a bias-corrected confidence interval that did not include 0.[57]

Results

Attrition and Adherence

Out of 294 eligible women approached, 191 consented to participate; 13 dropped out before, and 15 after, randomization, for a baseline sample size of 163 (YG = 53; ST = 56; WL = 54). Measurements were obtained for 80% of the sample at 6 months (n = 131; YG = 43, ST = 42, WL = 46; see original clinical trial[45] for CONSORT). Out of a maximum

possible 18 classes, 87% of YG and 85% of ST participants attended ≥12 classes (YG = 13.8; ST = 14.7). Only 3 patients in each group attended fewer than half the classes. There were no significant differences in demographic, medical, or baseline self-report scores between those who attended ≥75% of classes compared with those who did not. For the YG group, self-reported practice outside of class was high (≥twice per week) at 1 month posttreatment and then declined at 3 and 6 months (71%, 55%, and 45%, respectively). For the ST group, self-reported practice outside of class (≥twice per week) was lower at 1 month and then increased somewhat at 3 and 6 months (53%, 69%, and 60%, respectively). WL participants were offered the YG program after data collection was complete, but no data were collected from the WL during or after yoga.

There were also no group, demographic, or baseline self-report differences between those who completed the 6-month follow-up assessment and those who did not ($Ps > .14$), with the exception that older adults were more likely to complete the 6-month assessment.

Baseline Sample Characteristics

The 3 groups were similar on all medical and demographic variables (Table 1). There were no statistically significant differences among the groups on any of the self-reported variables at baseline, apart from the SF-36 general health subscale. Women in YG reported lower baseline general health compared with those in ST ($P = .01$). Depending on the time point, 21% to 34% of participants did not provide saliva samples. There were no differences between patients providing samples and those who did not based on group assignment, medical, demographic, or outcome measures. We present the baseline and follow-up means of self-reported variables in Table 2.

Hypothesis 1: Baseline Depressive Symptoms and Sleep Disturbance as Moderators of Intervention Outcomes

There were no significant Group × Baseline Depressive Symptom (CES-D) interaction effects on mental health–related QOL (SF-36 MCS). However, there was a significant Group × Time × Baseline CES-D interaction effect on SF-36 MCS ($F_{(6, 324)} = 2.40$; $P < .03$), suggesting that the effect varied by time. We decomposed the interaction according to high and low (mean ± ½SD) baseline CES-D scores. There were no statistically significant differences in SF-36 MCS scores between groups for those with low or high baseline depressive symptoms at any assessment point (Figure 1A). However, women with high baseline depressive symptoms in YG had a trend toward higher SF-36 MCS scores at 3 months compared with WL ($P = .107$), and

their 1-, 3-, and 6-month SF-36 MCS scores were no different from those of women scoring low on baseline depressive symptoms. There were no significant Group × Baseline CES-D or Group × Time × Baseline CES-D interaction effects on physical health–related QOL (SF-36 PCS).

There was no significant Group × Baseline sleep disturbance (PSQI) interaction effects on mental health–related QOL (SF-36 MCS). However, there was a significant Group × Time × Baseline PSQI interaction effect on SF-36 MCS ($F_{(6, 318)} = 3.40$, $P < .01$). We decomposed the interaction according to high and low (mean ± ½SD) baseline PSQI scores. There were no significant differences in SF-36 MCS scores between groups for those with low baseline sleep disturbances at any assessment point (Figure 1B). However, among the women with high baseline sleep disturbances, there was a significant Group × Time effect ($F_{(6, 83)} = 3.52$; $P = .003$). Specifically, women with high sleep disturbances in YG reported higher 3-month SF-36 MCS scores than their counterparts in WL ($t_{(83)} = 3.15$; $P = .002$) and higher 6-month SF-36 MCS scores than their counterparts in ST ($t_{(83)} = 2.56$; $P = .012$), and their SF-36 MCS scores at each time point were no different from that of women reporting low sleep disturbance at baseline. There were no significant Group × Baseline sleep disturbance (PSQI) or Group × Time × Sleep disturbance (PSQI) interaction effects on physical health–related QOL (SF-36 PCS).

Hypothesis 2: Mediators of Intervention Effect on QOL

Posttraumatic Stress Symptoms. Results revealed no significant Group × Time interaction effect on IES total scale, intrusive thoughts, or avoidance behaviors subscales scores ($Ps > .5$). Additionally, there were no main effects of group or time on the IES total scale or intrusive thoughts subscale ($Ps > .2$). There was a main effect of group ($F_{(2,132)} = 3.17$; $P = .05$), but not time ($P = .6$), for the IES avoidance subscale. Specifically, YG was associated with greater IES avoidance scores (LSM = 11.31; SE = 0.82) compared with WL (LSM = 8.52; SE = 0.76; $P = .01$). IES avoidance scores did not differ between ST (LSM = 10.16; SE = 0.79) and YG or WL ($Ps > .1$). Figure 2A presents LSMs of IES avoidance for groups across time.

The time point at which groups differed most on IES avoidance was at 6 months ($F_{(2, 112)} = 3.23$; $P = .04$; Cohen's $d = 0.40$), with women in YG (LSM = 11.29; SE = 1.18; $P = .02$) and ST (LSM = 10.14; SE = 1.19; $P = .09$) reporting greater IES avoidance scores compared with women in WL (LSM = 7.34; SE = 1.69). Using the 6-month time point for the mediator does not enable examining a temporal relationship between the mediator and outcome, and there were no significant group differences at earlier time points, precluding examination of IES avoidance as an intervention mediator.

Table 1. Baseline Characteristics of Study Participants, by Group.

	Yoga		Stretch		Waitlist	
	n = 53 (33%)		n = 56 (34%)		n = 54 (33%)	
Disease stage, n (%)						
0	5	10	6	11	7	13
I	16	30	18	32	17	31
II	15	28	14	25	15	28
III	17	32	18	32	15	28
ER/PR status (n = 156), n (%)						
ER+/PR+	32	62	33	62	31	61
ER+/PR−	7	13	7	13	6	12
ER−/PR+	1	2	0	0	3	6
ER−/PR−	12	23	13	25	11	21
Surgery, n (%)						
Mastectomy (without reconstruction)	12	23	17	31	12	22
Mastectomy (with reconstruction)	6	11	3	5	5	9
Breast conserving	35	66	36	64	37	69
Chemotherapy, n (%)						
Yes	36	68	34	61	34	63
Hormone treatment (n = 156), n (%)						
Yes	33	62	38	70	34	67
Marital status (n = 151), n (%)						
Married and living together	31	67	37	71	34	64
Not cohabiting	15	33	15	29	19	36
Ethnicity (n = 150), n (%)						
Black/African American	9	19	9	17	7	13
White/Caucasian	32	68	28	55	37	71
Latino/Hispanic/Mexican	4	9	8	16	5	10
Asian/Oriental/Pacific Islander	2	4	4	8	1	2
Other	0	0	2	4	2	4
Employment status (n = 140), n (%)						
Employed part-/full-time	15	33	21	43	18	39
Employed, taken time off	11	25	10	20	5	11
Not employed	19	42	18	37	23	50
Education (n = 152), n (%)						
Some college or lower	27	57	26	50	32	60
College and higher education	20	43	26	50	21	40
Income (n = 149), n (%)						
>$75 000	31	67	26	51	26	50
<$75 000	15	33	25	49	26	50
Age (mean, SE)	52.38	1.35	51.14	1.32	52.11	1.34

Abbreviations: ER = Estrogen receptor; PR = Progesterone receptor

Benefit Finding. Results revealed no significant Group × Time interaction effect on BFS scores ($P = .9$). However, there was a main effect of group ($F_{(2,132)} = 4.60; P = .01$) and a main effect of time ($F_{(3,335)} = 3.12; P = .03$) on benefit finding. Specifically, YG was associated with greater benefit finding (LSM = 46.21; SE = 1.28) compared with ST (LSM = 42.24; SE = 1.23; $P = .03$) and WL (LSM = 41.05; SE = 1.19; $P < .01$). Benefit finding did not differ between ST and WL ($P = .5$). Figure 2B presents LSMs of benefit finding for groups across time.

Women in YG reported higher levels on benefit finding relative to WL at 1, 3, and 6 months and relative to ST at 3 and 6 months ($Ps < .05$), with no differences between ST and WL. Groups differed most on benefit finding at 3 months ($F_{(2, 103)} = 3.12; P = .05$; Cohen's $d = 0.38$), with women in YG reporting greater benefit finding scores (LSM = 46.32; SE = 1.85) compared with ST (LSM = 40.90; SE = 1.78; $P = .04$) and WL (LSM = 40.57; SE = 1.69; $P = .02$). Therefore, 3-month benefit finding was examined as a mediator of group's effects on physical health–related QOL

Table 2. Raw Means and SDs of Measures at Baseline and Follow-up.[a]

		Yoga		Stretch		Waitlist	
		Mean	SD	Mean	SD	Mean	SD
Primary outcome variables	SF-36 PCS						
	Baseline	41.9	9.6	43.4	8.6	44.5	9.4
	Post-XRT	42.3	9.2	44.5	8.1	44.1	8.4
	1 Month	47.0*	8.1	46.9	9.1	45.4**	7.6
	3 Months	48.2*	7.3	47.6	8.8	45.8**	7.8
	6 Months	46.9[b]	9.3	47.5	8.6	46.6	7.5
	SF-36 MCS						
	Baseline	42.1	12.4	45.6	10.3	42.2	12.9
	Post-XRT	47.2	13.5	49.7	8.9	46.8	11.5
	1 Month	46.2	13.1	47.1	11.2	49.0	10.1
	3 Months	46.5	12.6	49.8	10.2	46.9	12.2
	6 Months	46.8	12.7	50.8	9.5	48.8	9.9
Moderator variables	CES-D						
	Baseline	15.5	10.5	11.9	5.9	14.9	10.2
	Post-XRT	12.2	9.7	10.3	7.5	12.4	9.6
	1 Month	13.1	10.7	11.6	9.6	12.3	8.3
	3 Months	13.9	10.8	9.6	8.8	12.9	10.5
	6 Months	13.9	11.8	10.4	9.3	11.5	9.0
	PSQI						
	Baseline	8.3	3.9	8.5	4.0	8.2	3.7
	Post-XRT	6.7	3.1	8.3	4.0	7.3	3.7
	1 Month	7	3.8	7.5	4.2	5.9	3.6
	3 Months	6.5	3.1	7.2	3.3	6.5	3.8
	6 Months	7	3.5	7.2	3.9	6.4	4.1
Mediator variables	IES total						
	Baseline	22	15.2	20.1	13.3	20.4	13.3
	Post-XRT	17.3	13.9	17.8	15	15.8	12.1
	1 Month	17.1	13.5	16.9	13	14.4	12.1
	3 Months	18.2	13	17.1	15.7	15.7	13.7
	6 Months	18.7	16.6	16.4	12.8	11.9	10.6
	IES intrusive thoughts						
	Baseline	10.4	8.5	8.9	7.3	8.7	7.6
	Post-XRT	6.5	6.3	7.5	7.2	6.8	6.4
	1 Month	5.8	6.5	6.9	6.4	5.8	6.5
	3 Months	6.9	6.3	7.4	8.7	5.8	5.9
	6 Months	7.2	8.0	6.8	6.3	4.6	4.9
	IES avoidance						
	Baseline	11.6	8.7	11.2	7.9	11.8	8.8
	Post-XRT	11.1	8.9	10.4	9	9	7.6
	1 Month	11.3	8.2	10	7.9	8.6	7.8
	3 Months	11.3	8.4	9.7	8.7	9.9	9.5
	6 Months	11.6*	10.4	9.7	8.4	7.3**	7.0
	BFS						
	Baseline	42.5	13.4	44.1	16	44.3	13.8
	Post-XRT	46.3	14.1	45.9	16.7	42.9	15.1
	1 Month	44.4*	16.1	43.8	17.2	41.6**	13.7
	3 Months	43.9*	17.7	42.7**	18.1	40.8**	16.3
	6 Months	41.8*	16.9	42.1**	17.4	38**	16.4
	Cortisol slope						
	Baseline	−0.104	0.04	−0.118	0.04	−0.113	0.04
	Post-XRT	−0.104*	0.04	−0.084**	0.05	−0.084**	0.05
	1 Month	−0.098*	0.04	−0.090	0.05	−0.065**	0.05
	3 Months	−0.086	0.06	−0.091	0.04	−0.078	0.05
	6 Months	−0.090	0.06	−0.095	0.04	−0.099	0.04

Abbreviations: SF-36, 36-item Short Form; PCS, physical component scale; MCS, mental component scale; XRT, radiotherapy treatment; CES-D, Centers for Epidemiological Studies–Depression; PSQI, Pittsburgh Sleep Quality Index; IES, Impact of Event Scale; BFS, Benefit Finding Scale.
[a]Means with asterisk and double asterisk differ at $P < .05$ based on multilevel modeling analyses.
[b]Though groups did not differ significantly on physical health–related quality of life (SF-36 PCS) at 6 months, the original trial found that women in the yoga group reported significantly higher scores on the physical functioning subscale of the SF-36 PCS at 6 months compared with the waitlist control group.
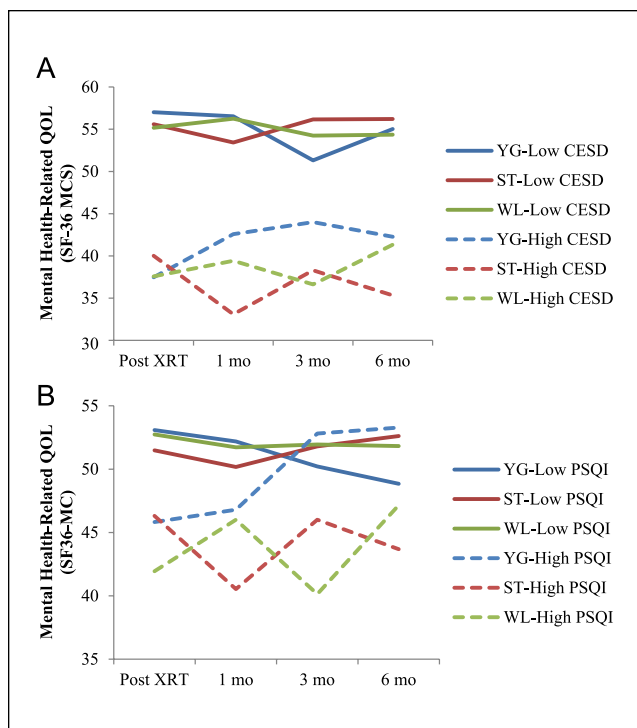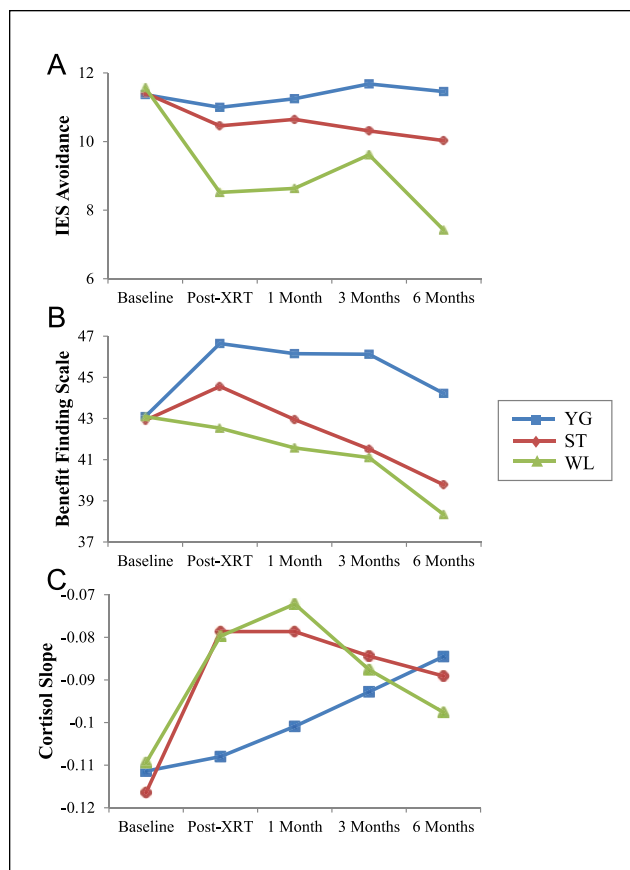
Figure 1. The least-squared means of mental health–related QOL (SF-36 MCS) are from a multilevel modeling analyses controlling for baseline MCS score, baseline SF-36 general health subscale, and randomization factors. Figures illustrate a Group × Time interaction for those with (A) high and low baseline depressive symptoms (mean ± ½SD) on the Center for Epidemiologic Studies (CES-D) and (B) high and low baseline sleep disturbances (mean ± ½SD) on the Pittsburgh Sleep Quality Index (PSQI). Higher SF-36 MCS scores represent greater QOL.

Abbreviations: CES-D, Centers for Epidemiological Studies–Depression; QOL, quality of life; SF-36, 36-item Short Form; MCS, mental component scale; YG, yoga group; ST, stretching control group; WL, or waitlist control group; XRT, radiotherapy treatment; PSQI, Pittsburgh Sleep Quality Index.

(SF-36 PCS) at 6 months because the physical health subscale of the SF-36 PCS was the only outcome associated with group differences assessed after 3 months.

Hayes and Preacher's bias-corrected bootstrap test of indirect effect[57] revealed that group did indirectly affect physical health–related QOL (SF-36 PCS) at 6 months via benefit finding at 3 months (Figure 3). First, YG resulted in higher 3-month benefit finding compared with WL (the a_1 pathway; $P = .04$), whereas ST and WL did not differ in 3-month benefit finding (the a_2 pathway; $P = .84$). Second, holding group constant, those who reported higher benefit finding at 3 months reported higher 6-month physical health–related QOL (the b pathway, $P = .04$). Third, relative to WL, women in YG reported higher 6-month physical health–related QOL in part because of the positive effect of


Figure 2. Group differences on posttraumatic response across time: these figures represent the least-squared means (adjusted for the baseline level of the outcome variable, baseline SF-36 general health subscale, and randomization factors) of a multilevel modeling analysis for each of the mediators over time.

Abbreviations: SF-36, 36-item Short Form; IES, Impact of Event Scale; XRT, radiotherapy treatment.

YG on 3-month benefit finding. Indeed, a bootstrap estimate of the indirect effect of YG compared with WL on 6-month physical health–related QOL via 3-month benefit finding revealed a 95% bias-corrected and accelerated (BCa) confidence interval that did not cross zero ($B = 0.77$; $SE = 0.58$; $CI = 0.01$ and 2.58). Thus, 3-month benefit finding partially mediated the effect of YG on 6-month physical health–related QOL. Conversely, the BCa confidence interval for the indirect effect of ST compared with WL did cross zero and was, therefore, not significant ($B = 0.07$; $SE = 0.43$; $CI = -0.84$ and 0.88). Thus, the effect of ST on 6-month physical health–related QOL was not mediated by 3-month benefit finding.

Cortisol. Results revealed no significant group or time effect on cortisol slope ($P > .3$). There was a trend for a Group × Time interaction effect ($F_{(6,189)} = 1.83$; $P = .096$). Specifically, YG was associated with a steeper cortisol slope
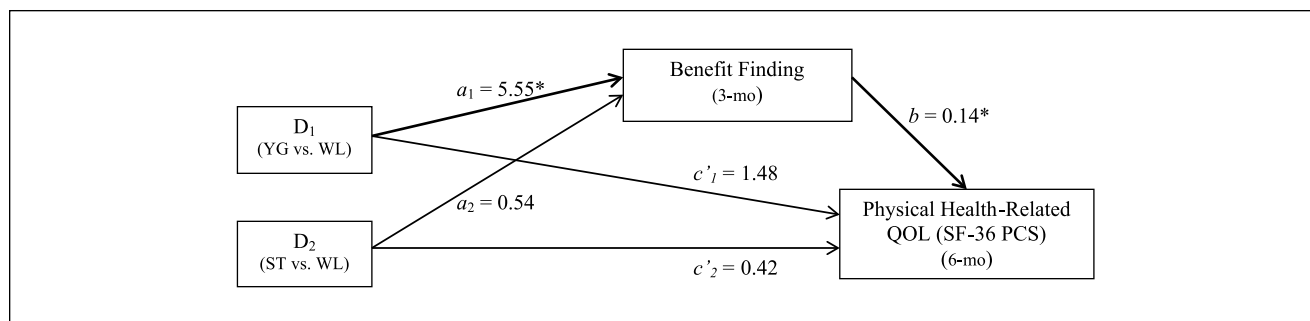
Figure 3. Yoga indirectly affects physical health–related QOL (SF-36 PCS) at the 6-month follow-up via increased benefit finding (BFS) at 3 months. Values on each path are unstandardized path coefficients taken from bootstrapping analyses controlling for age, stage of disease, time since diagnosis, type of surgery, chemotherapy type, and baseline benefit finding (BFS), physical health–related QOL (SF-36 PCS), and the SF-36 general health subscale. The a_1 and a_2 paths correspond to the mean differences in 3-month BFS between YG relative to WL and ST relative to WL, respectively. Thus, YG resulted in 3-month BFS scores that were $a_1 = 5.55$ units higher than WL ($P = .04$), and ST resulted in BFS that were $a_2 = 0.54$ points higher than WL ($P = .84$). The b pathway corresponds to the relation between 3-month BFS and 6-month SF-36 PCS when group is held constant. Thus, for every 1 point increase in 3-month BFS, individuals reported an average $b = 0.14$-point increase in 6-month SF-36 PCS ($P = .04$). The relative indirect effects of group can be determined by multiplying the a and b paths. Thus, relative to WL, YG resulted in SF-36 PCS scores that were $a_1b = 0.77$ units higher as a result of the positive effect of YG on BFS, which corresponds to a significant indirect effect of YG versus WL on 6-month SF-36 PCS via 3-month BFS ($B = 0.77$; SE = 0.58; 95% bias-corrected and accelerated [BCa] CI = 0.01 and 2.58). Conversely, there was no significant indirect effect of ST versus WL on 6-month SF-36 PCS via 3-month BFS ($B = 0.07$; SE = 0.43; BCa CI = −0.84 and 0.88). Abbreviations: QOL, quality of life; SF-36, 36-item Short Form; PCS, physical component scale; BFS, Benefit Finding Scale; YG, yoga group; ST, stretching control group; WL, or waitlist control group.
*$P < .05$.

compared with ST and WL ($Ps < .03$) immediately after radiotherapy (post-XRT), and YG was associated with a steeper cortisol slope compared with WL at 1 month ($P = .02$). Figure 2C represents LSMs of cortisol slope for groups at each time point. Because the effects of group and Group × Time on cortisol slope did not reach significance, it was not examined as a mediator.

Exploratory Analyses: Changes in IES and Outcomes

Because women in WL reported unexpectedly lower IES avoidance scores over time compared with women in YG, we explored the association between changes in IES avoidance and QOL outcomes by regressing group, change in IES avoidance at 6 months (the time point associated with significant group differences), and the interaction on QOL outcome variables (physical and mental health–related QOL (SF-36 PCS and MCS), depressive symptoms (CES-D), and sleep disturbance (PSQI)) at the final follow-up time point (ie, 6 months). There were significant interaction effects for mental health–related QOL ($P = .05$) and depressive symptoms ($P = .04$). Pearson correlations within each group revealed no association between change in IES avoidance scores and 6-month mental health–related QOL or depressive symptoms for YG or ST, whereas a greater increase in IES avoidance scores was associated with worse 6-month mental health–related QOL ($r = −0.31$; $P = .03$)

and higher depressive symptoms ($r = 0.42$; $P < .01$) for the WL group.

Discussion

The present study hypothesized that participating in a yoga intervention during radiotherapy would be particularly beneficial for women with high baseline depressive symptoms and sleep disturbances on posttreatment QOL compared with their counterparts participating in stretching or waitlist control groups. We also hypothesized that trauma responses (ie, change in posttraumatic stress symptoms and increased benefit finding) and better stress hormone regulation (ie, steeper cortisol slope) would mediate the effect of yoga on primary outcomes. Results partially supported each of the hypotheses.

Consistent with previous research suggesting that cancer patients with higher distress derive greater benefit from psychosocial interventions,[18,58-61] the yoga intervention provided the greatest mental health–related benefits for women with elevated sleep disturbance and, to a lesser extent, depressive symptoms prior to the start of radiotherapy. This effect varied by time, with differences emerging especially 3 and 6 months after radiotherapy. Thus, yoga was especially helpful for those women with disturbed sleep and depressive symptoms at the start of radiotherapy. In fact, the women in the yoga group who had sleep disturbances at study entry had mental health scores at 3 and 6 months after

radiotherapy equivalent to those of women who did not have sleep disturbances at study entry. A similar pattern was seen for the benefits of yoga for those with high depressive symptoms at baseline.

Regarding our mediation hypotheses, yoga led to increased benefit finding across the follow-up period relative to the stretching and waitlist control groups, where there was consistent decrease over time. Importantly, we found that yoga indirectly affected physical health–related QOL assessed 6 months after radiotherapy via increased benefit finding reported 3 months after radiotherapy. In other words, part of the effect of yoga on physical health–related QOL at the long-term follow-up can be attributed to the increased benefit finding experienced by yoga participants midway through the follow-up period. Of note, the longitudinal nature of the data enabled the time-lagged mediation analyses, which are critical for determining mechanisms of effect. This is a particular strength of the present article because such mediation analyses are often lacking in intervention study designs.

Surprisingly, women in the waitlist group reported less avoidance behaviors (eg, "I tried not to think about it;" "I stayed away from reminders about it") 6 months following radiotherapy compared with women in the yoga group, who reported little change in avoidance behaviors from baseline, and there was no evidence of a decrease in intrusive thoughts over time for any group. This finding was counter to our hypotheses and that of other studies, which have found mind-body practices in general, and yoga in particular, to be associated with reductions in avoidance-related coping.[62,63] However, exploratory analyses suggested that the typical deleterious effect of avoidance behaviors on QOL[64,65] was not found for those in either of the active groups (yoga or stretching) but remained for those in the waitlist group. This finding was somewhat consistent with our previous pilot trial, in which the yoga group reported short-term increases in intrusive thoughts relative to the waitlist control group.[10] Furthermore, a meta-analysis by Helgeson et al[66] found that increased intrusive or avoidant thoughts about a stressor were associated with increase in benefit finding, which was in turn associated with greater well-being. Thus, it could be that yoga may not reduce posttraumatic stress symptoms (ie, cognitive interference or avoidance) in the acute phase, but this in turn may facilitate improved long-term adjustment.

There are several limitations to recognize in this study. The majority of participants were white, non-Hispanic, married, and highly educated. Thus, future research is needed to test the generalizability of these findings to more diverse populations. Participants also were not blinded to study condition, and no measure of treatment expectation was collected, which could have biased the findings because of the subjective nature of the outcomes. In addition, although these data suggest that women with elevated levels of depressive symptoms and sleep disturbances show a greater treatment response, these findings need to be interpreted with caution because the patients were not selected based on pretreatment symptomatology. The study may have also been underpowered for the mediation analyses. In a study of empirical power simulations, Fritz and MacKinnon[67] indicated that very large sample sizes are required for tests of mediation to be conducted with at least 80% power. Thus, the sample size of the present study likely limits our ability to determine mediators with full power, and the same limitation may be true for moderation analyses. Additionally, the reduced reliability of cortisol slopes assessed at later follow-up points (because of a smaller sample size) may have limited our power to detect the effects of cortisol slopes as a mediator in particular. Finally, we followed participants for only a 6-month period, so the long-term effectiveness of yoga in patients with breast cancer remains to be determined. To address these limitations, we are conducting an ongoing yoga trial using a quasi-double-blinded design, with patients not knowing the details of the intervention groups at baseline and then only knowing the specifics of their assigned group. Additionally, assessors are blind to group assignment. Treatment expectations are also being measured, and patients complete a 1-year follow-up assessment.

In conclusion, the current study provides a greater understanding of who will benefit most from a yoga intervention and how a yoga intervention produces change. These results suggest that future studies of the effect of yoga on cancer patients may benefit from screening for participants who report poor sleep or depressive symptoms because yoga may buffer the negative effect of poor sleep or low mood on mental health–related QOL indices in the months following treatment for cancer. Additionally, these findings imply that yoga may improve physical health–related QOL by increasing one's ability to find benefit in the cancer experience. Finally, yoga appears to increase women's endorsement of symptoms typically associated with posttraumatic stress (ie, intrusive thoughts and/or avoidance behaviors) but disassociates the typically harmful link between these symptoms and QOL. Based on these results, we recommend that future research continues to identify pretreatment psychosocial factors that predict intervention response, seeks mechanisms by which interventions work, and begins implementing targeted, tailored, evidence-based mind-body interventions to optimize recovery and QOL in patients affected by cancer.

Authors' Note

Chelsea G. Ratcliff and Kathrin Milbury contributed equally to the article and are both considered first authors.

Declaration of Conflicting Interests

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