

Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial

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Abstract

Objectives: Cancer survivors often report cognitive problems. Furthermore, decreases in physical activity typically occur over the course of cancer treatment. Although physical activity benefits cognitive function in noncancer populations, evidence linking physical activity to cognitive function in cancer survivors is limited. In our recent randomized controlled trial, breast cancer survivors who received a yoga intervention had lower fatigue and inflammation following the trial compared with a wait list control group. This secondary analysis of the parent trial addressed yoga's impact on cognitive complaints.

Methods: Posttreatment stage 0–IIIA breast cancer survivors ($n = 200$) were randomized to a 12-week, twice-weekly Hatha yoga intervention or a wait list control group. Participants reported cognitive complaints using the Breast Cancer Prevention Trial Cognitive Problems Scale at baseline, immediately postintervention, and 3-month follow-up.

Results: Cognitive complaints did not differ significantly between groups immediately postintervention ($p = 0.250$). However, at 3-month follow-up, yoga participants' Breast Cancer Prevention Trial Cognitive Problems Scale scores were an average of 23% lower than wait list participants' scores ($p = 0.003$). These group differences in cognitive complaints remained after controlling for psychological distress, fatigue, and sleep quality. Consistent with the primary results, those who practiced yoga more frequently reported significantly fewer cognitive problems at 3-month follow-up than those who practiced less frequently ($p < 0.001$).

Conclusions: These findings suggest that yoga can effectively reduce breast cancer survivors' cognitive complaints and prompt further research on mind–body and physical activity interventions for improving cancer-related cognitive problems.

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Background

Breast cancer survivors commonly experience cognitive impairment during survivorship [1,2]. Accumulating evidence suggests that cancer and its treatment can negatively impact neuropsychological test performance [3–5], although these findings are not without controversy [1,6]. Cancer-related neuropsychological problems appear to dissipate over time; however, for a subset of cancer survivors, mild impairment may persist over the long term in several focused cognitive domains, such as verbal ability [6].

In addition to poorer neuropsychological test performance, survivors often report cognitive problems [7]. Although subjective cognitive dysfunction is consistently

associated with psychological distress [7,8], the relationships between subjective and objective cognitive function is less clear. Cross-sectional studies indicate that cognitive complaints may parallel neuropsychological test performance in some domains. For example, breast cancer survivors who reported more memory problems had lower scores on a standardized verbal memory task than those who reported fewer memory problems [9]. On the other hand, breast cancer survivors who just stopped adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors) continued to report cognitive problems over the following year, despite improvement in objective neuropsychological test scores [10]. Whether or not perceptions are mirrored by objective neuropsychological measures,

perceived cognitive dysfunction can be disruptive to cancer survivors. For example, 1 year after cancer treatment, women with more cognitive complaints had lower quality of life scores than those with fewer cognitive complaints [11]. Accordingly, subjective cognitive problems are bothersome for some cancer survivors.

Physical activity benefits cognitive function in noncancer populations [12,13], but evidence linking physical activity to cognitive complaints in cancer survivors is limited. Significant deconditioning and decreases in physical activity typically occur over the course of cancer treatment [14,15]. Consequently, cognitive complaints among cancer survivors may be at least partially linked to decreased physical activity. A recent meta-analysis concluded that physical activity interventions improved cancer survivors' overall quality of life but did not consistently affect their perceived cognitive problems [16]. However, several limitations of the meta-analysis precluded strong conclusions, including the small sample sizes of many studies, as well as the relatively limited number of trials that reported cognitive outcomes. Taken together, these findings suggest that further research is necessary to determine whether physical activity impacts cognitive function for cancer survivors.

Yoga is a particularly appealing exercise intervention for improving cognitive function in breast cancer survivors. With gentle physical activity, breathing practices, and meditation, yoga can be easily adapted for breast cancer survivors who may be experiencing common physical symptoms such as pain or fatigue [17]. Indeed, recent randomized controlled trials (RCTs) demonstrated that cancer survivors derived both physical and psychological benefits from yoga [17–19]. In addition, healthy college-aged females performed better on a working memory and inhibitory control task immediately following a yoga practice session compared with a baseline or aerobic exercise session [20]. Yoga can also reduce inflammation [19], one proposed mechanism that may contribute to breast cancer survivors' cognitive symptoms [21–23].

Several meta-analyses suggest that yoga improves cancer survivors' fatigue, distress, and quality of life [24–26], but yoga's impact on cognitive function following cancer treatment is unclear. Indeed, a recent meta-analysis of randomized controlled yoga trials for breast cancer survivors concluded that there was insufficient evidence to evaluate yoga's cognitive effects, because too few trials reported cognitive outcomes [27]. Studies with larger samples of posttreatment breast cancer survivors, appropriate covariates, and supporting adherence data are necessary to evaluate whether yoga decreases subjective cognitive problems. In our recent RCT, a brief yoga intervention reduced fatigue and inflammation compared with a wait list control group [19]. In the current paper, we report secondary analyses that examined whether yoga also affected self-reported cognitive complaints.

Methods

Participants

Female stage 0–IIIA breast cancer survivors ($n=200$) were recruited from breast cancer physicians and clinics, community announcements, and breast cancer groups and events for an RCT investigating yoga's effects on inflammation, fatigue, and depression from 2007 to 2012 (ClinicalTrials.gov identifier: NCT00486525). The sample size was calculated to ensure adequate (80%) power to detect differences in these primary endpoints, requiring 85 participants per group and assuming a 15% attrition rate [19]. Participants' cancer stage at diagnosis was determined using medical records. Women were eligible for the study if they had completed breast cancer treatment (except for tamoxifen/aromatase inhibitors) between 2 months and 3 years previously. Women were ineligible if they engaged in over 5 h of vigorous physical activity per week, if they had a prior history of any other cancer (except basal or squamous cell skin cancer), or if they suffered from major medical conditions such as anemia, diabetes, multiple sclerosis, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, uncontrolled hypertension, or liver or kidney failure. Women were also excluded if they had severe cognitive impairment (e.g., dementia or Alzheimer's disease) or abused alcohol or drugs. Those who reported current yoga practice or prior yoga practice exceeding 3 months were also excluded. The recruitment and randomization procedures have been described in detail in the primary RCT paper [19]. The institutional review board approved this study, and each participant provided informed consent.

Procedures

Participants completed a variety of self-report measures (described in the succeeding texts) during study visits at the Clinical Research Center. Following a baseline study visit, a data manager (who had no participant contact) used an online randomization program to assign participants to a 12-week Hatha yoga intervention ($n=100$) or a wait list control condition ($n=100$). Immediately postintervention and at the 3-month follow-up, participants completed additional questionnaires and provided fasting morning blood samples. Participants were asked not to share their group assignment with the study personnel during study visits.

Trained yoga instructors delivered the yoga intervention, which outlined poses for the 24, twice-weekly, 90-min sessions (see [19] for detailed information on the yoga protocol). Each of the 25 yoga groups (i.e., cohorts) included between 4 and 20 participants. Sessions were audiotaped, and raters assessed 50% of the tapes for protocol drift. To maximize adherence, yoga instructors called women who missed a class to discuss missed material

and to assess barriers for participation. Participants received pamphlets that detailed the poses and breathing exercises from class and were encouraged to practice at home. Women were also given a commercial yoga video for cancer survivors as a home practice aide. Although instructors did not give specific instructions or requirements for the length of home practice, they gave suggestions for ways to complete the poses at home. Women in the yoga condition used weekly logs to record their combined yoga class and home practice time during the 12-week intervention period; the combined total was used to calculate their average daily minutes spent practicing yoga during the intervention period. Instructors also encouraged yoga participants to continue to practice yoga after the 12-week intervention period ended. However, participants did not log their yoga practice during the follow-up period. Wait list control participants were told to continue normal activities and refrain from beginning any yoga practice; all participants reported adhering to this guideline. After their 3-month follow-up, women in the wait list group were offered the option to participate in the yoga classes.

Measures

Self-reported cognitive problems

Participants rated how much they were bothered by cognitive symptoms (i.e., forgetfulness, difficulty concentrating, and being easily distracted) in the past 4 weeks (0 'not at all' to 4 'extremely') as part of the Breast Cancer Prevention Trial (BCPT) Symptom Checklist [28]. The BCPT Symptom Checklist contains several subscales, and factor analytic studies from four samples demonstrated that the three-item BCPT Cognitive Problems Scale is psychometrically and conceptually appropriate for evaluating cognitive symptoms [29]. The individual item scores were averaged to index cognitive problems, with higher scores indicating more cognitive complaints. The scale demonstrates good internal consistency and discriminant validity [28]; Cronbach's alpha in our sample was 0.91 at baseline, 0.91 at the postintervention visit, and 0.93 at 3-month follow-up.

Covariates

In our primary trial, yoga improved sleep quality and fatigue [19]. In addition, prior research has demonstrated that cognitive complaints are linked to depressive symptoms, anxiety symptoms, and fatigue [7,29]. Accordingly, we assessed depressive symptoms, anxiety symptoms, fatigue, and sleep quality in order to account for the possibility that they could be responsible for yoga-related differences in self-reported cognitive function.

Women reported current levels of depressive symptoms using the Center for Epidemiological Studies Depression Scale, a valid, reliable, and widely-used measure of depressive symptoms [30]. Anxiety symptoms were measured with the Beck Anxiety Inventory, which has well-

established internal consistency and test-retest reliability [31]. Participants rated sleep quality and disturbances using the Pittsburgh Sleep Quality Index, which has been used extensively in sleep assessment [32]; higher scores reflect poorer sleep quality. Participants reported vitality in the last month using the Medical Outcomes Study Short Form Health Survey (SF-36) Energy Scale [33], which provided a measure of general energy without assessing the overlapping construct of cognitive fatigue. Higher scores indicate greater vitality and thus lower fatigue.

Inflammation

As part of the parent RCT, fasting blood samples were assayed for lipopolysaccharide (LPS)-stimulated production of interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumor necrosis factor alpha (TNF- α). LPS-stimulated cytokines were measured from isolated peripheral blood mononuclear cells according to Meso Scale Discovery kit instructions (see [19] for detailed methods).

General activity level

At each study visit, the Community Healthy Activities Model Program for Seniors questionnaire was used to assess the average frequency and duration of participants' engagement in various physical activities in the last month [34,35]. For each participant, weekly hours spent engaging in activities of moderate-to-high intensity were calculated.

Statistical analyses

In preliminary analyses, we tested for baseline between-group differences in cognitive complaints using an independent samples *t*-test. In primary analyses, linear mixed models tested whether self-reported cognitive function differed between groups following the intervention. Intervention group, visit, the group by visit interaction, and baseline cognitive complaints were entered as predictors of postintervention cognitive complaints. To account for repeated postintervention assessments of each participant and the yoga class cohorts (resulting in partially nested data), subject and intervention cohort were included as random effects. Significant group by visit interactions were decomposed using planned contrasts that tested whether cognitive complaints differed for the yoga and wait list groups both immediately postintervention and at 3-month follow-up. A second set of planned contrasts tested the effect of visit within each group, addressing whether cognitive complaints changed significantly from the immediate postintervention to 3-month follow-up visits for each group.

We conducted two sets of ancillary analyses. First, we examined whether potential confounds could account for yoga's effect on cognitive function. To accomplish this goal, we simultaneously included levels of depression, anxiety, fatigue, and sleep quality in the primary model

Table 1. Demographic and baseline characteristics of total sample

| Variable | Total sample (n = 200) | | | | Yoga (n = 100) | | | | Wait list (n = 100) | | | |
|---|------------------------|------|------|--------|----------------|----|------|--------|---------------------|----|-------|--------|
| | n | % | M | (SD) | n | % | M | (SD) | n | % | M | (SD) |
| Age (years) | | | 51.6 | (9.2) | | | 51.8 | (9.8) | | | 51.3 | (8.7) |
| BMI (kg/m ²) | | | 27.8 | (5.7) | | | 27.9 | (5.3) | | | 27.6 | (6.0) |
| BCPT cognitive problems | | | 1.5 | (1.0) | | | 1.5 | (1.0) | | | 1.4 | (1.0) |
| CES-D depressive symptoms | | | 10.7 | (8.2) | | | 10.2 | (8.2) | | | 11.2 | (8.2) |
| BAI anxiety symptoms | | | 10.1 | (7.1) | | | 9.8 | (7.2) | | | 10.33 | (7.1) |
| SF-36 vitality | | | 46.5 | (20.6) | | | 48.6 | (20.2) | | | 44.4 | (20.9) |
| PSQI sleep quality | | | 7.5 | (3.5) | | | 7.9 | (3.9) | | | 7.2 | (3.1) |
| CHAMPS moderate-to-high intensity activity (h/week) | | | 6.3 | (5.8) | | | 6.8 | (6.3) | | | 5.8 | (5.1) |
| Race/ethnicity | | | | | | | | | | | | |
| White | 176 | 88.5 | | | 88 | 88 | | | 88 | 88 | | |
| Black | 18 | 9 | | | 8 | 8 | | | 10 | 10 | | |
| Asian | 5 | 2.5 | | | 3 | 3 | | | 2 | 2 | | |
| Marital Status | | | | | | | | | | | | |
| Single | 26 | 13 | | | 18 | 18 | | | 8 | 8 | | |
| Married | 140 | 70 | | | 68 | 68 | | | 72 | 72 | | |
| Separated/divorced | 29 | 14.5 | | | 14 | 14 | | | 15 | 15 | | |
| Widowed | 5 | 2.5 | | | 0 | 0 | | | 5 | 5 | | |
| Education level | | | | | | | | | | | | |
| High school or less | 12 | 6 | | | 5 | 5 | | | 7 | 7 | | |
| Some college | 49 | 24.5 | | | 27 | 27 | | | 22 | 22 | | |
| College graduate | 62 | 31 | | | 29 | 29 | | | 33 | 33 | | |
| Postgraduate | 77 | 38.5 | | | 39 | 39 | | | 38 | 38 | | |
| Employment status | | | | | | | | | | | | |
| Employed | 137 | 68.5 | | | 71 | 71 | | | 66 | 66 | | |
| Unemployed | 35 | 17.5 | | | 15 | 15 | | | 20 | 20 | | |
| Retired | 28 | 14 | | | 14 | 14 | | | 14 | 14 | | |
| Income level (\$) | | | | | | | | | | | | |
| 0–25,000 | 10 | 5.5 | | | 3 | 3 | | | 7 | 7 | | |
| 25,000–50,000 | 33 | 18 | | | 18 | 18 | | | 15 | 15 | | |
| 50,000–75,000 | 35 | 19.1 | | | 17 | 17 | | | 18 | 18 | | |
| 75,000–100,000 | 46 | 25.1 | | | 23 | 23 | | | 23 | 23 | | |
| >100,000 | 59 | 32.2 | | | 30 | 30 | | | 29 | 29 | | |
| No report | 17 | 8 | | | 9 | 9 | | | 8 | 8 | | |
| Type of treatment | | | | | | | | | | | | |
| Surgery only | 26 | 13 | | | 13 | 13 | | | 13 | 13 | | |
| Surgery plus radiation | 52 | 26 | | | 28 | 28 | | | 24 | 24 | | |
| Surgery plus chemotherapy | 46 | 23 | | | 23 | 23 | | | 23 | 23 | | |
| Surgery plus radiation plus chemotherapy | 76 | 38 | | | 36 | 36 | | | 40 | 40 | | |
| Cancer stage at diagnosis | | | | | | | | | | | | |
| 0 | 18 | 9 | | | 9 | 9 | | | 9 | 9 | | |
| I | 89 | 44.5 | | | 46 | 46 | | | 43 | 43 | | |
| IIA | 52 | 26 | | | 27 | 27 | | | 25 | 25 | | |
| IIB | 23 | 11.5 | | | 10 | 10 | | | 13 | 13 | | |
| IIIA | 18 | 9 | | | 8 | 8 | | | 10 | 10 | | |
| Tamoxifen/aromatase inhibitor use | 143 | 71.5 | | | 72 | 72 | | | 71 | 71 | | |
| Postmenopausal | 153 | 81 | | | 76 | 76 | | | 77 | 77 | | |
| Time since diagnosis (months) | | | 17.3 | (8.1) | | | 16.3 | (7.5) | | | 18.3 | (8.5) |
| Time since treatment (months) | | | 10.9 | (7.9) | | | 9.9 | (7.1) | | | 11.8 | (8.5) |

SD, standard deviation; BMI, body mass index; BCPT, Breast Cancer Prevention Trial; CES-D, Center for Epidemiological Studies Depression Scale; BAI, Beck Anxiety Inventory; SF-36, 36-item Medical Outcomes Study Short Form Health Survey; PSQI, Pittsburgh Sleep Quality Index.

[7,19,29]. Because these variables were measured at each study visit, they were included as time-varying covariates.

The second set of ancillary analyses examined whether women who practiced yoga more frequently derived more benefit from the intervention. To test this hypothesis, we repeated the primary analyses and replaced intervention group with the participants' average minutes of yoga

practice per day, which included time spent practicing in class and at home during the intervention. Significant practice by visit interactions were decomposed using planned contrasts that tested the effect of yoga practice at each post-intervention visit. To examine whether yoga practice was associated with change in cognitive complaints over time, a second set of planned contrasts tested the effect of visit

at no yoga practice (wait list participants, 0 min per day), lower frequency yoga practice (25th percentile, 18 min per day), and higher frequency yoga practice (75th percentile, 29 min per day).

Given prior research linking inflammation, physical activity, and cognitive function [13,20], we also explored the possibility that inflammation mediated yoga's effect on cognitive complaints. The parent RCT demonstrated that women in the yoga group had lower levels of LPS-stimulated IL-6, IL-1 β , and TNF- α than women in the wait list control group at 3-month follow-up [19]. Levels of LPS-stimulated IL-6, IL-1 β , and TNF- α did not differ between yoga and wait list groups immediately postintervention. In exploratory analyses, we tested whether levels of inflammation were associated with cognitive complaints. We tested this possibility in two ways. First, we added each inflammatory marker separately to the primary model individually as a time-varying covariate. These analyses allowed us to examine whether inflammation significantly predicted cognitive complaints. Next, we calculated changes in LPS-stimulated cytokines by subtracting 3-month follow-up values from baseline values; we investigated whether changes in inflammation predicted cognitive problems scores at 3-month follow-up (controlling for baseline cognitive complaints). Levels of LPS-stimulated IL-6, IL-1 β , and TNF- α were natural log transformed to reduce skew.

Finally, to gain information about participants' activity level during the follow-up period, we conducted a post hoc exploratory analysis to test the effect of group on moderate-to-high physical activity levels following the intervention. To do so, we repeated the primary analyses and replaced the cognitive complaints variable with the activity level outcome variable while controlling for baseline activity levels.

Results

Sample description

Demographic and baseline characteristics of the sample are presented in Table 1. Participants were primarily employed (68.5%), Caucasian (88.5%), postmenopausal (81%) women. On average, participants were 10.9 (± 7.9 standard deviation (SD)) months posttreatment, with the exception of hormonal therapy. Demographic and disease-related characteristics did not differ significantly between groups. Four women (two in the yoga group and two in the wait list group) experienced a recurrence of their breast cancer during study enrollment. Importantly, BCPT Cognitive Problems Scale scores did not differ significantly between the two groups at baseline ($t(198) = -0.45, p = 0.654$). On average, participants reported slight-to-moderate bother from cognitive symptoms, which is consistent with previous reports using the BCPT Cognitive Problems Scale [28].

Protocol adherence

Of the 200 women in the initial sample, 186 provided post-intervention data across the wait list ($n = 90$) and yoga ($n = 96$) groups. Women who did not provide postintervention data were more likely to be separated or divorced compared with women who provided data ($X^2 = 8.28, p = 0.041$). Other demographic characteristics did not differ significantly between women who provided postintervention data and those who did not ($ps > 0.100$). However, women who dropped out of the study had higher anxiety symptoms ($t(198) = 2.57, p = 0.011$) and worse sleep quality ($t(197) = 1.94, p = 0.053$), as well as slightly more cognitive complaints ($t(198) = 1.68, p = 0.094$) at baseline than those who completed the intervention.

On average, women who received the yoga intervention attended 18.13 (± 4.52 SD) of 24 classes (75.4%) and reported 24.69 (± 10.62 SD) min per day of yoga practice during the 12-week intervention. None of the wait list control participants reported practicing yoga over the course of the intervention.

Primary analyses

Table 2 summarizes the results from the primary linear mixed model, which tested group differences in cognitive complaints over time. The group by visit interaction was a significant predictor of self-reported cognitive problems, suggesting that change in cognitive complaints differed for yoga versus wait list groups ($F(1, 176) = 4.11, p = 0.044$; Table 2 and Figure 1(A)). The first set of planned contrasts tested group differences at each time point (Table 3). Cognitive complaints did not differ significantly between yoga ($M = 1.15$) and wait list ($M = 1.26$) groups immediately following the intervention ($t(86) = 1.16, p = 0.250$). However, at 3-month follow-up visit, yoga participants ($M = 1.03$) reported 23% fewer cognitive

Table 2. *F*-tests for all predictors of Breast Cancer Prevention Trial Cognitive Problems Scale scores at the postintervention visits in primary and ancillary analyses

| Effect | <i>F</i> | DF | <i>p</i> |
|-------------------------------|----------|--------|----------|
| <i>Primary model</i> | | | |
| Baseline cognitive complaints | 243.73 | 1, 183 | <0.001 |
| Visit ^a | 0.27 | 1, 176 | 0.608 |
| Group | 5.60 | 1, 55 | 0.022 |
| Visit \times group | 4.11 | 1, 176 | 0.044 |
| <i>Ancillary model</i> | | | |
| Baseline cognitive complaints | 159.77 | 1, 198 | <0.001 |
| Visit | 0.66 | 1, 172 | 0.417 |
| Group | 1.42 | 1, 59 | 0.238 |
| Visit \times group | 3.08 | 1, 173 | .081 |
| Depressive symptoms | 5.78 | 1, 347 | 0.017 |
| Anxiety symptoms | 8.32 | 1, 351 | 0.004 |
| Fatigue | 11.43 | 1, 323 | 0.001 |
| Sleep quality | 0.507 | 1, 343 | 0.477 |

Bolded *p* values indicate statistically significant at $p < 0.05$

^aImmediate postintervention visit versus 3-month follow-up visit.

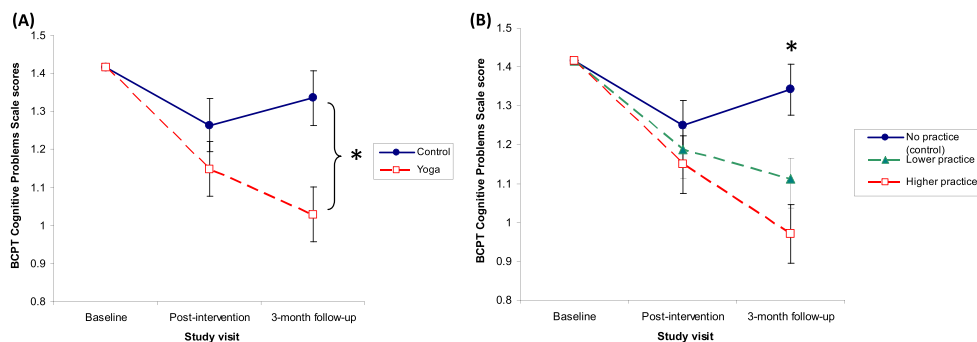


Figure 1. (A) Breast Cancer Prevention Trial (BCPT) Cognitive Problems Scale scores at baseline, immediately postintervention, and 3 months postintervention in yoga and control groups. The plot shows estimated marginal means (\pm SE) from a linear mixed model adjusting for baseline BCPT Cognitive Problems Scale scores. Yoga participants reported significantly fewer cognitive problems at 3-month follow-up visit compared with wait list control participants (* * indicates significant group contrast, $p < 0.05$). (B) BCPT Cognitive Problems Scale scores at baseline, immediately postintervention, and 3-month follow-up based on yoga practice frequency. The plot shows estimated marginal means (\pm SE) from a linear mixed model adjusting for baseline BCPT Cognitive Problems Scale scores at no yoga practice (wait list participants, 0 min per day), lower frequency yoga practice (25th percentile, 18 min per day), and higher frequency yoga practice (75th percentile, 29 min per day). At 3-month follow-up, those who practiced yoga more frequently reported fewer cognitive problems than those who practiced less frequently (* indicates significant slope of yoga practice, $p < 0.05$)

Table 3. Contrasts comparing cognitive complaints across groups and over time from the primary linear mixed effects model

| Contrast | Mean differences in BCPT Cognitive Problems Scale scores | | | |
|--|--|------|---------------|--------------|
| | Mean difference | SE | 95% CI | <i>p</i> |
| <i>Comparing groups</i> | | | | |
| Yoga versus wait list immediately postintervention | 0.12 | 0.10 | −0.08 to 0.32 | 0.250 |
| Yoga versus wait list at 3-month follow-up | 0.31 | 0.10 | 0.11 to 0.51 | 0.003 |
| <i>Comparing visits</i> | | | | |
| Immediately postintervention to 3-month follow-up in yoga group | 0.07 | 0.07 | −0.06 to 0.20 | 0.291 |
| Immediately postintervention to 3-month follow-up in wait list control group | 0.12 | 0.07 | −0.01 to 0.25 | 0.071 |

BCPT, Breast Cancer Prevention Trial; SE, standard error; CI, confidence interval.

problems than wait list participants ($M=1.34$; $t(88) = -3.02$, $p=0.003$). A second set of contrasts tested the effect of visit within each group. For the control group, cognitive complaints did not differ significantly from immediately postintervention to 3-month follow-up visits ($t(175)=1.06$, $p=0.291$). However, cognitive complaints improved over time in the yoga group, although this effect approached significance ($t(177)=-1.82$, $p=0.071$).

Ancillary analyses

In secondary analyses, we adjusted for the concurrent effects of depression, anxiety, fatigue, and sleep quality (Table 2). The results of the primary analysis remained the same, albeit slightly weaker; the group by visit interaction approached significance with all of the covariates included ($F(1, 173)=3.08$, $p=0.081$). Planned contrasts reflected the primary results. Specifically, cognitive complaints did not differ significantly between groups immediately following the intervention ($t(97)=-0.18$, $p=0.858$). However, yoga participants tended to report

fewer cognitive problems than wait list participants at 3-month follow-up ($t(101)=-1.89$, $p=0.062$). For the control group, cognitive complaints did not differ significantly from immediately postintervention to 3-month follow-up ($t(171)=0.66$, $p=0.511$). However, cognitive complaints decreased from immediately postintervention to 3-month follow-up for women in the yoga group, although again this effect was trending toward significance ($t(173)=-1.84$, $p=0.068$).

Analyses that examined the effect of yoga practice on self-reported cognitive function bolstered the primary analyses examining the assigned intervention group (Figure 1(B)). The yoga practice by visit interaction was significant ($F(1, 174)=8.81$, $p=0.003$). Follow-up tests revealed that the effect of yoga practice frequency on cognitive function was not significant immediately following the intervention ($b = -0.003 \pm 0.003$ standard error, $t(126) = -1.02$, $p=0.308$). However, women who spent more time practicing yoga during the course of the trial reported significantly fewer cognitive problems at 3-month follow-up visit than those who practiced yoga less frequently

($b = -0.01 \pm 0.003$ standard error; $t(127) = -3.79$, $p < 0.001$). A second set of contrasts examined the effect of visit on cognitive complaints for those with different levels of yoga practice. Among women who spent no time practicing yoga (i.e., wait list controls, 0 min per day), cognitive complaints did not change significantly from immediately postintervention ($M = 1.25$) to 3-month follow-up ($M = 1.34$; $t(175) = 1.53$, $p = 0.128$). Similarly, those with lower yoga practice frequency (i.e., 25th percentile, 18 min per day) did not report significant changes from immediately postintervention ($M = 1.19$) to 3-month follow-up ($M = 1.11$; $t(176) = -1.54$, $p = 0.125$). However, among women with higher yoga practice frequency (i.e., 75th percentile, 29 min per day), cognitive complaints decreased significantly from immediately postintervention ($M = 1.15$) to 3-month follow-up ($M = 0.97$; $t(175) = -2.58$, $p = 0.011$). Adjusting for depression, anxiety, sleep quality, and fatigue did not change the results.

Exploratory analyses

Yoga decreased inflammation in the parent RCT; accordingly, we examined whether changes in inflammation contributed to group differences in cognitive complaints. We added each inflammatory marker to the primary model as a time-varying covariate; IL-6, IL-1 β , and TNF- α levels were not significant predictors of cognitive complaints ($ps > 0.369$). Changes in IL-6, IL-1 β , and TNF- α levels from baseline to 3-month follow-up did not significantly predict cognitive complaints at 3-month follow-up ($ps > 0.474$).

We also examined whether general physical activity levels as measured by the Community Health Activities Model Program for Seniors differed between groups following the intervention. The main effect of group predicting moderate-to-high intensity activity hours was significant ($F(1, 78) = 5.69$, $p = 0.019$), and the group by visit interaction was not significant ($p = 0.751$). Immediately postintervention, yoga participants ($M = 6.60$) tended to report greater moderate-intensity activity hours compared with wait list participants ($M = 5.23$), and this effect approached significance ($t(145) = 1.83$, $p = 0.068$). At 3-month follow-up, yoga participants ($M = 6.80$) reported significantly greater moderate-to-high intensity activity hours than wait list participants ($M = 5.17$, $t(148) = 2.17$, $p = 0.032$).

Conclusions

On average, breast cancer survivors who received a brief yoga intervention had 23% lower self-reported cognitive problems scores than wait list participants at 3-month follow-up visit. Among women in the intervention group, those who practiced yoga more frequently during the intervention had larger decreases in cognitive complaints than those who practiced less frequently, suggesting that

components of yoga were beneficial. The current findings suggest that yoga may be useful for reducing cognitive complaints in breast cancer survivors.

These results extend the current literature on cognitive function, yoga, and breast cancer survivorship in an important new direction. RCTs and meta-analyses have demonstrated that yoga reduces common behavioral symptoms for breast cancer survivors, such as psychological distress, fatigue, and sleep disturbances [17–19,25,26]. However, limited research has addressed yoga's effect on perceived cognitive problems, another important aspect of cancer survivors' well-being [27]. With good adherence (greater than 90%), inclusion of relevant covariates (i.e., psychological distress), and supporting yoga practice frequency data, this study addresses limitations of the few yoga intervention trials reporting cognitive outcomes. Importantly, group differences in cognitive complaints remained even after controlling for psychological distress, fatigue, and sleep quality, which are often related to perceived cognitive problems [7,8]. Indeed, our results indicated that lower distress and fatigue may have contributed to yoga's beneficial effect on cognitive function but could not entirely explain it.

In this study, group differences in cognitive complaints were significant at 3-month follow-up but not immediately following the intervention. This pattern is consistent with the primary outcomes of this trial; yoga participants had significantly lower LPS-stimulated IL-6, IL-1 β , and TNF- α and fatigue than waitlist participants at 3-month follow-up, but group differences were not significant immediately postintervention. One possibility is that women may have continued to practice yoga beyond the intervention period, accruing its positive effects on physical, emotional, and cognitive well-being over time. Although women reported their at-home and in-class yoga practice during the intervention, we did not ask participants to track their yoga activities following the 12-week intervention period, a limitation of this study. However, women reported their participation in other activities at each study visit, including the 3-month follow-up visit. Compared with waitlist participants, yoga participants reported more hours of moderate-to-high intensity activity both immediately postintervention and at 3-month follow-up. These data suggest that women who received the yoga intervention sustained greater overall physical activity levels over time, which could have produced the cognitive benefits that were evident at 3-month follow-up. Future RCTs may be strengthened by including follow-up periods and continuing to measure participants' yoga practice after the intervention ends.

There are several plausible mechanisms through which yoga may reduce breast cancer survivors' cognitive complaints. Prior research suggests that inflammation contributes to breast cancer survivors' cognitive symptoms [21–23]. However, reductions in the inflammatory markers studied

here did not explain yoga-related changes in cognitive complaints in the current study, which suggests that yoga likely affected cognitive complaints through other pathways. Physical activity can benefit cognitive function by increasing cerebral blood flow, neurogenesis, and neurotrophic factors that support neuronal health [36]. In addition, yoga may decrease cognitive complaints by reducing negative performance expectations. For example, women who received chemotherapy and were reminded about its negative cognitive effects performed more poorly on a subsequent memory task and reported more cognitive problems than those who did not receive such reminders [37]. Breathing exercises and meditation during yoga may help to focus attention to the present moment; emerging research suggests that mindfulness can impact cognitive function [38]. Accordingly, yoga may reduce perceived cognitive deficits by increasing physical fitness and/or mindfulness. Finally, it is possible that yoga participants' expectations of the intervention's benefits may have influenced their likelihood to engage in practice or perceive cognitive improvement. Comparing yoga with other physical activity interventions in future trials would help to further assess yoga's utility in improving post-treatment cognitive problems, as well as the mechanisms through which yoga affects cognitive function.

Women in our study reported relatively low levels of cognitive problems; on average, they were 'slightly' or 'moderately' bothered by forgetfulness, difficulty concentrating, and distractibility. These data are consistent with breast cancer survivors' reports in other studies [28,39]. Those who dropped out of the intervention reported slightly more cognitive problems and fatigue [19] than those who completed the trial. Consequently, our results may actually underestimate the true effect of yoga on cognitive function, one limitation. Alternatively, yoga may be less feasible for those with the greatest fatigue and self-reported cognitive problems. Of note, women who dropped out of the study represent a small percentage of the overall sample; the trial had excellent retention, with

an attrition rate of less than 10%. In addition, because we did not assess objective measures of cognitive function, these data cannot address whether yoga benefits objective cognitive performance, another limitation. Although future trials that examine neuropsychological test performance would help to answer whether yoga also affects objective cognitive function, it is also important to note that better subjective cognitive function could substantially improve quality of life [9,11].

Given the improved efficacy of cancer treatments, long-term health and quality of life following cancer is increasingly important. Breast cancer survivors often report and experience cognitive problems following cancer treatment, and perceived cognitive dysfunction may continue even after neuropsychological test performance improves [10]. These findings suggest that yoga can effectively reduce breast cancer survivors' cognitive complaints and prompt researchers to further explore mind-body and physical activity interventions for improving cancer-related cognitive problems.

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Conflict of interest

All authors declare no conflicts of interest.

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