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Efficacy of Cognitive Behavioral Therapy for Insomnia in Breast Cancer: A Meta-Analysis

Yan Ma[1,2], **Daniel L. Hall**[3], **Long H. Ngo**[4,5], **Qingqing Liu**[1,6], **Paul A. Bain**[7], **Gloria Y. Yeh**[2,4]

[1.]Division of Interdisciplinary Medicine and Biotechnology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

[2.]Osher Center for Integrative Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.

[3.]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

[4.]Division of General Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

[5.]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, United States

[6.]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China

[7.]Countway Library of Medicine, Harvard Medical School, Boston, MA, United States

Summary:

Insomnia is highly prevalent among patients with breast cancer (BC). Although cognitive behavioral therapy for insomnia (CBT-I) is available in integrative oncology settings, it poses unique challenges for BC survivors. Our review aimed to assess the evidence for the therapeutic effects of CBT-I on insomnia in BC. Randomized controlled trials (RCTs) that included patients/survivors with BC andinsomnia, and at least one validated self-report measure of sleep quality were included in the review. Of the 14 included RCTs (total N=1363), the most common components incorporated in CBT-I interventions were sleep hygiene, stimulus control and sleep restriction. Pooled effect sizes favored CBT-I at post-intervention (Hedges' g=−0.779, 95% CI= −0.949, −0.609), short-term follow-up (within six months, Hedges' g=−0.653, 95% CI=−0.808, −0.498), and long-term follow-up (12 months, Hedges' g=−0.335, 95% CI=−0.532, −0.139). In

*Correspondences will be addressed to: **Yan Ma**, M.D., dr.yan.ma@gmail.com Phone: 1-617-955-3419, Division of Interdisciplinary Medicine and Biotechnology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Address: 330 Brookline Avenue, Suite KSB-28, Boston, MA, 02215, United States.

Author contributions statement

Y.M. designed the study, conducted the analysis, drafted the manuscript, and interpreted the results. P.B. developed the search strategy and conducted data retrieval. Y.M. and D.H. screened the abstracts. Y.M. and Q.L. conducted the full text screening and data extraction. L.N. and G.Y. supervised the meta-analysis and contributed to the interpretation of the results. D.H., L.N. and G.Y. revised the manuscript and contributed to the discussion.

Conflict of interest

The authors report no conflict of interest in this review.

sub-analyses, CBT-I had similar effect sizes regardless of potential modifiers (comparison design, delivery formats, etc.). As an integrative oncology intervention, CBT-I is efficacious for reducing insomnia and improving sleep quality in women treated for BC, with medium-to-large effect sizes that persist after intervention delivery ends. Given the variability in the CBT-I components tested in RCTs, future studies should investigate the optimal integration of CBT-I components for managing insomnia during BC survivorship.

Keywords

Cognitive behavioral therapy for insomnia; breast cancer; meta-analysis; efficacy; randomized controlled trial

INTRODUCTION

Insomnia in patients with cancer is persistent, chronic, and two to three times more prevalent compared to that in the general population (50–60% versus 12–25%) [1–6]. The greater rate of insomnia in the cancer population is attributed to the emotional consequences of cancer diagnosis and to the direct effects of cancer treatments and their side effects. To date, most of the studies on sleep problems in cancer have been conducted in women with breast cancer [6–8]. In fact, prevalence rates of insomnia have shown to be the highest in breast cancer (42% to 69%) compared to other cancer sites (e.g. prostate, gynecologic, head and neck, urinary or GI, etc.) [2]. Notably, women with breast cancer are prone to insomnia for multiple reasons (e.g., discomfort, pain, hot flashes, endocrine therapy and other hormonal changes associated with the breast cancer treatment, fear of recurrence) [9–11]. Patients with breast cancer or survivors with breast cancer history experiencing insomnia are also more likely to endorse high uncertainty about cancer and cancer treatment [12]. Greater insomnia severity is also linked with worsened depression, pain, deregulated circadian rhythm, fatigue, reduced quality of life, disease progression, and even decreased survival [3, 13]. It has also been suggested that cancer-related fatigue provides a false cue for sleep extension and this contributes to insomnia [14]. In addition, breast cancer itself may increase the risk of insomnia and vice versa.

Cognitive behavioral therapy for insomnia (CBT-I) is the gold standard treatment for insomnia, and its efficacy has been well established for primary insomnia and insomnia with a variety of medical or psychiatric comorbid conditions [15–19]. Johnson *et al* conducted a meta-analysis to investigate the efficacy of CBT-I specifically in cancer survivors [6]. Based on the eight studies included in their analysis, results indicated that CBT-I improved sleep efficiency, sleep onset latency, wake after sleep onset, and insomnia symptom severity. However, only five studies reported on outcomes of women with breast cancer. Therefore, the effect of CBT-I in the particularly affected population with breast cancer history remains unclear.

CBT-I usually consists of multiple weekly sessions as a multi-component treatment that includes sleep hygiene (SH), stimulus control (SC), sleep restriction (SR), cognitive therapy (CT), and relaxation training (RT). In clinical research and practice, there may be variability in whether and how each of these skills is taught. For example, SR is considered as a core

component of CBT-I [20], SR alone is not sufficient for sleep improvement [21]. A combined approach is often preferred because that can address several dimensions of insomnia. The objective of CBT-I is to change factors that perpetuate insomnia, including behavioural factors (poor sleep habits, irregular sleep schedules), psychological factors (unrealistic expectations, worry, unhelpful beliefs), and physiological factors (mental and somatic tension, hyperarousal) [22]. CBT-I is typically delivered in the context of four to eight therapy sessions at weekly intervals. The number of follow-up visits can vary as a function of insomnia severity, comorbidity, and patient motivation [22]. Compared to pharmacotherapy, CBT-I may have better long-term beneficial effects that may last well beyond termination of treatment [15], because during CBT-I, patients can learn coping skills to tackle acute insomnia as well as to prevent or mitigate in severity future insomnia episodes [23]. However, the durability of CBT-I in patients with cancer has yet to be determined.

Although CBT is not readily available in most clinical settings, access and delivery can be made easier through use of innovative methods [22]. Currently, CBT-I interventions can be delivered in a wide variety of formats, including individual, group, in person, remote by phone or video, or online. Many of those formats have been proven to be efficacious in studies (e.g., self-help [24], group [25], online [26]), however, are dependent on patients' engagement. Given that patients with cancer experience physical and psychological challenges, the feasibility of implementing CBT-I in routine clinical oncology practice remains unclear [27]. In Johnson and colleagues' review published in 2016 [6], they were not able to directly compare the efficacy of CBT-I as delivered via different formats, given the limited number of RCTs published and included at that time in cancer population when they conducted the meta-analysis. Considerable challenges remain to make CBT-I available and accessible to meet population needs, particularly in patients with cancer.

In the present review, we aimed to systematically analyze the available literature to include recent trials and conduct a meta-analysis of randomized controlled trials (RCTs) to determine a more precise estimate of the efficacy of CBT-I on insomnia in patients with breast cancer. In addition, we aimed to compare the effect sizes of CBT-I via different delivery medium (e.g., in-person versus remote technologies) and to evaluate the durability of CBT-I by assessing the short-term (e.g., within 6 months) and long-term (e.g., 12 months) efficacy in this population.

METHODS

Search strategies

A professional medical librarian (P.B.) at Countway Library of Medicine (Harvard) developed and conducted searches in MEDLINE (PubMed), Embase (Elsevier), and PsycINFO (Ebsco), and Web of Science (Clarivate Analytics). Search strategies were customized to each database and included controlled vocabulary and free text synonyms comprising the concepts of insomnia, breast cancer and cognitive behavioral therapy, including individual interventional component (e.g., sleep restriction, stimulus control, etc.). Search strategy for each database is provided in detail (Appendix S1). Bibliographies of included studies and relevant meta-analyses were examined by hand to identify additional

studies. Registered clinical trials were also searched on clinicaltrials.gov for completed but not published studies. Search dates were from the year of inception of each database to April 2020.

Study selection

Two of the authors (YM and DH) independently reviewed all identified abstracts for eligibility. We only included RCTs. All RCT studies evaluating CBT-I among patients with breast cancer or survivors with breast cancer history were selected for full text review. Articles were retained if they met the inclusion criteria: (1) Insomnia was clearly diagnosed based on DSM, ICSD, or research diagnostic criteria for insomnia; (2) Measures of insomnia severity or sleep quality were reported; (3) Patients/survivors with breast cancer were the primarily targeted population; (4) CBT-I included, at minimum, three components; (5) CBT-I was used alone, not combined with other active treatment; and (6) Study design was randomized controlled trial. Authors were contacted if their studies were with qualified design but insufficient information. Qualified studies were identified after full-text reading by two authors (YM and QL) independently. Any disagreements were discussed and resolved by consensus with a third author (GY).

Data extraction

All available data from included studies were extracted and double entered into a database for computational analyses. Data extraction was conducted independently by two authors (YM and QL) following Cochrane guidelines and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. Discrepancies were discussed and reconciled with a third expert reviewer (GY). Data were extracted from all qualified studies using a standardized data extraction form including publication information (title, first author, year, journal), sample characteristics and study design (sample size, age, cancer stage, insomnia duration, diagnostic criteria used, allocation and control condition), CBT-I duration (number, frequency, and length of sessions), modality (individual and group), delivery medium (e.g., in-person or by remote technologies), intervention components (stimulus control, sleep hygiene and/or sleep education, sleep restriction, relaxation training, or relaxation therapy, cognitive therapy, cognitive restructuring), time points for assessments, outcome measure, and compliance/adherence (drop-out). If an included article had missing data on outcomes of interest, authors were contacted by e-mail to obtain data necessary for effect size calculation, otherwise, missing data were calculated and converted from given data following the conduct guidance from *Cochrane Handbook for Systematic Reviews of Interventions* [29].

Outcome measures

The primary outcome variable of interest was the score from one of the most frequently used self-report sleep questionnaires, the Insomnia Severity Index (ISI). Pittsburgh Sleep Quality Index (PSQI) was used as outcome variable if ISI was not available, or if both ISI and PSQI were included in a study. For both instruments, higher score indicates more severe insomnia (ISI) or worse sleep quality (PSQI).

ISI is a brief, seven-item instrument that assesses insomnia according to the criteria from the Diagnostic and Statistical Manual for Mental Disorders - 4th Edition (DSM-IV) and the International Classification of Sleep Disorders. It is commonly used in clinical as well as research activities [2, 30–32]. Its reliability, validity, and sensitivity to treatment response have been documented in the general population and with patients presenting with primary insomnia and insomnia in cancer settings.

PSQI is a 19-item instrument which assesses sleep quality and disturbances over a one-month time interval. The measure consists of seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these components yields one global score. PSQI can be used as a screening tool for psychiatric practice and research [33], and can evaluate sleep quality, sleep dysfunction in clinical and non-clinical samples [34, 35], and it also has a high test-retest reliability and a good validity for patients with primary insomnia [5].

Because the conduct of CBTI usually includes the use of sleep diaries, more than half of the included studies have total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO) and sleep efficiency (SE, %) data. Some of the studies published sleep diary data in separate papers [36–38], we broadened our search to find sleep diary data and conducted a meta-analysis as the secondary outcomes.

Risk of bias assessment

Two authors (YM and QL) independently assessed risk of bias for all included studies according to Cochrane criteria [29], including 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). Each criterion was rated as low, high, or unclear. A global score was assigned to each study (sum of domains with "low risk of bias"), thus the score ranges from 0–7, with higher score indicates lower risk of bias and better quality of study.

Statistical analysis

Statistical analyses were performed using Comprehensive Meta-Analysis Version 3.0 (Biostat, Inc., USA). All measures for pre- and post-intervention, as well as each follow-up time were extracted for analysis. Data entry included common formats from reported results including mean and standard deviation in each group, mean and p (or t) in each group, raw difference and standard error, mean change and standard deviation of difference in each group.

Data conversion followed the conduct guidance from *Cochrane Handbook for Systematic Reviews of Interventions* [29]. As the pre-test and post-test measure correlations were unavailable in all of the individual study results, correlation level of 0.3 was used with no appreciable differences to the meta-analytic results.

All analyses were weighted to account for variability in sample sizes across studies. Following Cochrane guidelines, for studies that included two CBT-I intervention groups with different delivery format, we split the 'shared' control group, conducted two comparisons and adjusted the computed sample size of the control group ($n/2$) to avoid overestimation of potential intervention effects [29].

Standardized mean differences (SMD) expressed the size of the intervention effect in each study relative to the variability observed. SMD was calculated by the difference in mean outcome between groups divided by the pooled standard deviation of outcome among participants [29].

For common measure of effect across studies, we report Hedges' (adjusted) g. Forest plots were generated to visually assess the Hedges'g and corresponding 95% confidence intervals (CI) across studies. A negative estimate means the treatment group has a lower or better score. Random effects models were chosen based on the smaller number of studies. The heterogeneity test I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than random sampling error. I^2 is calculated by ((Q-df)/Q)*100%, where Q is the chi-squared statistic and df is its degrees of freedom. An I^2 value > 50% indicates substantial heterogeneity. Evidence of publication bias was assessed through visual inspection of a funnel plot and evaluation of the Egger's test.

RESULTS

Included studies

A total of 789 studies were identified through database searching and 272 duplicate records were removed (Figure 1). The 517 unique records were imported to the Covidence platform for abstract screening, then 52 records were identified and full text articles were retrieved and reviewed in detail for eligibility. Of these, thirteen eligible studies were included in the meta-analysis. Reasons for exclusion included non-breast cancer subjects, insomnia diagnosis not clear, not RCT, not CBT-I intervention, and no sleep measures of interest.

Details from the final sample of k=14 RCTs for qualitative synthesis are provided in Table 1, including participants' characteristics, cancer stages, insomnia diagnostic criteria, insomnia duration, sample size of each group, mean age, CBT-I treatment components, delivery format, length/numbers of CBT-I sessions, follow-up time points, outcome measures, and study quality score. The 14 RCTs [38–53] included 1363 subjects (mean age 52–61 years, 722 CBT-I and 641 controls). Studied subjects include patients/survivors with breast cancer at all stage, and most of them had chronic insomnia. Only the five studies with mixed cancer samples included male subjects, which accounted for a small ratio in the total sample (n=47, 3.4%).

Separate analyses were conducted for all 14 studies and for comparisons between some of the sub-group studies. The studies provided CBT-I intervention in a wide variety of formats, including individual versus group, in person versus by phone, video, or online). The overall quality score was 4.64 out of 7, with 7 being the best.

CBT-I components and sessions

Most CBT-I interventions incorporated at least three of the main components. All studies included stimulus control and sleep restriction; 92.9% of the studies included sleep hygiene/education; fewer studies included cognitive restructuring/therapy (71.4%), relaxation training (35.7%) or other components (28.6%). In general, CBT-I interventions in the included studies were delivered on a weekly basis, but significant variations were found in the length and numbers of sessions. In-person classes can be short (ranged from 15 to 30 minutes) or long (ranged from one to two hours), while by-phone sessions were typically short (ranged from15 to 30 minutes). The total duration of intervention ranged from six weeks to three months. Follow-up length varied with short-term (ranged from one to six months) or long-term (12 months).

Durability of CBT-I

Results from studies using ISI as outcome measure (Figure 2) showed that pooled effect sizes favored CBT-I at post-intervention (Hedges'g=−0.848, 95% CI=−1.040, −0.655, I^2=44.5%), short-term follow-up (within six months, Hedges'g=−0.731, 95% CI=−0.922, −0.541, I^2=58.0%), and long-term follow-up (after one year, Hedges'g=−0.431, 95% CI=−0.768, −0.095, I^2=46.3%).

The combination of studies using ISI or PSQI showed similar results (Figure 3), pooled effect sizes favored CBT-I at post-intervention (Hedges'g=−0.779, 95% CI=−0.949, −0.609, I^2=58.6%), short-term follow-up (within six months, Hedges'g=−0.653, 95% CI=−0.808, −0.498, I^2=59.1%), and long-term follow-up (after one year, Hedges'g=−0.335, 95% CI=−0.532, −0.139, I^2=18.5%).

Subgroup analysis

Study population.—Of the fourteen studies, five studies included mixed cancer types but with breast cancer as the majority (79%, 68%, 64%, 48% and 54% respectively). There was no significant difference between effect size in studies with only breast cancer versus mixed cancers (p=0.115). In the studies with only breast cancer, effect size favored CBT-I at post-intervention (Hedges'g=−0.674, 95% CI=−0.843, −0.505, I^2=44.7%), while the effect size was larger in the mixed population (Hedges'g=−0.987, 95% CI=−1.337, −0.637, I^2=63.0%).

Outcome measures.—Seven out of the fourteen studies applied PSQI as the main outcome measure, and they showed effect size favored CBT-I at post intervention (Hedges'g=−0.659, 95% CI=−0.977, −0.341, I^2=70.6%). The effect size from the twelve studies using ISI also favored CBT-I, but to a larger magnitude (Hedges'g=−0.848, 95% CI=−1.040, −0.655, I^2=44.5%). The effect sizes between studies using ISI and PSQI were not significantly different (p=0.320).

Comparison groups.—Among the identified trials, six studies used an inactive control (e.g., waiting list control or usual care) and eight studies used an active control (e.g., healthy eating, Tai Chi Chih, mindfulness-based stress reduction, exercise, etc.). The effect size of CBT-I with inactive controls was Hedges'g =−0.874 (95% CI=−1.038, −0.709, I^2=18.1%), and with active controls was Hedges'g =−0.663 (95% CI=−960, −0.367, I^2=72.5%). The

difference was not significant (p=0.224). To further understand the potential placebo effect, we separately presented the results for both ISI- and PSQI-based outcomes in Table 3. CBT-I has slightly larger effect size when compared to inactive controls, but it shows large effect size regardless of comparison designs.

Group and individual interventions.—The ten studies using individual interventions showed effect size of Hedges'g =−0.784 (95% CI=−0.972, −0.596, I^2=51.1%). The four studies involving group interventions showed a similar effect size, Hedges'g = −0.792 (95% CI=−1.228, −0.356, I^2=76.7%), with no significant differences between them (p=0.975).

Delivery format.—Traditional in-person CBT-I showed effect size of Hedges'g = −0.754 (95% CI=−1.089, −0.419, I^2=71.8%), CBT-I with combination of in-person and phone sessions showed effect size of Hedges'g = −0.821 (95% CI=−1.068, −0.574, I^2=5.5%). Virtually delivered CBT-I showed effect size of Hedges'g =−0.786 (95% CI=−1.082, −0.491, I^2=64.0%). Differences were not significant (p=0.950).

The sub-analyses showed that CBT-I remained similarly efficacious regardless of potential modifiers (comparison design, delivery formats, length/numbers of CBT-I sessions).

Sleep dairy outcomes

Results derived from sleep diary outcomes showed that pooled effect sizes favored CBT-I for all the studied measures in this analysis (Table 4), including total sleep time (Hedges'g=0.218), sleep onset latency (Hedges'g=−0.486), wake after sleep onset (Hedges'g=−0.363) and sleep efficieny (Hedges'g=0.531) at post-intervention. The CBT-I effect remained significant during short-term follow-up on all the above sleep measures. For long-term effects, CBT-I effects remained significant on sleep onset latency and sleep efficiency (Table 4).

Study quality and risk of bias

The quality score of included studies ranged from 3–7, where higher score indicates lower risk of bias and better quality of study. Eight studies with score 3 or 4 identified as low quality showed Hedges'g = −0.744 (95% CI=−0.992, −0.496, I^2=38.4%); while six studies with score 5, 6 or 7 identified as high quality showed Hedges'g = −0.825 (95% CI=−1.071, −0.579, I^2=72.7%), with no difference between groups (p=0.650). No significant patterns were found on the funnel plot of standard error by Hedges' g, indicating that there was low risk of publication bias.

DISCUSSION

Cognitive behavioral therapy for insomnia (CBT-I) has been supported broadly as a gold standard non-pharmacological treatment for insomnia, including endorsement by the American College of Physicians as first line treatment [54]. Despite the high prevalence and impact of insomnia among adults treated for cancer, insomnia is rarely addressed systematically in the oncology clinic [11], and the efficacy of CBT-I among patients with cancer has to date remained unclear. One recent meta-analysis found that CBT-I has only small-to-moderate sized improvements in several aspects of sleep among cancer survivors

[6]; however, findings were not specific to breast cancer survivors, for whom body changes and adjuvant hormone therapies often complicate insomnia treatment. Here, we address this gap and offer recommendations to advance the science and practice of insomnia treatment among patients with breast cancer.

As in other studied populations, CBT-I in patients with breast cancer produced moderate to large treatment effects, and clinically significant effects last up to a year after therapy [55]. Overall, the existing RCTs yield statistically and clinically significant improvements in insomnia and sleep quality by subjective measures, and our findings have critical implications for research and clinical practice.

A unique element of our meta-analysis was identifying components of interventions yielding the greatest effects in sleep quality, including feasibility metrics of duration and modality of delivery. Indeed, 10 years ago, a widely circulated commentary was published: “Despite effectiveness, behavioral therapy for chronic insomnia still underused” [56]. Unfortunately, little has changed to address underutilization of CBT-I among cancer survivors, for whom barriers include time limitations, travel, and illness burden constraints [46, 57]. In the present meta-analysis, sub-analyses revealed CBT-I remained similarly efficacious regardless of potential modifiers (comparison design, delivery formats, length/numbers of CBT-I sessions). The most common CBT-I approach includes behavioral components (SC, SR, RT) combined with a cognitive (CT) and an educational (SH) component. In our analysis, most CBT-I interventions incorporated at least three of the main components (sleep hygiene, stimulus control and sleep restriction). About one third of studies included full components as standard CBT-I, while some studied incorporated other elements (e.g. stress management, relapse prevention, chronorehablitation) with major CBT-I components as a customized package. No significant differences were found between number/length of sessions or modality in the published studies. Since individual, face-to-face therapy with a sleep specialist is not always feasible, alternative treatment delivery models can improve access to CBT [22]. Virtual CBT-I showed slightly more efficacious compared to conventional face-to-face CBT-I or a combination of in-person and by-phone sessions, although differences were not significant. These findings suggest that CBT-I delivered virtually may not only be a pragmatic option for enhancing access to care; it may be comparably efficacious to in-person visits at improving sleep quality. Self-help approaches using printed materials, videos, or internet-based programs are helpful as stand-alone treatments or as additions to professionally administered therapy [22].

Further studies are encouraged to address remaining gaps highlighted by this analysis. First, some subgroups of patients with breast cancer might be under-represented, for example, younger female or breast cancer patients with comorbid psychiatric disorders. Second, if one wants to optimize CBT-I or make it briefer to deliver, our results suggest the need for adaptive trial designs (i.e., sequential multiple assignment randomized trial, SMART; multiphase optimization strategy, MOST) to determine optimal sequence of delivering skills. Recently, Zhou et al.[58] found that a stepped care model for delivering CBT-I to patients with cancer was acceptable and feasible, suggesting that some patients may benefit from a minimal dosage (e.g., one group-delivered session on the topic of sleep hygiene), whereas other patients will benefit from the full CBT-I content. Future studies using adaptive designs

could test the optimal sequence and dosage of CBT-I for patients with breast cancer, including virtual vs. in-person sessions, group vs. individual delivery, and number of CBT-I components patients are exposed to. Finally, our findings implicate the potential for virtual delivery of CBT-I. As more insurances offer coverage of eHealth modalities for interfacing with healthcare providers, the acceptability and feasibility of implementing telehealth CBT-I for breast cancer survivors in routine care will be critical future area of research.

Strengths and limitations

Our meta-analysis has focused on a specific population with unique needs, which enhances our confidence in these findings yet limits our ability to generalize to other cancer populations. In existing literatures, CBT-I in cancer population is predominantly targeting breast cancer, possibly because patients with breast cancer have relatively better prognosis, less complications, and longer survivorship. However, we did not see a significantly different effect size in mixed cancer populations. It remains unclear whether sleep disorders differ per cancer type, as we were not able to explore this due to the small number of subjects with cancers other than breast cancer in our analysis. More studies of CBT-I are needed in other cancer population, and future studies are encouraged to explore CBT-I efficacy by comparing subjects with different cancer types. In this review, we did not include objective sleep measures or physiological measures. The reliance on self-reported insomnia and sleep quality may be influenced by recall bias. Due to the study subjects of interest, almost all participants are female, which makes it difficult to explore whether there are sex differences on the CBT-I responses. Insomnia may present prior to or after cancer diagnosis, however information in the pulished studies did no tallow us to differentiate these groups. Due to limited information in the included studies, our analysis was not able to explore the change in daytime function or fatigue levels subsequent to the improvement of sleep quality. We also had heterogeneous population that included patients across the spectrum from new diagnosis to survivorship. Despite these limitations, this meta-analysis provides valuable information on CBT-I treatment in a particularly vulnerable population. It also provides information on durability and the effect of different delivery formats of CBT-I.

CONCLUSIONS

The existing RCTs yield statistically and clinically significant improvements in insomnia and sleep quality by subjective measures. As an integrative oncology intervention, CBT-I is efficacious for reducing insomnia in women treated for BC, with medium-to-large effect sizes that persist up to one year after intervention delivery ends. Given the variability in the CBT-I components tested in RCTs, future studies should investigate the optimal integration of CBT-I components for managing chronic insomnia during BC survivorship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BBT-CI	brief behavioral therapy for cancer-related insomnia
BC	breast cancer
CBT-I	cognitive behavioral therapy for insomnia
CI	confidence intervals
CR	cognitive restructuring
DSM	Diagnostic and Statistical Manual of Mental disorders
EMA	early morning awakening
FACIT-F	Functional Assessment of Chronic Illness Therapy for Fatigue
ISI	Insomnia Severity Index
MFI	Multidimensional Fatigue Inventory
MFSI	Multidimensional Fatigue Symptom Inventory
PCBT-I	professionally administered CBT-I
PFS	Piper Fatigue Scale
POMS-F	Profile of Mood States - Fatigue Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
RCT	randomized controlled trial
RT	relaxation training
SC	stimulus control
SE (%)	sleep efficiency
SE	sleep education
SH	sleep hygiene
SMD	standardized mean difference
SOL	sleep onset latency
SR	sleep restriction
TCC	Tai Chi Chih

TIB	time in bed
TST	total sleep time
TWT	total wake time
VCBT-I	video-based CBT-I
WASO	wake after sleep onset

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Practice Points

1. Most studies on cognitive behavioral therapy for insomnia (CBT-I) in cancer have been conducted in breast cancer.
2. CBT-I is efficacious for reducing insomnia in women treated for BC, with medium-to-large effect sizes that persist up to one year after intervention delivery ends.
3. CBT-I had similar effect sizes regardless of comparison design, delivery formats, length/numbers of CBT-I sessions.

Research Agenda

1. Given the variability in the CBT-I components tested in RCTs, future studies should investigate the optimal integration of CBT-I components for managing chronic insomnia during BC survivorship.
2. Optimal design of CBT-I sessions and delivery formats need to be further studied to maximize the efficacy and cost-effectiveness.
3. Sex differences and the response to CBT-I remains unclear and further studies to address this in a breast cancer population are encouraged.
4. Further studies are encouraged to investigate the multidimentional correlation of CBT-I, sleep improvement, daytime function and fatigue.

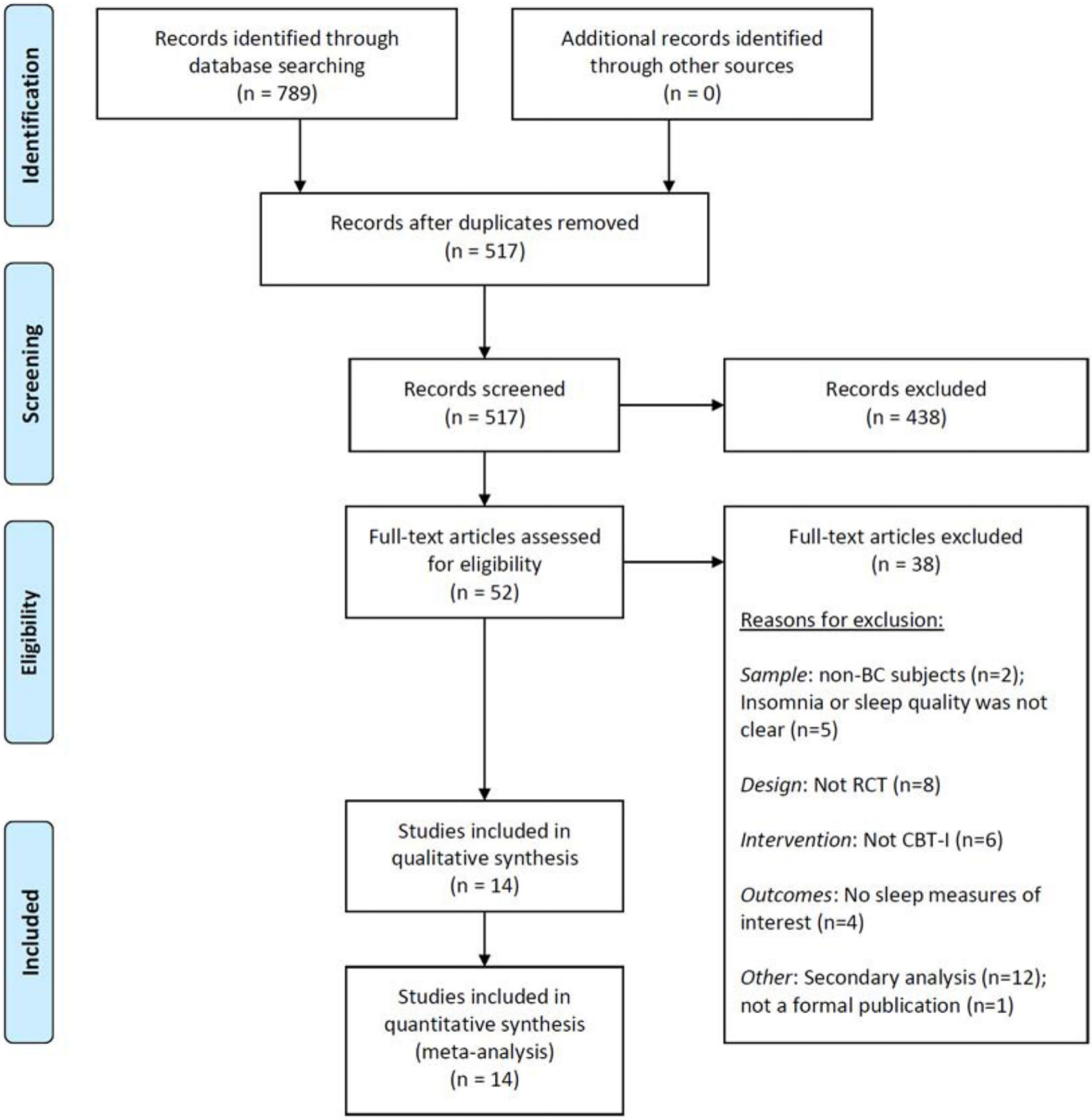

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

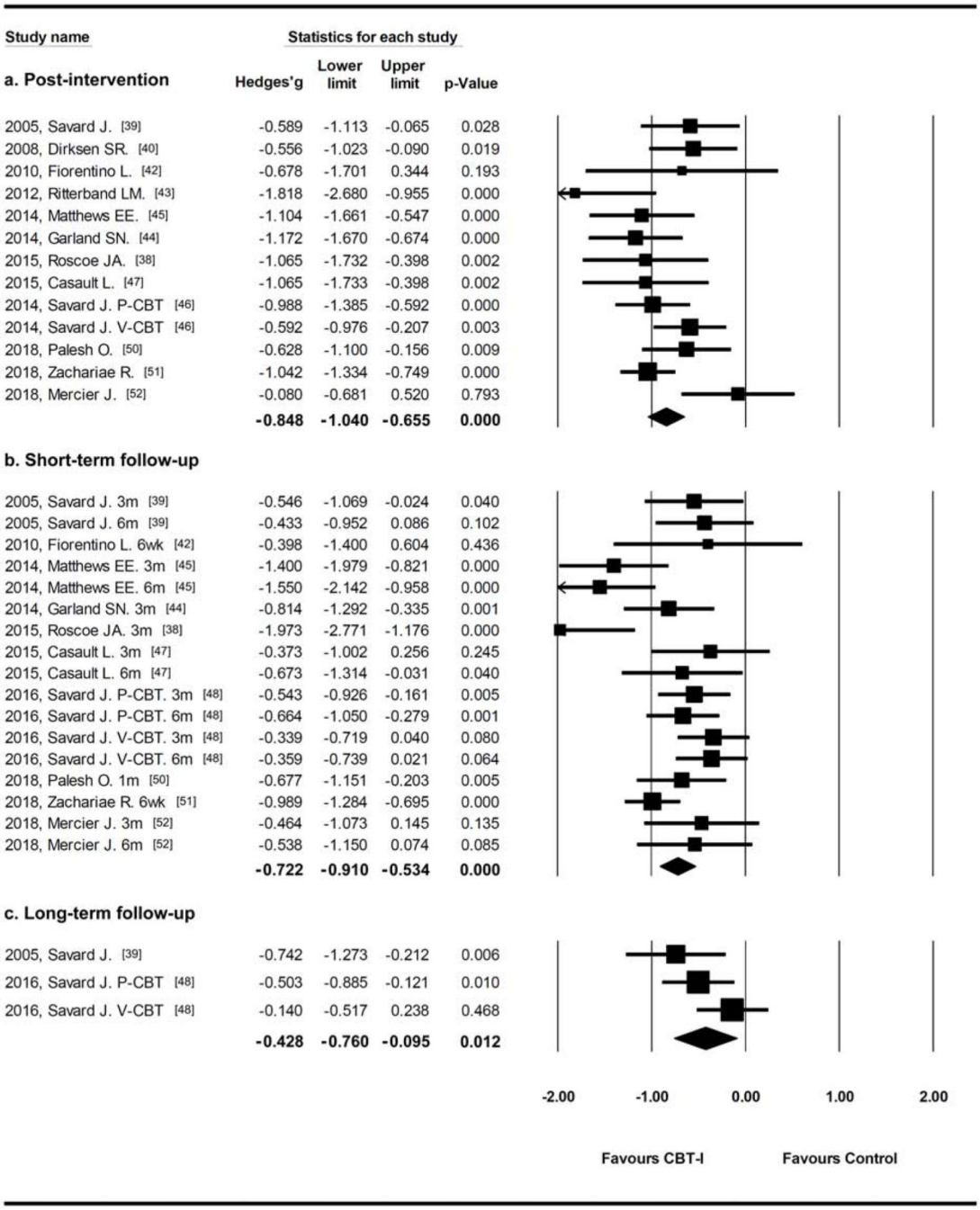

Figure 2.
Durability analysis from studies with ISI as outcome measures.

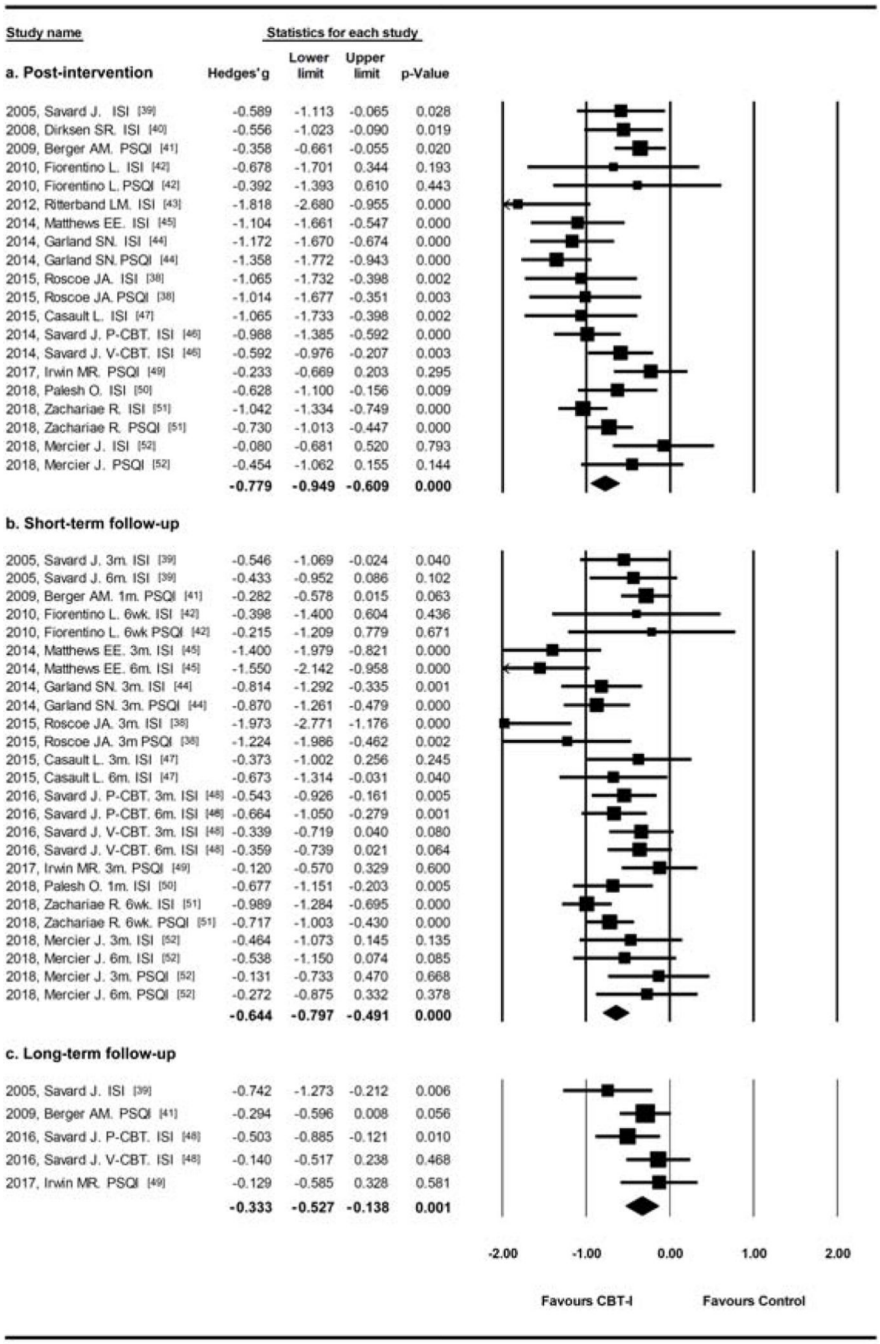

Figure 3.
Durability analysis from studies with ISI or PSQI as outcome measures.

Group by	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Studied subjects							
BC only	-0.674	0.086	0.007	-0.843	-0.505	-7.811	0.000
Mixed	-0.987	0.178	0.032	-1.337	-0.637	-5.529	0.000
Outcome measures							
ISI	-0.848	0.098	0.010	-1.040	-0.655	-8.639	0.000
PSQI	-0.659	0.162	0.026	-0.977	-0.341	-4.062	0.000
Comparison groups							
Active controls	-0.663	0.151	0.023	-0.960	-0.367	-4.386	0.000
Inactive controls	-0.874	0.084	0.007	-1.038	-0.709	-10.413	0.000
Group/Individual							
Group	-0.792	0.222	0.049	-1.228	-0.356	-3.560	0.000
Individual	-0.784	0.096	0.009	-0.972	-0.596	-8.189	0.000
Delivery formats							
In person	-0.754	0.171	0.029	-1.089	-0.419	-4.414	0.000
In person + by phone	-0.821	0.126	0.016	-1.068	-0.574	-6.508	0.000
Virtual	-0.786	0.151	0.023	-1.082	-0.491	-5.212	0.000
Risk of bias							
Low (high quality scores)	-0.825	0.126	0.016	-1.071	-0.579	-6.563	0.000
High (low quality scores)	-0.744	0.127	0.016	-0.992	-0.496	-5.874	0.000

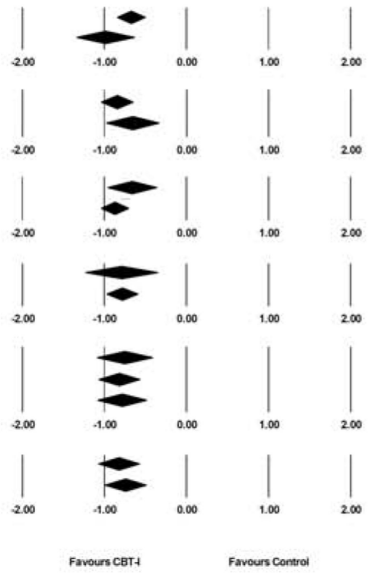

Figure 4.
Sub-group analysis from all pre- and post-intervention comparisons.

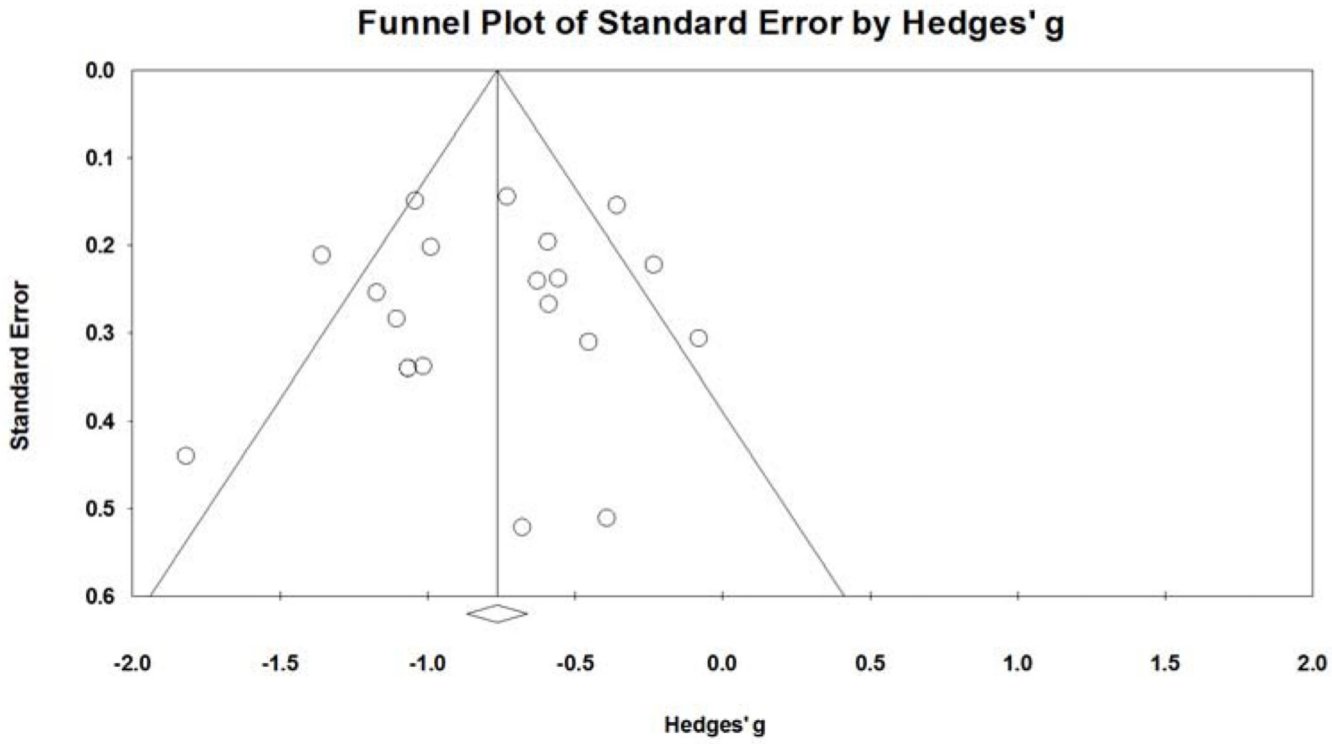

Figure 5.
Funnel plot of standard error by Hedges's g.

Table 1.

Characteristics of included RCTs of CBT-I.

Study [a]	Subjects characteristics	BC Stages	Insomnia defined by	Insomnia duration	CBT-I group, n [b]	Comparison group, n [b]	Mean age (yrs)	Treatment components	Length/ numbers of CBT-I sessions	Measures and Follow-up	Outcome measures	Sleep diary measures	Fatigue
Savard J, 2005 [39]	BC survivors, completed radio-/ chemotherapy	I-III	DSM-IV, ICSD, IIS	Chronic	CBT-I (n = 27)	Waiting-list control (n = 30)	54.1	SC, SR, CR, SH/SE, fatigue and stress management	8 weekly 90min sessions, one booster session, in groups of 4–6 patients.	pre, post, 3m, 6m, 12m	ISI	SE (%), TWT, TST, SOL, WASO	MFI
Dirksen SR, 2008 [40]	BC survivors, completed cancer treatment≥3m	I-III	DSM-IV-TR, ICSD	Chronic	CBT-I (n = 40)	Component control (n = 41)	58.3	CBT-I group: SC, SR, SH/SE Component control group: SH/SE	6 weeks, in-person classes (~1 or 2 hours) or 15min by-phone sessions	pre, post	ISI	None	POMS-F
Berger AM, 2009 [41, 53]	BC patients, enrolled before initial chemotherapy.	I-IIIa	Self-reported history of diagnosis	Chronic	Behavioral therapy (n = 113)	Healthy eating (n = 106)	52.1	SC, SR, RT, SH	Plan: 90 min at randomization. Revising BT plan: 30 min, 2 days before each treatment and 30 days after the last treatment. 15 minute, in-person sessions 7 to 9 days after each revision.	pre, post, 1m, 3m, 12m	PSQI	TST, awakenings, WASO, SE (%)	PFS
Fiorentino L, 2010 [42]	BC survivors, completed BC treatment	I-IIIa	DSM-IV	Chronic	Individual CBT-I (n = 11)	Delayed treatment control condition (n = 10)	61	SR, SC, SH/SE, RT, CT	6 weekly individual CBT-I sessions	pre, post, 6wk	ISI, PSQI	TST, WASO, awakenings, SE (%)	None
Ritterband LM, 2012 [43]	Mixed cancer patients, completed active treatment; 64.3% BC	I-IV + unknown	DSM-IV-TR + symptom criteria	Chronic	Online-CBT-I (n = 14)	Waitlist control (n = 14)	56.7	SR, SC, CR, SH, relapse prevention	6–9 weeks, including 6 online cores (45–60 min each)	pre, post	ISI	SE (%), TST, SOL, WASO, TIB, awakenings	MFSI - Short Form
Matthews EE, 2014 [45]	BC survivors, completed BC treatment	I–III	ISI≥8 + IIS	Chronic	P-CBT-I (n=32)	Behavioral placebo	52	SR, SC, SH, CT	Individual, 6 weekly in-person CBTI	pre, post, 3m, 6m	ISI	SE (%), SOL, WASO,	PFS

Study [a]	Subjects characteristics	BC Stages	Insomnia defined by	Insomnia duration	CBT-I group, n [b]	Comparison group, n [b]	Mean age (yrs)	Treatment components	Length/ numbers of CBT-I sessions	Measures and Follow-up	Outcome measures	Sleep diary measures	Fatigue
						treatment (n=28)			sessions (30–60 min each) or by phone (15–20 min each).			TST, awakenings	
Garland SN, 2014 [44]	Mixed cancer, 48% BC	nonmetastatic cancer	DSM-IV, ICSD-2	>1month	CBT-I (n = 47)	MBSR (n = 64)	58.9	SC, SR, CT, RT	8 weekly, 90-minute sessions, for a total of 12 contact hours, in groups of 6–10 patients	pre, post, 3m	ISI, PSQI	SOL, WASO, TST, SE (%)	None
Roscoe JA, 2015 [38]	Mixed cancer survivors, 68% BC	N.C.	N.C.	Chronic	CBTI + placebo (n=24)	Placebo (n=25)	55.4	SH, SC, SR, (CT, RT)	7 individual sessions occurring once per week. Sessions conducted in person (30–60 min), and by phone (15–30 min).	pre, post, 3m	ISI, PSQI	SOL, WASO, TST [36]	None
Casault L, 2015 [47]	Mixed cancer patients, 79% BC	N.C.	ISI≥8, IIS, regular hypnotic medication usage for more than 6 months	Acute	Self-administered minimal CBT-I (n = 20)	No treatment control (n = 18)	56.9	SC, SR, CR, SH	Self-help CBT, 6 short booklets and 3 phone consultations with a psychologist, over 6 weeks	pre, post, 3m, 6m	ISI	SOL, WASO, awakenings, TST, SE (%)	MFI
Savard J, 2014, 2016 [46, 48]	BC patients, with radiation therapy within the past 18m	0-III	ISI≥8 or psychotropic medication as a sleep aid≥2 nights in the past 2 wks;	Chronic	PCBT-I (n = 81) VCBT-I (n = 80)	No treatment control (n = 81)	54.4	SC, SR, SH	6 weeks of CBTI P-CBT-I: weekly, 50min individual session V-CBT-I: video segment (5–20min each) + booklets each week	pre, post, 3m, 6m, 12m	ISI	SOL, WASO, EMA, TWT, TST, SE (%)	MFI
Irwin MR, 2017 [49]	BC survivor, completed BC treatment	N.C.	DSM-IV-TR, DSM-V, ICSD-2	N.C	Group CBT-I (n = 45)	TCC (n = 45)	60.0	SC, SH, SR, RT, CT	CBT-I teaching 2 months + 1 month of skill consolidation and adherence; Groups of 7 to	pre, mid, post, 3m, 12m	PSQI	TST, SOL, SE (%), WASO	MFSI

Study [a]	Subjects characteristics	BC Stages	Insomnia defined by	Insomnia duration	CBT-I group, n [b]	Comparison group, n [b]	Mean age (yrs)	Treatment components	Length/ numbers of CBT-I sessions	Measures and Follow-up	Outcome measures	Sleep diary measures	Fatigue
									10 participants in weekly 120-minute sessions.				
Palesh O, 2018 [50]	Newly diagnosed BC patients, undergoing chemotherapy	I-III + unknown	ISI≥8	N.C.	BBT-CI (n = 34)	HEAL (n = 37)	52.5	SH, SC, SR, Sleep scheduling, Chronorehabilitation	Two 60min face-to-face session and four 15min phone call	pre, post, 1m	ISI	None	None
Zachariae R, 2018 [51]	BC survivors	0-III	PSQI>5 + structured screening interview	Chronic	Online-CBT -I (n = 133)	Waitlist control (n = 122)	53.1	SR, SC, SH, CR, relapse prevention.	9 weeks including 6 successively delivered cores (45–60min each)	pre, post, 6wk	ISI, PSQI	SOL, awakenings, WASO, EMA, TIB, TST, SE (%), Sleep medication	FACIT-F
Mercier J, 2018 [52]	Mixed cancer survivors, 53.7% BC	I-III + unknown	ISI≥8	N.C.	CBT-I (n = 21)	Home-based aerobic exercise (n=20)	57.1	SC, SR, CR, SE/SH	6-weeks: 60min video (5–20min each) + 6 booklets	pre, post, 3m, 6m	ISI, PSQI	SOL, WASO, TST, SE (%)	None

Abbreviations:

awakenings, the number of awakenings; BBT-CI, brief behavioral therapy for cancer-related insomnia; BC, breast cancer; CBT-I, Cognitive Behavioral Therapy for Insomnia; CR, cognitive restructuring; DSM, Diagnostic and Statistical Manual of Mental disorders; EMA, early morning awakening; FACIT-F, Functional Assessment of Chronic Illness Therapy for Fatigue; ISI, Insomnia Severity Index; m, month; MFI, Multidimensional Fatigue Inventory; MFSI, Multidimensional Fatigue Symptom Inventory; mid, in the middle of intervention period; N.C., not clear; PCBT-I, professionally administered CBT-I; PFS, Piper Fatigue Scale; POMS-F, Profile of Mood States - Fatigue Scale; post, post-intervention; pre, pre-intervention; PSQI, Pittsburgh Sleep Quality Index; RT, relaxation training; SC, stimulus control; SE (%), sleep efficiency, calculated as (TST/TIB)*100; SE, sleep education; SH, sleep hygiene; sleep medication, the proportion of nights on which participants took sleep medication; SOL, sleep onset latency; SR, sleep restriction; TCC, Tai Chi Chih; TIB, time in bed; TST, total sleep time; TWT, total wake time; VCBT-I, video-based CBT-I; WASO, wake after sleep onset; wk, weeks.

a. Studies are listed in chronological order.

b. Number reported in the table are for enrolled subjects in each group in each study.

Table 2.

Risk of bias assessment and quality score of studies[a].

	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other sources of bias	Overall
Reference	**Random sequence generation**	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Baseline imbalance**	**Score**
Savard J, 2005 [39]	Unclear	Unclear	High	Unclear	Low	Low	Low	3
Dirksen SR, 2008 [40]	Low	High	High	Unclear	Low	Low	Low	4
Berger AM, 2009 [41]	Low	Low	High	Unclear	Low	Low	Low	5
Fiorentino L, 2010 [42]	Low	Low	High	Unclear	High	Low	Low	4
Ritterband LM, 2012 [43]	Low	Low	High	Unclear	Low	Low	High	4
Matthews EE, 2014 [45]	High	High	High	Unclear	Low	Low	Low	3
Garland SN, 2014 [44]	Low	Low	Low	Low	High	Low	Low	6
Roscoe JA, 2015 [38]	Low	Low	High	High	High	Low	Low	4
Casault L, 2015 [47]	Low	Low	High	Unclear	Low	Low	Low	5
Savard J, 2014 [46]	Low	Low	Low	Low	High	Low	Low	6
Irwin MR, 2017 [49]	Low	Low	Low	Low	Low	Low	Low	7
Palesh O, 2018 [50]	Unclear	Unclear	High	Unclear	Low	Low	Low	3
Zachariae R, 2018 [51]	Low	Low	Low	Low	Low	Low	Low	7
Mercier J, 2019 [52]	Low	Low	High	Unclear	Low	Low	High	4

[a]. Studies are listed in chronological order.

Table 3.

Efficacy of CBT-I compared with active and inactive controls.

Subjective sleep outcome measures	Pre-intervention		Post-intervention		Difference between pre- and post-intervention means		Number of Studies	Number of subjects	Weighted overall effect for between group comparasons [b]		
	Mean [a]	SD	Mean [a]	SD	Value	%			Hedges' g	SE	95% CI
ISI											
CBT-I	15.73	4.03	8.04	3.89	−7.69	−48.89	12	509			
Active control	17.59	3.23	12.83	3.84	−4.76	−27.06	5	153	−0.72	0.19	(−1.08, −0.35)
Inactive control	14.54	4.34	11.95	4.62	−2.59	−17.81	7	269	−0.93	0.11	(−1.14, −0.71)
PSQI											
CBT-I	10.04	3.08	6.71	2.49	−3.33	−33.17	7	326			
Active control	9.91	3.05	8.98	3.16	−0.93	−9.38	4	213	−0.60	0.27	(−1.12, −0.08)
Inactive control	10.78	2.86	9.55	3.07	−1.23	−11.41	3	127	−0.75	0.13	(−1.00, −0.50)

[a] The weighted means are calculated by formula (Σ[u*N]/Σ[N]), where u is the mean of the individual study.

[b] The weighted overall effect is calculated by comparing CBT-I with active control or inactive control separately.

Note: Sleep quality ratings were standardized across studies so that lower scores indicate better sleep quality.

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.

Table 4.

CBT-I effects and durability on sleep diary outcomes.

Sleep diary outcomes	Number of studies	Number of subjects	*Q*	Weighted overall effect			
				Hedges'g	SE	95% CI	p-vale
TST							
Post-intervention	10	980	5.79	0.218	0.065	(0.091, 0.345)	0.001
Short-term follow-up	6	649	4.39	0.190	0.065	(0.062, 0.318)	0.004
Long-term follow-up	3	371	0.38	0.182	0.107	(−0.028, 0.393)	0.089
SOL							
Post-intervention	9	816	10.08	−0.486	0.077	(−0.637, −0.335)	0.000
Short-term follow-up	5	483	5.82	−0.200	0.072	(−0.341, −0.059)	0.006
Long-term follow-up	5	371	2.22	−0.295	0.108	(−0.507, −0.084)	0.006
WASO							
Post-intervention	10	950	4.05	−0.363	0.065	(−0.490, −0.236)	0.000
Short-term follow-up	6	651	3.90	−0.149	0.065	(−0.277, −0.021)	0.022
Long-term follow-up	3	371	0.51	−0.099	0.107	(−0.309, 0.111)	0.355
SE (%)							
Post-intervention	9	939	13.89	0.531	0.087	(0.361, 0.702)	0.000
Short-term follow-up	6	651	9.32	0.226	0.065	(0.098, 0.354)	0.001
Long-term follow-up	3	402	1.80	0.278	0.108	(0.067, 0.489)	0.010

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error; SE (%), sleep efficiency; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.