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Mind-body interventions for fear of cancer recurrence: A systematic review and meta-analysis

Daniel L. Hall[1,2], **Christina M. Luberto**[1], **Lisa L. Philpotts**[3], **Rhayun Song**[4], **Elyse R. Park**[1,5,6], and **Gloria Y. Yeh**[2]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

[3]Treadwell Library, Massachusetts General Hospital, Boston, MA, USA

[4]College of Nursing, Chungnam National University, South Korea

[5]Massachusetts General Hospital Cancer Center, Boston, MA, USA

[6]Mongan Institute Health Policy Center, Massachusetts General Hospital, Boston, MA, USA

Abstract

Objective—Fear of cancer recurrence (FCR) is a common existential concern and source of distress among adults with a cancer history. Multiple randomized controlled trials (RCTs) have examined mind-body approaches to mitigating FCR. We summarized characteristics of these trials and calculated their pooled effects on decreasing FCR.

Methods—Six electronic databases were systematically searched from inception to May 2017, using a strategy that included multiple terms for RCTs, cancer, mind-body medicine, and FCR. Data extraction and reporting followed Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pooled effect sizes on self-report measures of FCR were computed by using random-effects models.

Results—Nineteen RCTs (pooled N = 2806) were included. Most studies (53%) were published since 2015 and targeted a single cancer type (84%; mostly breast). Intervention sessions (median = 6, mode = 4) tended to last 120 minutes and occur across 1.5 months. Delivery was predominantly in-person (63%) to either groups (42%) or individuals (42%). Most interventions incorporated multiple mind-body components (53%), commonly cognitive-behavioral skills (58%), or meditative practices (53%). Small-to-medium pooled effect sizes were observed post-intervention (Hedges' g = −0.36, 95% CI = −0.49, −0.23, $P < .001$) and at follow-up assessments (median = 8

Correspondence: Daniel L. Hall, PhD, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, One Bowdoin Square, 7th Floor, Boston, MA 02114, USA. hall@mgh.harvard.edu.

CONFLICT OF INTEREST

The authors have no conflicts of interests to declare.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

SUPPORTING INFORMATION

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months, $P < .001$). Potential modifiers (control group design, group/individual delivery, use of cognitive-behavioral or mindfulness skills, number of mind-body components, cancer treatment status, and number of sessions) did not reach statistical significance.

Conclusions—Mind-body interventions are efficacious for reducing FCR, with small-to-medium effect sizes that persist after intervention delivery ends. Recommendations include testing effects among survivors of various cancers and exploring the optimal integration of mind-body practices for managing fundamental uncertainties and fears during cancer survivorship.

Keywords

cancer; fear; meta-analysis; mind-body; oncology; systematic review

1 | BACKGROUND

Due to advances in early detection and treatment, cancer survivorship has increased over the last 50 years, with 19 million survivors projected to be living in the United States by 2024. After active treatment, cancer survivors are faced with prognostic uncertainty about survival, long-term symptoms, surveillance, and consequences of treatment (eg, infertility and cognitive difficulties), which collectively poses an existential dilemma confronting survivors.[1,2] Struggles with coping with the unknown, uncertainty regarding death, consequences for loved ones, and role changes make coping with fear of cancer recurrence (FCR) the most prominent and common existential difficulty facing cancer survivors.[3–5] Survivors' worries about disease recurrence and associated consequences on one's psychological and physical health may continue for years after treatment ends[6–9] and can persist at levels equal to that experienced at the time of diagnosis[10].

Several theoretical models have been developed to understand and contextualize antecedents and consequences of FCR, as well as mediating processes (eg, appraisals of threat) that may inform intervention development and refinement (for review, see Simonelli et al[11]). In broad terms, models of FCR emphasize the centrality of prognostic uncertainty in generating maladaptive cognitive, emotional, and behavioral responses based on fear, including elevated worry, anxiety, and reassurance-seeking or avoidance behaviors.[12–16] In extreme cases, catastrophic appraisals of uncertainty may lead to hopelessness, demoralization, and even suicidal ideation[17]. Survivors' struggles with FCR are triggered by a variety of stimuli that arise throughout survivorship, including external (eg, follow-up appointments, public health campaigns, and new diagnoses in family or friends)[6,9,18] and internal events (eg, somatic symptoms such as fatigue, pain, and insomnia).[19,20]

To manage FCR, cancer survivors may engage in maladaptive behaviors in an attempt to assert control over the unpredictability of their health.[15] Guided by FCR theoretical models, emerging evidence suggests that these responses may include reassurance seeking (eg, via unscheduled visits with their oncologists or primary care physicians and requesting additional scans) and avoidance behaviors (eg, skipping or delaying planned follow-up visits, substance use, sedentary behavior, or social isolation).[8,10,13,21–25] Both of these scenarios may place cancer survivors at risk for poorer outcomes. Cancer survivors who seek reassurance through additional testing risk exposure to the physical and emotional harms of

overscreening or overtreatment.[26,27] Alternatively, avoiding follow-up care increases the risk not just for cancer recurrence but also late effects like pain, fatigue, insomnia, osteoporosis, heart disease, and second malignancies.[21–25] Several potential targets for interventions have been identified, including tolerance of uncertainty, optimism (eg, reappraisal of uncertainty as an opportunity), meaning-making in the face of uncertainty, and clarification of ambiguity.[11,13,19,20,28]

Recent calls for interventions targeting FCR have emphasized the need for evidence-based treatments.[29–32] Increasingly, cancer survivors are using integrative modalities that use holistic approaches to manage their concerns,[33–35] and a growing number of randomized controlled trials (RCTs) have begun to examine the efficacy of these approaches. Chief among these are *mind-body interventions,* defined by the National Center for Complementary and Integrative Health as techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Mind-body interventions, including cognitive behavioral therapies, meditation, relaxation techniques, and use of the creative arts, have been studied extensively in oncology populations.[36,37] In recent years, clinical guidelines have begun to include recommending mind-body practices to promote quality of life among cancer patients and survivors.[38] Notably, those with higher FCR are more likely to use mind-body interventions,[28] suggesting the unique relevance of these techniques for patients struggling with uncertainty and worries about their future health. To date, narrative and systematic reviews of mind-body interventions in oncology have focused on a single modality (e.g., Mindfulness-Based Stress Reduction), specific cancer population (e.g., breast cancer survivors), or on a broad array of outcomes.[39–41] Over the last 15 years, a growing number of RCTs have tested mind-body practices for reducing FCR; however, characteristics of these trials, and the magnitude and direction of their pooled effects on FCR, have not been examined.

A systematic review and meta-analysis is warranted to offer a clear synthesis of key findings from RCTs testing these approaches and to provide recommendations for future trials in this area. The present study therefore aimed to (a) describe mind-body interventions for FCR, (b) estimate the pooled effect of these interventions on FCR from pretreatment to posttreatment, and (c) evaluate whether any effects observed were maintained over follow-up assessments.

2 | METHODS

2.1 | Search strategy

A literature search was conducted by a medical librarian (L. P.) in the Ovid (MEDLINE), PsycINFO, Embase, CINAHL, Cochrane Library, and Web of Science databases from the year of inception of each database until May 2017. The search strategy included free text synonyms and controlled vocabulary for the concepts of fear, worry, concern, or uncertainty related to recurrence or progression, cancer, and mind-body, existential, and/or psychotherapy interventions. The full Ovid (MEDLINE) search strategy is available (see Appendix S1). The results were limited to English language using database limits and were further limited to RCTs using a search strategy developed by Royle and Waugh.[42] In databases that use controlled vocabulary, articles on pediatric populations were also excluded from the search.

2.2 | Inclusion and exclusion criteria

Studies included in this systematic review and meta-analysis met multiple inclusion criteria. Regarding methodology, only RCTs were included to support conclusions about causality. Interventions were considered only if they incorporated mind-body approaches among oncology populations[37,43]: cognitive behavioral skills (eg, cognitive restructuring of persistent somatic symptoms and/or behavioral exposure to FCR triggers), relaxation (eg, progressive muscle relaxation, deep breathing, and guided imagery), meditation (eg, mindfulness meditation, seated meditation, and/or meditative movement such as yoga, tai chi, and qigong), and other techniques that include therapies involving spirituality or expressive arts (eg, meaning therapy, experiential-existential therapy, cognitive-existential therapy, visual art, music, or dance), biofeedback, hypnosis, and autogenic training. Control conditions were permitted to be active (e.g., attention and/or time-matched) or inactive (e.g., usual care). Nononcology or nonadult samples were excluded. Observational studies, commentaries, conference abstracts, and reviews were also excluded. In outcome assessment, studies were required to include a self-report measure of FCR. Because of the conceptual overlap of FCR with fear of progression[44,45] and cancer-related uncertainty,[9,46] and their integration into the Delphi consensus definition of FCR,[29] these outcomes were included. One manuscript included in the systematic review was excluded from the meta-analysis due to conflicting reports of results.

2.3 | Data extraction

All qualitative and quantitative data extraction was conducted independently by 2 reviewers (D. H. and C. L.) following Cochrane guidelines[47] and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48] Discrepancies were discussed and reconciled with a third expert reviewer (G. Y.). Data included a description of the sample (sample size, cancer type, and treatment status), duration (number, frequency, and length of sessions), modality (eg, individual and group), delivery medium (eg, in-person or remote technologies), mind-body components (categorized as cognitive-behavioral (CB) skills, relaxation skills, meditation techniques coded as seated meditation, meditative movement, and/or mindfulness meditation, and an “other” category for less common mind-body practices), control condition (active and inactive), timepoints for assessments (number and timing), outcome measure, and group-by-time effects on FCR outcomes. All available statistical data from included manuscripts were extracted and double entered into a database for computational analyses. Quantitative data extraction included the mean and standard deviation of the preintervention, postintervention, and longest follow-up test values for each group; the mean and standard deviation of change scores in each group; or measures of association (eg, *t* scores) with P-values within groups.

2.4 | Risk of Bias

Two reviewers independently assessed risk of bias for all included studies according to Cochrane criteria.[47] Reviewers were instructed to provide justifications in their assessments, which were used to reconcile discrepancies and generate consensus ratings. Criteria that were evaluated included selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias

(blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias (baseline imbalance and differential attrition). Each criterion was rated as low, high, or unclear.[47]

2.5 | Statistical analysis

Comprehensive Meta-Analysis (v3)[49] was used to calculate Hedges' g values, 95% confidence intervals (CIs), *P*-values, and *Q*-values for a series of models estimating pooled effect sizes with specific subgroup comparisons. The primary analysis calculated the proximal effects from preintervention to postintervention. As a preliminary examination of sustainability of mind-body intervention effects on FCR, we estimated the effect size from baseline to the longest follow-up assessment reported among studies with multiple follow-up assessments. For each of these analyses, pooled effect sizes were computed separately for studies with active versus inactive control groups. Finally, a series of exploratory subgroup comparisons were conducted to test whether effect sizes varied by factors identified through the systematic review to characterize the majority of extant mind-body interventions for FCR.

All analyses computed random-effects models, given the heterogeneity among included studies with respect to intervention design and cancer histories of the samples. Random-effects models also generate effect size estimates that are more conservative and less prone to bias than those from fixed-effects models.[50] Following Cochrane guidelines, for studies that included 2 control groups, we conducted 2 comparisons and adjusted the computed sample size of the intervention group (N/2) to avoid overestimation of potential intervention effects.[51] All analyses were weighted to account for variability in sample sizes across studies. I^2 values were examined as indicators of heterogeneity (>50% considered highly heterogeneous).[52] As an index of publication bias, funnel plots were generated with effect sizes graphed against their standard errors.[53] To estimate the number of studies with null effects that would be required to produce a nonsignificant ($\alpha \geq .05$) pooled effect size, classic fail-safe N was calculated. Group comparisons were evaluated by using *Q*-value statistics.

3 | RESULTS

3.1 | Studies

A total of 610 citations were identified via the database searches (Figure 1). Duplicate citations ($k = 342$) were removed by using bibliographic software, leaving 268 citations for title and abstract screening. Common reasons for exclusion were a lack of intervention ($k = 63$), no mind-body component ($k = 51$), or no FCR outcome ($k = 41$). After initial screening, 24 articles were reviewed in full. An additional 5 articles were excluded for not including a mind-body component ($k = 3$) or FCR outcome ($k = 2$).

As shown in Table 1, the final sample for qualitative synthesis consisted of 19 RCTs. Trends in publication dates were as follows. All studies were published since 2002 (median = 2015, range = 2002 to 2017), and over half ($k = 10$, 53%) were published since 2015. The modal year of publication was 2016 ($k = 7$). All studies used a validated self-report measure of

FCR (for review, see Koch et al[9]). Among the 10 measures reported, the most commonly used were the MUIS ($k = 6$), CARS ($k = 5$), and the FCRI ($k = 4$).

3.2 | Quality of trials and risk for bias

The quality of trials and potential for bias among studies is summarized in Appendix S2. Overall, bias was low or unclear across studies. All trials except for one[57] had at least one source of bias rated as unclear. Cumulatively, there was low evidence of selection bias, detection bias, and bias due to baseline imbalance across the majority of studies. However, there were several potential sources of bias that emerged. There was mixed evidence of bias due to differential attrition, with approximately half of trials reporting greater dropout rates among patients randomized to intervention groups as compared with control groups. Additionally, although all studies included some degree of selection bias due to patient interest in enrolling in a trial, one study required participants to have previous exposure to intervention content, potentially biasing results in favor of the intervention condition.[55] Indeed, this study fell outside of the funnel plot of effect sizes (Appendix S3), suggesting that it may be an outlier. To account for this potential bias, results from meta-analyses are reported with and without this study included.

3.3 | Samples

The pooled sample size was N = 2806. Sample sizes for included studies ranged from N = 26 to N = 509. The majority of studies recruited samples of one cancer site. These were breast ($k = 11$, 58%), prostate ($k = 3$, 16%), gynecological ($k = 1$, 5%), or melanoma ($k = 1$, 5%). Three studies (16%) included mixed cancer sites. Regarding treatment status, a minority of studies ($k = 5$, 26%) enrolled patients undergoing active treatment. Most ($k = 14$, 74%) enrolled patients had completed primary treatment for early-stage disease or were undergoing active surveillance (ie, watchful waiting).

Samples also differed by ethnicity or cultural identity, reflecting the international scope of included RCTs. Studies recruited in Belgium ($k = 1$), China ($k = 2$), Germany ($k = 2$), the Netherlands ($k = 1$), Thailand ($k = 1$), and the United States ($k = 12$), including one study that targeted recruitment to Asian-Americans. No studies specified previous exposure to mind-body interventions among inclusion or exclusion criteria except for one, which required participants to be self- identified Buddhists.[55]

3.4 | Duration

The duration of mind-body interventions across studies was highly variable, ranging from 9 days to 12 months (median = 1.5 months). The modal duration was 1 month ($k = 5$, 26%). Studies also varied by the number of sessions provided within the total intervention duration. Interventions ranged from 4 to 17 sessions (median = 6 sessions), and most commonly were comprised of four sessions. Session length was reported in most of the RCTs ($k = 17$), ranging from 10 to 165 minutes. Both the median and modal session length was 120 minutes. Across these factors, 720 minutes of content (ie, 6 and 120-minute sessions) appeared to characterize the typical intervention duration.

3.5 | Modality and medium

Interventions were evenly divided between delivery to participants one-on-one (ie, individual, $k = 8$) or in groups ($k = 8$). A minority of interventions included a combination of individual and group sessions ($k = 3$). Regarding medium of intervention delivery, the majority of interventions ($k = 11$, 58%) used multiple mechanisms for delivering intervention content (eg, telephone plus audio CD). Methods included in-person visits ($k = 12$, 63%), telephone calls ($k = 8$, 42%), audio tapes or CDs ($k = 6$, 32%), printed booklets ($k = 4$, 21%), or online forums, chats, or websites ($k = 3$, 16%). All trials using audio tapes, CDs, or printed booklets described these materials as serving to reinforce skills taught or reviewed in-session.

3.6 | Mind-body components

Interventions targeting FCR used a wide array of mind-body components. Many studies ($k = 9$) focused on a single mind-body technique, such as teaching participants about Traditional Chinese Medicine[56] or training in cognitive behavioral skills.[54,59,64,65,69,71] The remaining studies ($k = 10$) offered a combination of multiple mind-body practices.

Cognitive-behavioral (CB) skills were the most common mind-body component ($k = 11$, 58%). Strategies included teaching participant skills to identify patterns of thoughts, emotions, behaviors, and triggers of FCR; skills to cope with cognitive appraisals of uncontrollability by reframing them as less threatening; skills for problem-solving; or behavioral exposure skills to confront avoidance of cancer-related stimuli. Notably, several interventions described as primarily psychoeducational[57,59,69] taught CB skills in addition to providing information and were therefore included. The majority of interventions adopting CB skills did not combine this approach with any other mind-body component; however, exceptions included a small number of studies that incorporated relaxation skills ($k = 3$), hypnosis ($k = 1$), or mindfulness ($k = 1$).

Relaxation skills were included in 4 (21%) interventions, including progressive muscle relaxation, diaphragmatic breathing, and guided imagery. No interventions taught these practices as stand-alone skills for managing FCR; they were paired with CB skills ($k = 3$) or meditative movement ($k = 1$). Relaxation skills were often described as techniques for reducing somatic arousal (eg, in the context of acute distress, fears, or bodily tension) or for distraction from worries about cancer deemed by patients as distressing or interfering.

Meditation training was a common component of interventions targeting FCR ($k = 10$, 53%). Meditation techniques encompassed a variety of mental training practices that involve self-regulating one's attention toward a chosen object of awareness (eg, the breath, specific mantras, or phrases). Mindfulness meditation is one form of meditation. Four (21%) RCTs focused specifically on mindfulness meditation (eg, nonjudgmental present moment awareness). Strategies for teaching mindfulness meditation included exercises of mindful eating, mindful meditation (eg, "Leaves on a River"), or mindful movements through dance. Other forms of meditation included loving kindness meditation (eg, extending positive feelings toward others) and compassion meditation (eg, imagining another's suffering and reliving their suffering). Importantly, meditation training can be taught via seated meditation

practices or combined with physical exercise in practices such as yoga, tai chi, or qi gong (ie, meditative movement). Seated meditation skills were included in 4 (21%) interventions, which were comprised of compassion and loving-kindness meditations, as well as visualization exercises with focus on the breath. All 4 interventions offering these skills paired seated meditation with additional mind-body components. For example, 3 studies tested adaptations of Mindfulness-Based Stress Reduction, which also integrates mindfulness and meditative movement (ie, hatha yoga). Five (26%) interventions incorporated meditative movement, such as yoga, tai chi, or mindful dance. While these practices tended to overlap with formal mindfulness training ($k = 4$), one study did not describe instruction of tai chi as incorporating mindfulness practice.[73] Meditative movement was described to facilitate overall resilience, perceived self-agency, and access to emotional tension being retained in the body.

Other mind-body components were relatively rare, and included those rooted in positive psychology ($k = 2$; ie, gratitude journaling, noting appreciations, nonmeditative compassion exercises), Buddhist doctrine-based practice ($k = 1$), hypnosis ($k = 1$), and dance therapy ($k = 1$). For example, one study randomized cancer patients to a gratitude journaling exercise, which was meant to foster flexible appraisals of meaning through a goal-directed activity and downstream reductions in not only FCR, but fear of death as well.[70] Most trials examining these components paired them with CB skills or mindfulness meditation.

3.7 | Control groups

Studies with an active control condition ($k = 9$) tended to use attention and/or time-matched designs, such as scripted calls inviting participants to describe their experiences of cancer diagnosis, treatment, and survivorship.[61] One study gave participants randomized to the control condition a book describing mindfulness skills.[72] The remainder of studies ($k = 10$) used inactive control groups, such as waitlist control designs or usual care.

3.8 | Meta-analyses

3.8.1 | Primary analyses—First, we examined effects from preintervention to postintervention. Studies only reporting omnibus effects across multiple postintervention timepoints (eg, baseline to 3-month follow-up assessment) were excluded from this analysis. Overall, the length of time between baseline and postintervention assessment ranged from 9 days to 14 months (median = 2 months). The studies showed significant heterogeneity ($I^2 = 47.99$), supporting the a priori decision for a random effects model. Weighted effect sizes by control condition type are presented in Figure 2. To ensure that the particularly robust effects in one study[55] did not influence the meta-analytic results, sensitivity analyses were conducted with and without this study. Unless otherwise noted, inclusion of this study in meta-analyses did not influence the pattern of findings.

Overall, there was a small, significant pooled effect of mind-body interventions on reducing FCR from pretreatment to posttreatment (Hedges' $g = -0.36$, 95% CI = −0.49, −0.23, $P < .001$). The funnel plot (Supporting Information, Appendix S3) was mostly symmetric, yet suggested a paucity of positive findings from studies with higher standard errors, such as those with smaller samples. The classic failsafe N indicated that 247 missing studies with

null findings would be needed to move the *P*-value below α = .05. When examined separately, studies with active control groups had a smaller effect (Hedges' g = −0.30, 95% CI = −0.45, −0.15, $P < .001$) than those with inactive control groups (Hedges' g = −0.42, 95% CI = −0.63, −0.21, $P < .001$), although this difference was not statistically significant ($Q[1] = 0.78$, $P = .377$).

Next, we analyzed studies with follow-up assessments beyond postintervention. Studies were excluded from this analysis if follow-up data on FCR were not reported or authors did not respond to our requests for these data. Effects were estimated from preintervention to the most distal timepoint available. The length of time between baseline and the distal assessment ranged from 40 days to 24 months (median = 8 months). There was high heterogeneity among studies ($I^2 = 63.36$), again supporting our use of a random effects model. Weighted effect sizes by control condition type for these analyses are displayed in Figure 2.

The pooled effect size from baseline to the longest follow-up (Hedges' g = −0.31, 95% CI = −0.47, −0.16, $P < .001$) was smaller than from the preintervention to postintervention analysis, although still statistically significant. Studies with active control groups had a smaller effect (Hedges' g = −0.28, 95% CI = −0.45, −0.12, $P = .001$) as compared with those using inactive control groups (Hedges' g = −0.36, 95% CI = −0.63, −0.10, $P = .008$), although this difference was not statistically significant ($Q[1] = 0.24$, $P = .623$).

3.8.2 | Subgroup comparisons—Finally, a series of exploratory group comparisons were conducted to test whether effect sizes varied by delivery (group vs individual), content (inclusion of CB skills and inclusion of mindfulness meditation), number of mind-body components (1 vs 2+), treatment status (posttreatment vs current), or number of sessions (6 or fewer vs 7 or more), as combinations of these factors were observed to characterize the majority of mind-body interventions for FCR or might inform future studies. Pooled effects were compared from preintervention to postintervention as well as to the longest available follow-up. Full statistical results are presented in Table 2.

First, we compared effects of RCTs using group vs individual delivery. Studies using a combination of both[57,65,73] were excluded from this comparison. Although effects were larger among studies with group delivery vs no group delivery, this difference was not statistically significant. Next, effects of RCTs using CB skills were compared with those that did not. Interestingly, interventions that did not incorporate CB skills had slightly greater effects on FCR than interventions containing CB skills; however, these differences were not statistically significant. Among interventions that used CB skills, effects were small yet significant from preintervention to postintervention, which were reduced though still significant at long-term follow-up.

Effects of mindfulness meditation were also examined. Interventions using mindfulness exercises yielded larger effects as compared with interventions without such training, although again these differences did not reach statistical significance. When single versus multimodal interventions were compared, multimodal interventions were observed to have larger effects from preintervention to postintervention, which were reduced at the long-term

follow-up, although again this difference was not statistically significant. Next, we compared effects on participants' cancer treatment status. Effects were larger, though not significantly so, for trials with patients who had completed active treatment. Finally, the number of sessions was dichotomized at the median (6) and examined. Relatively shorter interventions appeared to yield higher effect sizes, although differences were not statistically significant.

4 | CONCLUSIONS

This systematic review and meta-analysis evaluated 19 RCTs of mind- body interventions measuring effects on FCR, one of the chief existential concerns facing adults with a cancer history. Overall, these interventions yielded significant, small-to-medium effects on FCR postintervention, which were maintained at follow-up assessments ranging from 40 days to 2 years postbaseline assessments.

Findings from our systematic review shed light on a myriad of mind-body approaches and methodologies tested to date to help cancer patients manage cancer-related fears and concerns. Across trials, there were few areas of uniformity (eg, restricting recruitment to breast cancer patients). Instead, interventions were largely heterogeneous with respect to duration, delivery medium, and the combinations of various mind-body components within intervention content. The typical duration of interventions was 720 minutes (ie, six, 120-minute sessions), which may indicate a target duration for future trials. The most common mind-body techniques were CB skills, which tended to be delivered without integration of other mind-body components. Although these protocols were often brief and individually delivered, they varied greatly in length as well as emphasis on skills for developing adaptive appraisals (eg, cognitive restructuring) versus those for reducing body-checking or assurance-seeking (eg, exposure-based behavioral exercises). Notably, consistency between trials was most evident for manualized interventions, such as the Managing Uncertainty in Cancer Studies[54,61,69] and those using Mindfulness-Based Stress Reduction.[66,67,72]

Many of the trials in this review tested interventions that emphasize (a) the harms of appraising ambiguous, complex, or unpredictable stimuli as threatening and/or (b) the benefits of focusing on the present moment. For cancer survivors, triggers for uncertainty are ubiquitous; over half of cancer news coverage contains ambiguous or conflicting information,[74] and the physical symptoms that might signal recurrence may increase in frequency and severity simply due to aging. In the presence of these triggers, successful management of FCR may require a shift in one's relationship with the unknown.[13] Among the most common mind-body components were CB and mindfulness approaches, which teach distinct yet complementary skills for how to cope with cancer-related uncertainty. For instance, interventions incorporating CB skills taught practices for thinking flexibly about the future, reducing reassurance-seeking or avoidance behaviors that interfere with patients learning to tolerate uncertainty, and considering helpful, balanced, and fair appraisals of uncertainty. In contrast, mindfulness interventions did not focus on the content of thoughts or behaviors; rather, they taught skills for letting go of thoughts and judgments, as well as an appreciation for impermanence, particularly about physical sensations. It may be that paying attention to the present moment involves focusing on what is certain (eg, somatic sensations and one's breath), which may offset otherwise overgeneralized perceptions of uncertainty

among those struggling with FCR. Integrated theoretical models of these distinct, yet complementary approaches are warranted.

Intervening on fears and uncertainties about cancer recurrence is challenging, in part because a variety of factors may make recurrence possible, if not probable. Ostensibly, this may require addressing existential questions about what cancer recurrence could represent: loss of quality of life (mental and physical), loss of external support structures (eg, job, finances, and family roles), and loss of life.[75] While we did not identify trials that tested existential therapies for reducing FCR, several interventions did incorporate aspects of these approaches. For example, Mishel and colleagues' trials aimed to foster "growth through uncertainty" by teaching cancer survivors to adopt a probabilistic and conditional understanding of the controllability and course of their future health; participants were encouraged to accept uncertainty as "the natural rhythm of life."[13] Similarly, the trial[55] reporting the largest effects on FCR was rooted in The Four Noble Truths, which purport that suffering is natural, inevitable, and can be eased by acceptance. However, discussing their current fears or anticipated difficulties in the event of recurrence in these terms may not appeal to some individuals. The latter trial restricted eligibility to self-described Buddhists, so it is unclear whether a similar intervention would be acceptable to others from a wider diversity of cultures and beliefs. Presumably, enrollees had practiced Buddhism prior to their cancer diagnosis, which may have enhanced their uptake of the intervention material. Similar acceptance-based, meaning-centered approaches have demonstrated positive effects on quality of life among advanced cancer patients, yet note challenges with attrition and low attendance.[67,68] Future studies might thus explore the acceptability of teaching mind-body skills to patients prior to cancer treatment (eg, upon diagnosis) as a potential buffer against FCR after treatment ends as well as formally testing existential therapies for managing FCR.

Less frequently, other mind-body approaches (eg, yoga, tai chi, and relaxation skills) were integrated into trials for FCR. These skills may have unique strengths to facilitate coping and healing. For instance, meditative movement therapies may foster self-agency, symbolic expression, and trust in one's own body,[58] resulting in less fear about one's current health or ability to cope with recurrence in the future. Techniques using body movement or manipulation may also result in greater physical activity, which cancer patients may view as protective against risk of recurrence. Interestingly, these mind-body approaches tended to be paired with CB skills or mindfulness training; few were tested in isolation. Thus, greater attention to these less- studied modalities may elucidate processes by which FCR can be managed from the "bottom-up".

Applying mind-body skills to target FCR appears to be efficacious, albeit with room for greater refinement as indicated by pooled small-to-medium effects. Future trials may explore the unique and shared benefits of these approaches through multicomponent mind-body interventions that target FCR and aim to enhance overall resilience.[76–78] Building on the findings reported here, we suggest that future RCTs begin to examine the optimal sequencing, integration, and dosing of the various mind-body skills tested thus far. To accomplish this, trials could adopt innovative designs, such as the multiphase optimization strategy (MOST),[79] to test empirically which skills should be packaged together and in what order (eg, teaching CB skills before or after teaching meditative movement). Such designs

would offer efficiency, as fewer subjects would be needed to evaluate optimal components, and would allow researchers to determine the additive or multiplicative benefits of integrating specific mind-body components into a cohesive intervention[79].

We also examined potential moderators to identify characteristics of the most effective FCR interventions. In our subgroup analyses, no significant differences emerged between active vs inactive control groups, group vs individual delivery, inclusion/omission of CB skills, inclusion/omission of mindfulness exercises, number of mind-body components included, cancer treatment status, or by number of sessions. However, we interpret these effects with caution, as we were likely underpowered to compare groups of studies on each of these factors. Still, several interesting trends emerged. For instance, preintervention and postintervention pooled effects from multimodal interventions (Hedges' g = −0.39) were larger than those from unimodal interventions (Hedges' g = −0.29), although this difference did not reach statistical significance. The largest difference in effect sizes was between interventions delivered to groups (Hedges' g = −0.74) vs individual cancer patients (Hedges' g = −0.20) from baseline to the longest available follow-up, suggesting that sustained FCR reductions are strongest when using group- based delivery. While these findings suggest key features of the most effective interventions for reducing FCR, additional work is needed to conclusively establish the comparative efficacy of these intervention characteristics.

4.1 | Clinical implications

Researchers and clinicians working with cancer patients should be aware of mind-body practices that may be efficacious for reducing patients' FCR. Patients who endorse FCR at higher levels have been shown to have higher uptake and use of integrative modalities,[28] seeking relief from their concerns. Our findings indicate that these patients are seeking modalities that indeed are efficacious in reducing recurrence-related fears.

Although trials in this review overall had low risk of bias, one area of concern was differential attrition, suggesting the need for mind-body interventions that address FCR with greater feasibility and acceptability to patients. For instance, patients may be reluctant to confront their own cognitive, emotional, or behavioral avoidance, prompting them to prematurely withdraw from a FCR intervention. This may be particularly true for interventions that include CB exposure skills for habituating to fearful stimuli and reducing interference behaviors that impact daily functioning. Indeed, almost all trials testing CB techniques had high or unclear risk of bias due to differential attrition. With the trend toward personalized medicine in oncology care, additional work is needed to identify patient-related factors (eg, gender, age, trait mindfulness, intolerance of uncertainty and cancer type), preferences (eg, delivery format), and behaviors (eg, amount, frequency, and quality of skills practice between sessions and assessments[80]) that predict optimal benefit from mind-body approaches for managing FCR and may promote larger effect sizes in FCR reductions.

Interventions targeting FCR may also begin to look at secondary outcomes that can have a significant impact on cancer patients' wellbeing. For instance, while accumulating evidence suggests that mind- body interventions can influence markers of neuroendocrine[81] and immune functioning,[81–83] it is unclear whether specifically targeting FCR may lead to downstream improvements in survivors' physiological health. Psychoneuroimmunological

models implicate distress states as having the potential to dysregulate immune functioning over time, worsening physical health symptoms, and even risk of disease recurrence.[84–87] To date, links between FCR and inflammatory biomarkers remain unexamined, yet could yield insights into the interdependence of FCR and somatic symptoms. Additionally, FCR may also impact survivors' clinical outcomes due to effects on health care use. It has been suggested that FCR may lead to either health care underuse (eg, avoidance of follow-up testing procedures)[11,31,88] or overuse (eg, ceasing active surveillance).[11,89] These scenarios may place survivors in jeopardy of worse clinical outcomes, so it would be prudent for mind-body interventions targeting FCR to assess effects on health care use as well.

4.2 | Study limitations

Several strengths and limitations of this report should be noted. All included trials used validated self-report measures, which strengthened our confidence in the results from meta-analyses. However, the heterogeneity in measures used across studies led us to choose random-effects models, which requires 5 or more studies for primary analysis. Several exploratory subgroup analyses had 1 group with less than 5 studies included, weakening our power to detect robust differences. Additionally, we were unable to ascertain clinically-significant reductions in FCR in our meta-analyses due to the limited use of measures with established clinical cut-off scores. This review was strengthened by representation of trials conducted globally, including 7 international studies. However, lack of resources prevented inclusion of non-English studies, which may limit the generalizability of our conclusions.

In summary, results suggest that mind-body interventions may be useful for reducing FCR, with small-to-medium effect size improvements lasting well beyond intervention delivery ends. Larger effects may result from incorporating a variety of mind-body skills (in particular CB and mindfulness practices), refinement to increase their feasibility and acceptability for addressing FCR, and identifying subgroups who may benefit the most from these interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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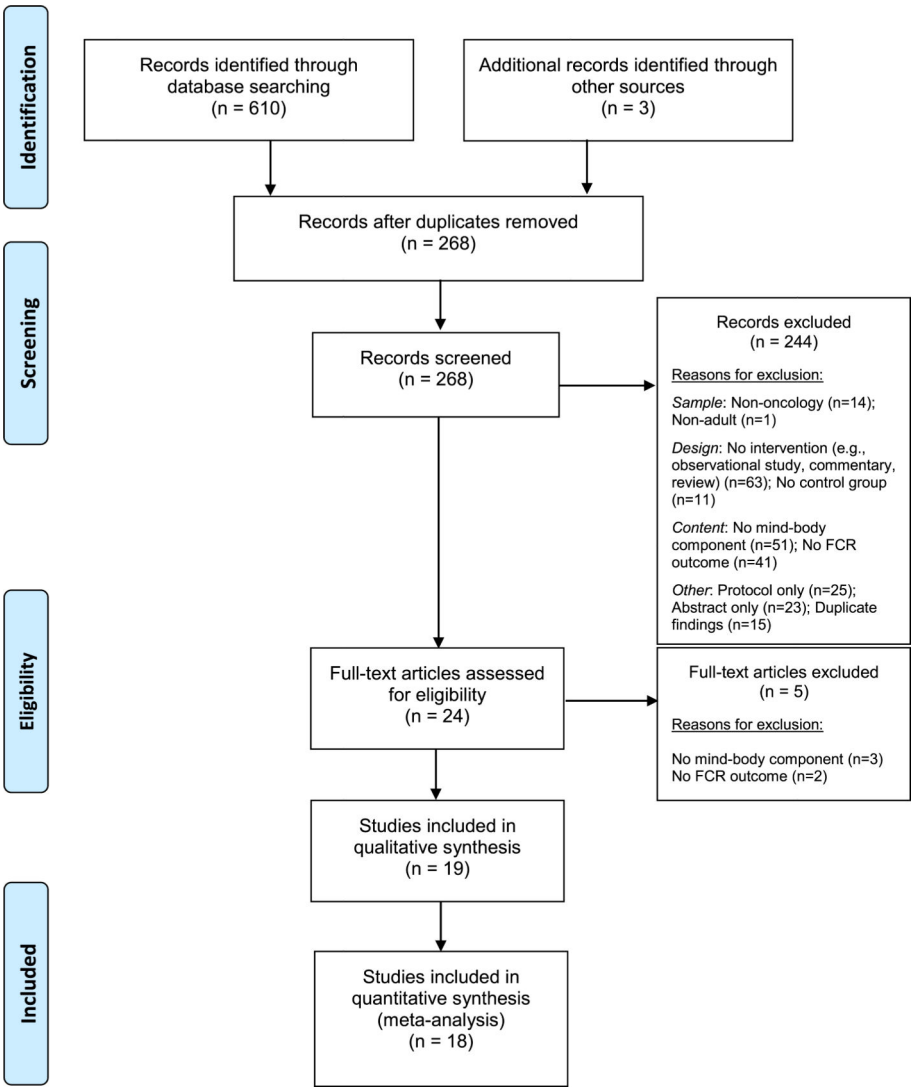
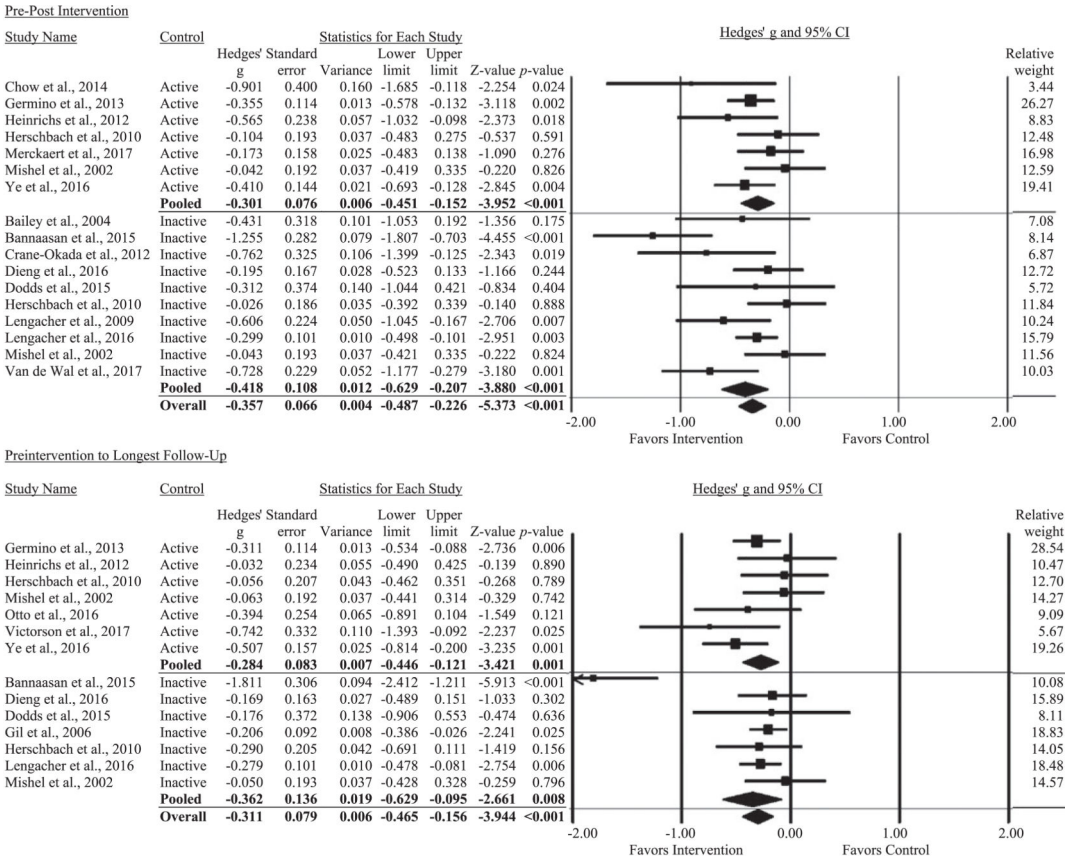


FIGURE 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram



Note: Studies only included within each analysis if results were reported for (a) postintervention assessments or (b) follow-up assessments, respectively.

FIGURE 2.

Pooled effects on fear of recurrence from preintervention to postintervention and longest follow-up

Table 1

Summary of studies

Study	Sample	Duration	Modality	Medium	MBC's	Control	Timepoints	Measure	Effects on FCR
Bailey et al[54]	Prostate cancer (N = 41). Early stage. Watchful waiting. United States.	1.25 months. 5 weekly sessions (5–26 min)	Individual	Telephone	CB	Inactive	2 (BL, +2.5 months)	GTUS	↑ new view of life subscale; NS other subscales and total score
Bannaasan et al[55]	Breast cancer (N = 59). Disease-free. 1–3 years post dx. Self-identified Buddhists. Thailand.	9 days. 5 sessions (~150 min) + 8 days of home practice	Group	In-person	Other	Inactive	4 (BL, +9 days, +25 days, +40 days)	CARS	↓ total score, maintained at follow-ups
Chee et al [56]	Breast cancer (N = 65). Current tx to 5 years post-tx. Asian American in United States.	1 month. Unrestricted access	Group	Internet forum	Other	Active	2 (BL, +1 month)	MUIS	NS total score
Chow et al[57]	Gynecological cancer (N = 26). Recent dx. China.	2 months. 4 sessions (33–60 min)	Group + individual	In-person + telephone	CB, R	Active	3 (BL, post-surgery, 2 months postsurgery)	MUIS	↓ information inconsistency subscale. Maintained at followup. NS other subscales and total score.
Crane-Okada et al[58]	Breast cancer (N = 49). Disease-free. 1+ years post-tx. Ages 50+. United States.	3 months. 12 weekly sessions (120 min)	Group	In-person	M Mov, MM	Inactive	3 (BL, +3 months, +4.5 months)	FCRS	↓ total score, maintained at follow-up
Dieng et al[59]	Melanoma (N = 154). Early stage. Post-tx. United States.	1 month. 3 sessions. (50–90 min)	Individual	Booklet + telephone	CB	Inactive	3 (BL, +1 month, +6 months)	FCRI	↓ severity subscale, maintained at followup; NS other subscales.
Dodds et al[60]	Breast cancer (N = 33). Disease-free. Up to 10 years post-tx. United States.	3 months. 8 weekly session (120 min) + 1 booster	Group	In-person	CB, other, SM	Inactive	3 (BL, +2 months, +3 months)	FCRI	↓ functional impairment subscale at +2 months, not maintained at

Study	Sample	Duration	Modality	Medium	MBC's	Control	Timepoints	Measure	Effects on FCR
									follow-up. NS other subscales.
Germino et al[61]	Breast cancer (N = 313). Disease-free. 2–4 years post tx. Ages <50. United States.	1 month. 4 weekly sessions (20 min)	Individual	Audio CD + booklet + telephone	CB, R	Active	3 (BL, +4–6 months, +8–10 months)	MUIS; GTUS; CARS	↓ MU IS total score, maintained at followup. T GTUS absence of fear and uncertainty subscale, maintained at follow-up. NS other subscales. NS CARS.
Gil et al[62,63]	Breast cancer (N = 509). Disease-free. 5–9 yrs post-tx. Ages 60+. United States.	1 month. 4 weekly sessions (30 min)	Individual	Audio CD + booklet + telephone	CB, R	Inactive	3 (BL, +10 months, +20 months)	MUIS; GTUS	↓ MUIS total score at 20-month follow-up, NS at 10-month follow-up. T GTUS total score, maintained at 20- month follow-up
Heinrichs et al[64]	Breast or gynecological cancer (N = 72). Recent dx. Early stage. Germany.	2 months. 4 sessions (120 min)	Individual	In-person	CB	Active	4 (BL, +2 months, +8 months, +14 months)	FoP	↓ at +2 months, NS at follow-ups.
Herschbach et al[65]	Mixed (N = 265). Current tx. Germany.	2 weeks. 4 sessions (90 min) + 2 booster (15 min)	Group + individual	In-person + telephone	CB	Active + inactive	4 (BL, +2 weeks, +3.5 months, +12.5 months)	FoP	↓ at 12.5 months in CBT and active control arms vs inactive control. NS at other follow-ups.
Lengacher et al[66]	Breast cancer (N = 84). Early stage. <18 months post-tx. United States.	1.5 months. 6 weekly sessions (120 min) + home practice	Group	In-person + audio CD	M Mov, MM, SM	Inactive	2 (BL, +1.5 months)	CARS	↓ total score
Lengacher et al[67]	Breast cancer (N = 322). Disease-free. 2 weeks - 2 years post-tx. United States.	1.5 months. 6 weekly sessions (120 min) + home practice	Group	In-person + audio CD	M Mov, MM, SM	Inactive	3 (BL, +1.5 months, +4.5 months)	CARS	↓ total score, maintained at follow-up

Study	Sample	Duration	Modality	Medium	MBC's	Control	Timepoints	Measure	Effects on FCR
Merckaert et al[68]	Breast cancer (N = 159). Early stage. <1 year post-tx.Belgium.	6 months. 15 weekly sessions (120 min)	Group	In-person	CB, other	Active	2 (BL, +6 months)	FCRI	↑ coping strategies subscale. 4-psychological distress subscale. NS other subscales.
Mishel et al[69]	Prostate cancer (N = 239). Early stage. Immediately post-surgery or < 3 weeks of radiation tx. United States.	2 months. 8 sessions (undefined length)	Individual	Audio tape + booklet + telephone	CB	Active + inactive	3 (BL, +4 months, +7 months)	MUIS	NS total score across follow-ups
Otto et al[70]	Breast cancer (N = 67). Early stage. Post-tx. United States.	1.5 months. 6 sessions (10 min)	Individual	Internet prompt	Other	Active	4 (BL, +1.5 months, +2.5 months, +4.5 months)	CARS	NS total score across follow-ups. 4- death worry subscale, maintained at followups
Van de Wal et al[71]	Breast, colorectal, or prostate cancer (N = 88). Diseasefree. 6 months - 5 years post-tx. Netherlands.	3 months. 8 sessions (5 in-person, 60 min; 3 internet chats, 15 min).	Individual	In-person + internet website + internet chat	CB	Inactive	2 (BL, +3 months)	CWS; FCRI	↓ CWS and FCRI total scores
Victorson et al[72]	Prostate cancer (N = 43). Early stage. Watchful waiting. United States.	2 months. 8 sessions (150 min) + half day retreat	Group	In-person + audio CD	M Mov, MM, SM	Active	4 (BL, +2 months, +6 months, +12 months)	IUS-SF; MAX-PC-FCR	NS total scores separately across follow-ups
Ye et al[73]	Breast cancer (N = 318). Early stage. Active tx. China.	12 months. 17 sessions (mode 150-180 min)	Group + individual	In-person + telephone	M Mov, other, R	Inactive	4 (BL, +14 months, +18 months, +24 months)	MUIS	↓ total score, maintained at follow-ups

Note: BL, Baseline; MUIS, Mishel Uncertainty in Illness Scale; CARS, Concerns About Recurrence Scale; CCSQ, Cognitive Coping Strategies Questionnaire; FCRS, Fear of Recurrence Scale; FCRI, Fear of Cancer Recurrence Inventory; FoP, Fear of Progression Scale; GTUS, Growth Through Uncertainty Scale; MCCS, Medical Communication Competence Scale; IUS-SF, Intolerance of Uncertainty Scale-Short Form; MAX-PC-FCR, Memorial Anxiety Scale for Prostate Cancer-Fear of Recurrence Subscale; MBCs, Mind-Body Components; CB, cognitive-behavioral skills; R, relaxation; M Mov, meditative movement; MM, mindfulness meditation; SM, seated meditation; Timepoints, + is time since BL; Effects, higher scores indicate higher levels of construct in measure or subscale name. NS, nonsignificant. Only group-by-time effects summarized for fear of recurrence (sub)scales as reported by study. If unadjusted and adjusted analyses reported, adjusted effects presented here.

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Table 2

Subgroup comparisons among RCTs

Subgroup Comparison	Assessments	(A) Effect Size	(B) Effect Size	Interaction Effect
Group (A) vs individual (B)	Preintervention and postintervention	Hedges' g = −0.52, *k* = 6, 95% CI = −0.81, −.23, *P* < .001	Hedges' g = −0.31, *k* =7, 95% CI = −0.48, −.13, *P* = .001	*Q* (1) = 1.46, *P* = .227
	Preintervention to longest follow-up	Hedges' g = −0.74, *k* = 4, 95% CI = −1.46, −.02, *P* = .043	Hedges' g = −0.20, *k* = 7 95% CI = −0.31, −.09, *P* < .001	*Q* (1) = 2.13, *P* = .144
CB (A) vs no CB (B)	Preintervention and postintervention	Hedges' g = −0.26, *k* = 12, 95% CI = −0.39, −.13, *P* < .001	Hedges' g = −0.39, *k* = 4, 95% CI = −0.54, −.24, *P* < .001	*Q* (1) = 1.64, *P* = .200
	Preintervention to longest follow-up	Hedges' g = −0.19, *k* = 9, 95% CI = −0.29, −.09, *P* < .001	Hedges' g = −0.37, *k* = 4, 95% CI = −0.53, −.22, *P* < .001	*Q* (1) = 3.81, *P* = .051
MM (A) vs no MM (B)	Preintervention and postintervention	Hedges' g = −0.45, *k* = 3, 95% CI = −0.72, −.18, *P* < .001	Hedges' g = −0.34, *k* = 14, 95% CI = −0.49, −.18, *P* < .001	*Q* (1) = 0.50, *P* = .481
	Preintervention to longest follow-up	Hedges' g = −0.40, *k* = 2, 95% CI = −0.80, <−.01, *P* = .049	Hedges' g = −0.30, *k* = 12, 95% CI = −0.48, −.12, *P* = .001	*Q* (1) = 0.21, *P* = .644
Unimodal (A) vs multimodal (B)	Preintervention and postintervention	Hedges' g = −0.29, *k* =8, 95% CI = −0.53, −.04, *P* = .021	Hedges' g = −0.39, *k* =9, 95% CI = −0.51, −.27, *P* < .001	*Q* (1) = 0.58, *P* = .448
	Preintervention to longest follow-up	Hedges' g = −0.32, *k* = 8, 95% CI = −0.62, −.01, *P* = .043	Hedges' g = −0.30, *k* =6, 95% CI = −0.62, −.01, *P* < .001	*Q* (1) = 0.01, *P* = .913
Postcancer treatment (A) vs current cancer treatment (B)	Preintervention and postintervention	Hedges' g = −0.38, *k* = 11, 95% CI = −0.54, −.21, *P* < .001	Hedges' g = −0.33, *k* =6, 95% CI = −0.40, −.19, *P* = .003	*Q* (1) = 0.12, *P* = .729
	Preintervention to longest follow-up	Hedges' g = −0.32, *k* =9, 95% CI = −0.53, −.12, *P* = .002	Hedges' g = −0.31, *k* =5, 95% CI = −0.54, −.07, *P* = .011	*Q* (1) = 0.01, *P* = .918
≤6 sessions (A) vs ≥7 sessions (B)	Preintervention and postintervention	Hedges' g = −0.54, *k* = 6, 95% CI = −0.83, −.26, *P* < .001	Hedges' g = −0.28, *k* = 11, 95% CI = −0.42, −.14, *P* < .001	*Q* (1) = 2.65, *P* = .104
	Preintervention to longest follow-up	Hedges' g = −0.43, *k* = 5, 95% CI = −0.78, −.07, *P* = .019	Hedges' g = −0.27, *k* =9, 95% CI = −0.39, −.15, *P* < .001	*Q* (1) = 0.67, *P* = .413

Note: CI, confidence interval; *k*, intervention-control group comparisons across studies; CB, cognitive-behavioral skills; MM, mindfulness meditation. For the group vs individual delivery comparison, studies using both methods (*k* = 3) were excluded. For the CB comparisons, Bannaasan et al[55] was excluded, as its large effects biased the pooled effect estimates and Q-values among subgroups of *k* ≤ 5 studies. Only one study[60] used CB and MM exercises.