Original Article

Effects of yoga on health-related quality, physical health and psychological health in women with breast cancer receiving chemotherapy: a systematic review and meta-analysis

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Background: Yoga receive more attention from breast cancer patients, however its feasibility and efficacy during chemotherapy remains conflicting. We performed this systematic review to assess the effects of yoga on health-related quality, physical health and psychological health in breast cancer patients undergoing chemotherapy.

Methods: A systematic search was conducted to retrieve randomized controlled trials (RCTs) which investigated the comparative efficacy of yoga versus comparators such as usual care among breast cancer patients for health-related quality, physical health and psychological health in PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CNETRAL), Nursing and Allied Health Literature (CINAHL), Chinese Biomedical Literature (CBM) Database, China Science and Technology Journal (CSTJ) Database, China National Knowledge Infrastructure (CNKI), and Wangfang Database from inception to December 2018. The latest search was updated on September 2020. All analyses were completed using RevMan version 5.3.

Results: Seven trials involving 693 breast cancer patients met inclusion criteria. Meta-analysis indicated a short-term improvement in fatigue [standard mean difference (SMD), –0.62; 95% confidence interval (CI), –1.17 to –0.07], sleep disturbance (SMD, –0.34; 95% CI, –0.55 to –0.12), depression (SMD, –0.50; 95% CI, –0.70 to –0.31) anxiety (SMD, –0.50; 95% CI, –0.70 to –0.31), and health-related quality of life (QoL) (SMD, 0.72; 95% CI, –0.12 to 1.56) in the yoga group; however beneficial medium- and long-term effects in fatigue, sleep disturbance were not identified. Moreover, qualitative analyses suggested that yoga was not associated with decreased adverse events (AEs) compared with control groups.

Conclusions: Yoga may benefit to reduce fatigue, depression and anxiety, improve sleep disturbance, and improve QoL in breast cancer patients receiving chemotherapy in the short-term; however, medium- and long-term effects should be further established owing to limitations.

Keywords: Brest cancer; chemotherapy; yoga; systematic review; meta-analysis

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Introduction

Breast cancer represents a major public health problem of great concern (1), with approximately 2.09 million new cases and 0.63 million deaths in 2018 (2). As one of the comprehensive therapeutic strategies for breast cancer, chemotherapy is widely applied to breast cancer patient in respective less of stages (3). However, chemotherapy is often accompanied by numerous adverse effects such as fatigue, sleep disturbance, depression, and anxiety and eventually decrease quality of life (QoL), all of which may outweigh treatment benefits (4-9). Pharmacological interventions have already been confirmed to counter some of these adverse effects but potential drug toxicity is a concern (10,11). Physical activity may be an attractive option for managing symptoms related to disease and treatment, because it can maintain psychological well-being and physical function, reduce cancer-related fatigue, mitigate breast cancer recurrence, and increase survival rates (12-15). In addition, physical activity can provide rehabilitative effects in QoL (16-18). Nevertheless, breast cancer survivors, especially who are receiving chemotherapy, often face severe physical fatigue and discomfort, and perceived barriers to participation in purely gymnastic exercise (19-22).

Compared to other exercise programs, yoga is highly flexible and adaptable and therefore has been used in cancer patients. Particularly, the postures of yoga can be easily modified to fit various functional impairments or limited mobility with harmless (23,24). Therefore, yoga may act as a more viable or suitable alternative for breast cancer patients receiving chemotherapy. As a complementary therapy, yoga deems patients' spirituality as relevant for disease management (25). Evidence suggests that yoga can enhance body awareness and normalize the stress and immune response, consequently assist patients returning to optimal homeostasis (26-31). Several randomized clinical trials (RCTs) have been examined the role of yoga in breast cancer patients undergoing chemotherapy, most of which (32-37) established the benefits of yoga in relieving fatigue, sleep disturbance, depression, anxiety or improving health-related QoL. However, a study conducted by Chaoul *et al.* (38) reported a conflicting conclusion, in which total sleep disturbances or fatigue levels over time among three groups were not significantly different. Thus, a definitive conclusion on the efficacy and safety of yoga among breast cancer survivors who were prescribed to receive chemotherapy has not yet been obtained.

A recent meta-analysis (39) explored the role of yoga in breast cancer patients, and revealed an improvement in QoL and mental health. However, patients receiving radiotherapy and chemotherapy were not separately investigated in this study, and thus the pure effect of yoga on patients underwent chemotherapy alone could not be identified. Considering above issues, the primary objective of this systematic review is to further determine the potential benefits of yoga interventions for health-related quality, physical health and psychological health in breast cancer patients undergoing chemotherapy alone through pooling the results from eligible RCTs.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1484).

Methods

This systematic review was carried out according to the recommendations released by the Cochrane Collaboration (40). We reported all results following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) statement (41) (details in Supplemental Digital Content 1). In this article, all analyses were performed based on published data, and thus the ethical approval and informed consent was not required. Moreover, the current systematic review and meta-analysis has not formal registered protocol.

Selection criteria

For inclusion, a trial should meet the following criteria: (I) patients (*P*): exclusively concerned women patients who were currently undergoing chemotherapy for breast cancer, regardless of dose and type of chemotherapy; (II) intervention (*I*): any types of yoga were viewed as the experimental intervention. Even if studies simply described the intervention as 'yoga' also met the requirement; (III) control (*C*): wait-list control, usual care, no therapy and any other active therapy were eligible as control intervention; (IV) outcomes (*O*): Health-related QoL, physical health (e.g., fatigue, sleep disturbance, nausea and vomiting) and psychological health (e.g., depression, anxiety and perceived stress) were regarded as the primary outcome. And if available, adherence and safety-related data served as secondary outcome measures; (V) study design (*S*): only RCTs published in English and Chinese language were considered. Full-text or abstract publications were accessed only when they can provide essential information on

research design, characteristics of participants, interventions and outcomes.

Studies were excluded if it covered at least one of the following criteria: (I) yoga was not the main intervention but a part of a multi-modal intervention (e.g., Mindfulness-Based Stress Reduction, mindfulness-based cognitive therapy), as the effects of yoga could not be isolated in such programs; (II) study was short of the essential information or primary data was unavailable to be obtained from authors; and (III) duplicates (develop from the same research project) with poor methodology and insufficient data would not be chosen.

Definition of outcomes

In this study, the QoL was assessed by using any validated generic or disease-specific self-report scale in each individual study. In terms of indicators related to physical or psychological health, we measured them by any validated self-report or clinician-rated scale in all individual trials. Safety-related data was acquired by monitoring and recording the number of women with adverse events (AEs).

Identification of citations

The following electronic databases were independently searched by two investigators including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CNETRAL), Nursing and Allied Health Literature (CINAHL), Chinese Biomedical Literature (CBM) database, Chinese Scientific and Technological Periodical (VIP) and China National Knowledge Infrastructure (CNKI), and Wangfang Database. All initial searches were completed by December 2018, with the latest search was updated on September 2020. The search terms including Breast Neoplasms, chemotherapy, Yoga and random were used to develop search strategy. The PubMed was used as an example to show how these search strategies were employed (details in Supplemental Digital Content 2). Besides, we scrutinized the reference lists of retrieved articles and relevant reviews manually to obtain any potential studies. After screening the titles and abstracts identified by the initial search, two independent investigators conducted full-text check to definitively determine eligibility. Any disagreements were resolved through discussion and consensus. We used the Kappa statistic to present the level of agreement between investigators.

Data extraction and quality assessment

A data extraction sheet was developed to extract essential information from the selected articles. We assigned two investigators to extract the following data: first author, publication year and country, age, sample size, stage of breast cancer, possible treatments, details of intervention regimes, and outcome measures. When multiple publications were identified from the same clinical trial, we cited the primary complete report of that trial. But data from all publications were extracted. It would introduce bias, if the same data were included repeatedly. Corresponding authors were contacted if the information of interest could not be extracted. Discrepancies were solved through discussion, if necessary, by consulting an independent a third reviewer.

We appraised the quality of individual studies using the Cochrane Risk of Bias Tool (42), which is based on the following six domains (40): randomization sequence generation, allocation concealment, blinding of participants, blinding of study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other bias. Items were graded in high, low or unclear risk of bias (40). Any conflicting results were resolved by consensus and arbitration by a third party arbitrated.

Statistical analysis

All data were statistically analyzed by RevMan version 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration). Risk ratio (RR) with 95% confidence interval (CI) was used to express the dichotomous outcomes, while we mean differences (MDs) with 95% CIs were calculated to express continuous outcomes. We described the heterogeneity in results across studies based on the Cochrane's Q statistic, and inconsistency was quantitatively estimate with the I^2 statistic (43,44) when clinical heterogeneity across eligible studies was not detected. When non-significant heterogeneity was detected (I^2<50%) across studies and a fixed-effects model was utilized to combine the data. In contrast, a random-effects model was utilized. We drew a funnel plot to inspect the publication bias when more than 10 eligible studies reported a same outcome. We evaluated the robustness of our overall analyses by conducting subgroup analyses. For multiple-arm studies, outcome data were extracted from all groups which satisfy the inclusion criteria as recommended in the Cochrane Handbook for Systematic Reviews of

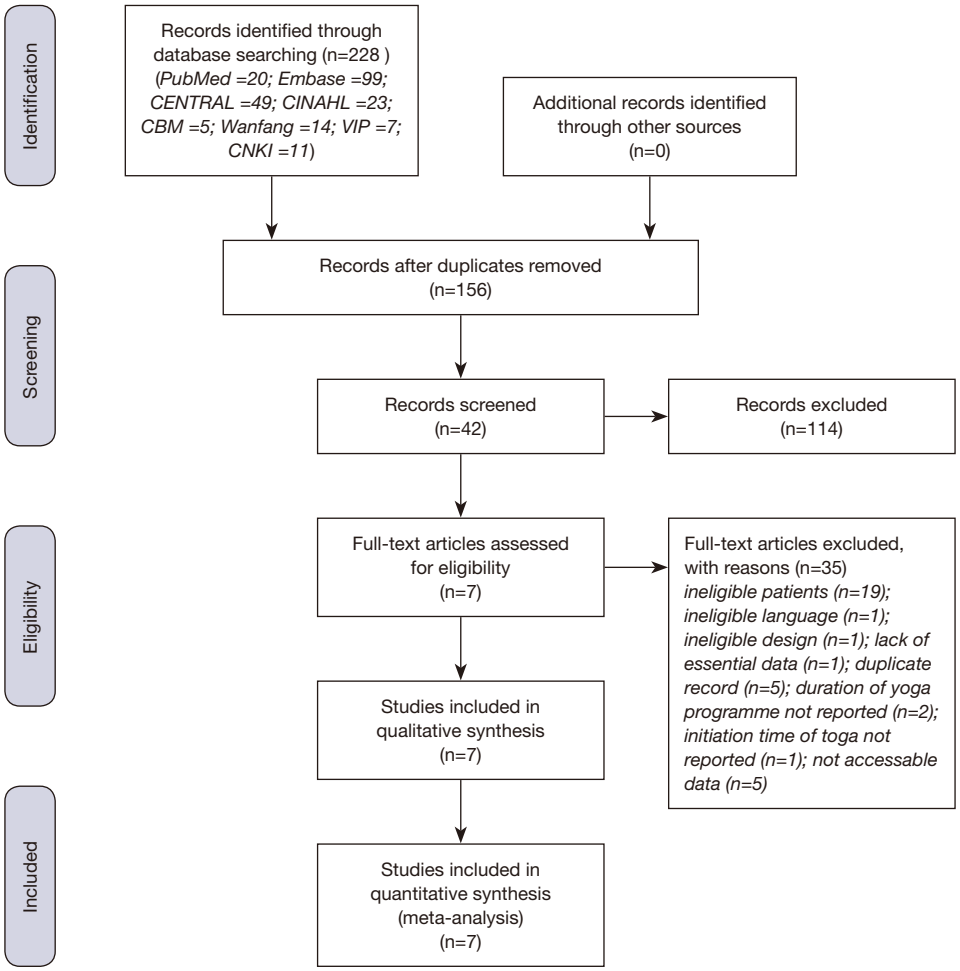

Figure 1 PRISMA flow diagram of retrieval and selection of literature. CNETRAL, Cochrane Central Register of Controlled Trials; CINAHL, Nursing and Allied Health Literature; CBM, Chinese Biomedical Literature; CSTJ, China Science and Technology Journal; CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial.

Interventions (40) and were reported individually. If the trials reported their continuous variables as mean with ranges, we would convert those variable into the mean and variance (standard deviation, SD) according to the method proposed by Hozo *et al.* (45). All disagreements between the investigators were discussed and resolved by consensus.

Results

Identification and selection of studies

Through a database search, a total of 228 potentially relevant records were retrieved, and no additional citation was added. After screening the title, abstract and full-text of 156 non-duplicate records, ultimately 7 articles published between 2013 and 2018 met our criteria and were included in qualitative synthesis. Of the 7 included studies, one (38) involving two control groups (yoga *vs.* usual care; yoga *vs.* exercise) was divided into two comparisons according to the purpose of the study. Besides, a small (n=40) study conducted by Danhauer *et al.* (32) posted addition results in Clinical Trials.gov which didn't present in current paper, so we integrated all results. A flow chart outlining the process of literature identification and selection was depicted in *Figure 1*.

Characteristics of eligible studies

The basic characteristics of 7 trials (8 RCTs) were summarized in *Table 1*. They were originated from China

Table 1 Characteristics of the included trials identified in the literature search

Study	Country	Age (EG/CG)	Stage of cancer	Treatments	Sample size (EG/CG)	Details of intervention regimes	Control regimes	Outcomes
Chaoul *et al.*, 2018a (38)	USA	49.5±9.8/ 49±10.1	I-III	Surgery, CT	74/85	Breathing techniques, yoga postures, meditation; 12 weeks, 4 times a week for 75 to 90 minutes. Contained out-of-class practice. Audio-visual teaching materials or printed materials	Usual care	PSQI; BFI; AEs
Chaoul *et al.*, 2018b (38)	USA	49.5±9.8/ 50.4±10.3	I-III	Surgery, CT	74/68	Breathing techniques, yoga postures, meditation; 12 weeks, 4 times a week for 75 to 90 minutes. Contained out-of-class practice; Audio-visual teaching materials or printed materials	Stretching program	PSQI; BFI; AEs
Lanctôt *et al.*, 2016 (33)	Canada	51.23±9.29/ 50.29+9.54	0-II	Surgery, CT	58/43	Breathing techniques, yoga postures, meditation, relaxation techniques; 8 weeks, once a week for 90 minutes. Contained out-of-class practice. Audio-visual teaching materials or printed materials	Standard care	BDI-II; STAI-Y; AEs
Taso *et al.*, 2014 (34)	China	49.27±10.23	I-III	CT, HT	30/30	Breathing techniques, yoga postures, meditation; 8 weeks, twice weekly for 60 minutes	Standard care	BFI-T; Profile of Mood State; Profile of Mood State; AEs
Jong *et al.*, 2018 (35)	The Netherlands	51±7.3/51±8	I-III	Surgery, CT, RT, IT	47/36	Breathing techniques, yoga postures, relaxation techniques, energy block release; 12 weeks, once a week for 75 minutes. Contained out-of-class practice. Audio-visual teaching materials or printed materials	Standard care	HADS
Jin *et al.*, 2017 (36)	China	60 [55–73]	n.r.	CT	50/50	Breathing techniques, yoga postures, relaxation techniques; 12 weeks, thrice weekly for 60 minutes. Contained out-of-class practice, Audio-visual teaching materials or printed materials	Standard care	SAS; SDS; FACT-B
Wang *et al.*, 2013 (37)	China	18–60	0-IV	Surgery, CT	40/42	Yoga postures, relaxation; 4 months, 4 times a week for 50 minutes. Contained out-of-class practice. Audio-visual teaching materials or printed materials	Standard care	PSQI; CFS; SAS; SDS; FACT-B;
Danhauer *et al.*, 2015 (32)	USA	50 [29–83]/ 45 [30–65]	I-III	Surgery, CT	22/18	Yoga postures, meditation; 10 weeks, once a week for 75 minutes (8-10 sessions in total). Contained out-of-class practice. Audio-visual teaching materials or printed materials	Wellness-education as active control	MOS Sleep; FACT–Fatigue; CES–D; FACT-B; AEs

EG, experiment group; CG, control group; n.r., not reported; PSQI, Pittsburgh Sleep Quality Index; BFI, the Brief Fatigue Inventory; BDI-II, Beck Depression Inventory II; STAI-Y, State-Trait Anxiety Inventory; BFI-T, Brief Fatigue Inventory-Taiwan version; HADS, the Hospital Anxiety Depression Scale; MFI, Multidimensional Fatigue Inventory; FQL, Fatigue Quality List; EORTC-QLQ-C-30, the 30-item Quality of Life Questionnaire-C of the European Organization for Research and Treatment of Cancer; CFS, The Cancer Fatigue Scale; SAS, Self-rating anxiety scale; SDS, Self-rating depression scale; FACT-B, Functional Assessment of Cancer Therapy-Breast; PSQ, Pitts-burgh Sleep Quality Index; MOS Sleep, Medical Outcomes Study Sleep Scale; FACT-Fatigue, Functional Assessment of Cancer Therapy-Fatigue; CES-D, Center for Epidemiologic Studies-Depression Scale; AEs, adverse events; CT, chemotherapy; RT, radiotherapy; IT, immunotherapy; HT, hormone therapy.

(3 trials), America (2 trials), Canada (1 trials), and The Netherlands (1 trials). The included studies recruited a total of 693 breast cancer patients, with sample size ranging from 40 to 159. Different yoga interventions were applied across the studies, including Tibetan, Bali, Anusara, Dru, and integrated yoga programs. The remaining two did not specify the yoga style adopted. The main instruction form is group coaching (5 trials) (32-34,36,37) and participants in 3 studies (32-34) received personalized yoga sessions led by experienced yoga instructors. The yoga interventions varied in duration from 8 weeks to 4 mouths and in frequency from 1 to 4 times a week for 50- to 90-minute sessions. Besides, the time point of longest follow-up ranged from 0 to 12 months. As repeated outcome assessments were conducted, statistical analysis was undertook separately according to the duration of follow-up: short-term (<6 months), medium-term (6–12 months) and long-term follow-up (≤12 months). In 6 trials (32-37) were categorize as assessing short-term effects; the remaining one (38) as assessing short-, medium- and long-term effects.

Methodological quality of studies

All eligible articles were described as randomized, however, only five (32-35,38) specified methods to generate random sequencing, such as a form of adaptive randomization or a computer-generated random table. Less than half of articles (33-35) provided sufficient information on allocation concealment, one study (37) fail to conceal allocation; and the remaining studies (32,36,38) were no mention of methods used to do so. The control group in most studies consisted of either wait-list or usual care, considering participants were aware of which intervention they received, it was hard to imagine how blinding of patients and personnel could be applicable. Because a subjective judgment of participants and researchers played an important role in the evaluation of outcome indicators, and this phenomenon may have caused an obvious Hawthorne effects. Thus, we rated these studies (33-38) as having a high risk of bias. However, the remaining studies (32,38) have used an active intervention as a control group whose frequency and duration is similar to yoga group, and no group differences was detected in target outcomes over time; thus it is unlikely to introduce bias without performing blinding (39). Five articles (34-38) reported no information on blinding of outcome assessors; and two (32,33) explicitly indicated that the researchers responsible for the outcome assessment were not blinded. In aspect of attrition bias, no attrition (34,36) and low attrition (32,33,37) were detected in 2 and 3 studies, respectively. One study (38) reported high dropout rate in each group, but well balanced across groups. Besides, group differences were not statistically significant between study completers versus non-completers on the basis of demographic and medical characteristics and outcome measures; and the remaining one (35) was graded as high risk of bias because a dropout rate >20%) (46). All studies provided no protocol but there was no hint of selective reporting, except for one study (35) that registered protocol and reported all pre-specified outcomes in a pre-specified way. No study suffered from other suggested bias, and we judged all studies as having a low risk of bias in this domain. We displayed a summary of the quality assessments in *Figure 2*.

Health-related QoL

With respect to health-related QoL, three RCTs (32,36,37) involving 216 participants investigated its short-term effects of yoga. No heterogeneity was detected across the included studies (P=0.24, I^2=29%), and then a random-effect model was adopted to calculate estimate. Pooled result suggested that the efficacy of yoga interventions is not inferior to the control groups in health-related QoL [SMD =0.72, 95% CI, –0.12 to 1.56, P=0.09] (*Figure 3*).

Fatigue

Four trials (32,34,37,38) comprising 442 patients investigated whether yoga can relieve cancer-related fatigue in short-term period. We divided the eligible studies into three subgroups based on different assessment period. Heterogeneity was low among two studies that fell into medium-term effects group (P=0.85, I^2=0%) and long-term effects group (P=0.89, I^2=0%), but statistical heterogeneity presented among five RCTs that fell into short-term effects group (P<0.000, I^2=86%). Therefore, a random-effects model was used. Meta-analysis revealed that statistically significant effects was detected on this dimension immediately postintervention [SMD =–0.62, 95% CI, –1.17 to –0.07, P=0.03 for short-term effects group]. However, the efficacy of yoga interventions returned to baseline at follow-up assessment [SMD =0.22, 95% CI, –0.05 to 0.49, P=0.85 for medium-term effects group and SMD =0.16, 95% CI, –0.13 to 0.44, P=0.89 for long-term effects group] (*Figure 4*).

Sleep disturbance

Regarding sleep disturbance, three trials (32,37,38) (348 participants) assessed short-term effects of yoga group versus control group. Among them, one RCTs (32) cannot provide available data to be used in meta-analysis. Thereby, we adopted a qualitative analysis. We divided the eligible studies into three subgroups based on different evaluation period. The heterogeneity test indicated statistical heterogeneity exists in short-term effects group (P=0.09, I^2=59% for short-term effects group) and no heterogeneity exists in remaining subgroups (P=0.50, I^2=0% for medium-term effects group and P=0.73, I^2=0% for long-term effects group). Therefore, a random-effects model was used. Pooled result suggested that yoga groups were significantly more effective than control groups in improving sleep disturbance when short-term effects was assessed (SMD =–0.34, 95% CI, –0.55 to –0.12, P=0.003). However, the efficacy of yoga interventions was unable to sustain at follow-up assessment (SMD =–0.09, 95% CI, –0.36 to 0.18, P=0.53 for medium-term group and SMD =0.00, 95% CI, –0.28 to 0.29, P=0.98 for long-term group) (*Figure 5*). Besides, Danhauer *et al.* (32) found that sleep disturbance from baseline to chemotherapy weeks 5 and 10 remained essentially unchanged for yoga participants (P>0.05).

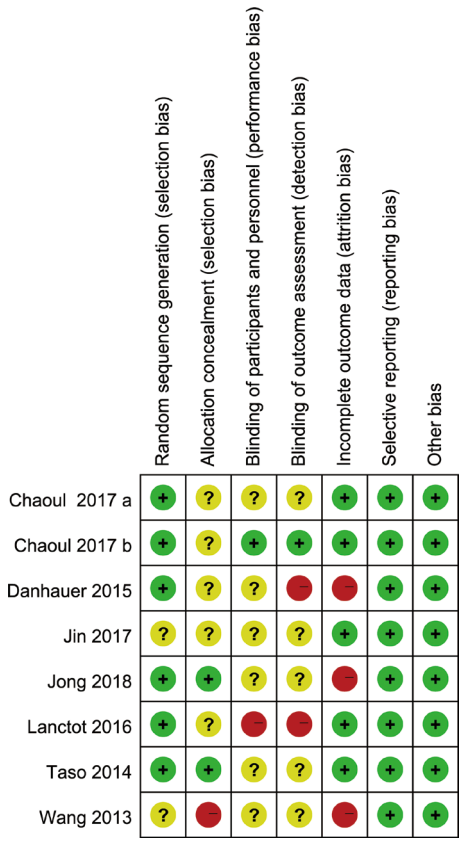

Figure 2 Risk of bias summary. Green, yellow and red represents low, unclear and high risk of bias respectively.

Depression

A total of six RCTs (32-37) compared short-term effects of yoga in 446 women on this outcome. Considerable heterogeneity was detected across the included studies (P<0.000, I^2=84%). Therefore, a random-effects model was used. Pooled result suggested that yoga groups were effective in improving this negative emotion as compared to control groups (SMD =–0.56, 95% CI, –1.05 to –0.07, P=0.03) (*Figure 6*).

Anxiety

Five RCTs (33-37) that enrolled 412 participants reported short-term effects of yoga on fatigue. Study results were homogeneous (P=0.11, I^2=46%). Therefore, a fixed-effects model was used. The pooled SMD was –0.50 (95% CI, –0.70 to –0.31, P<0.000), indicating statistically significant benefit from yoga (*Figure 7*).

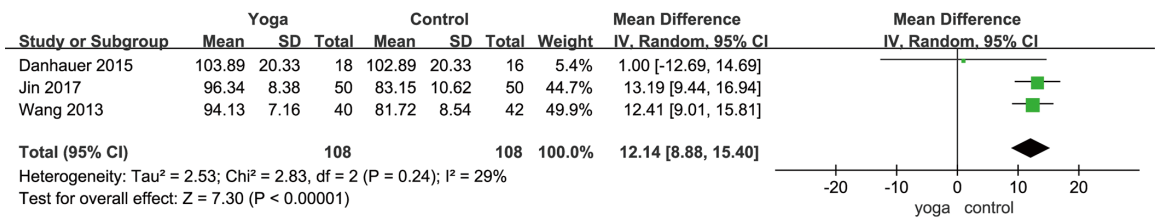

Figure 3 Meta-analysis of health-related quality of life.

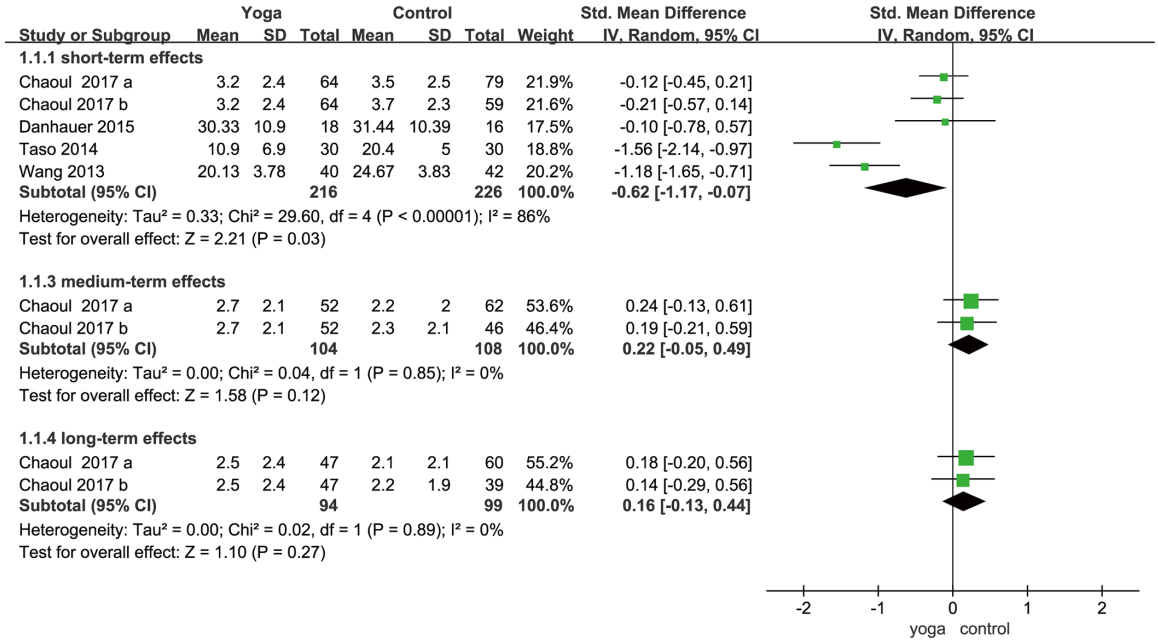

Figure 4 Meta-analysis of fatigue.

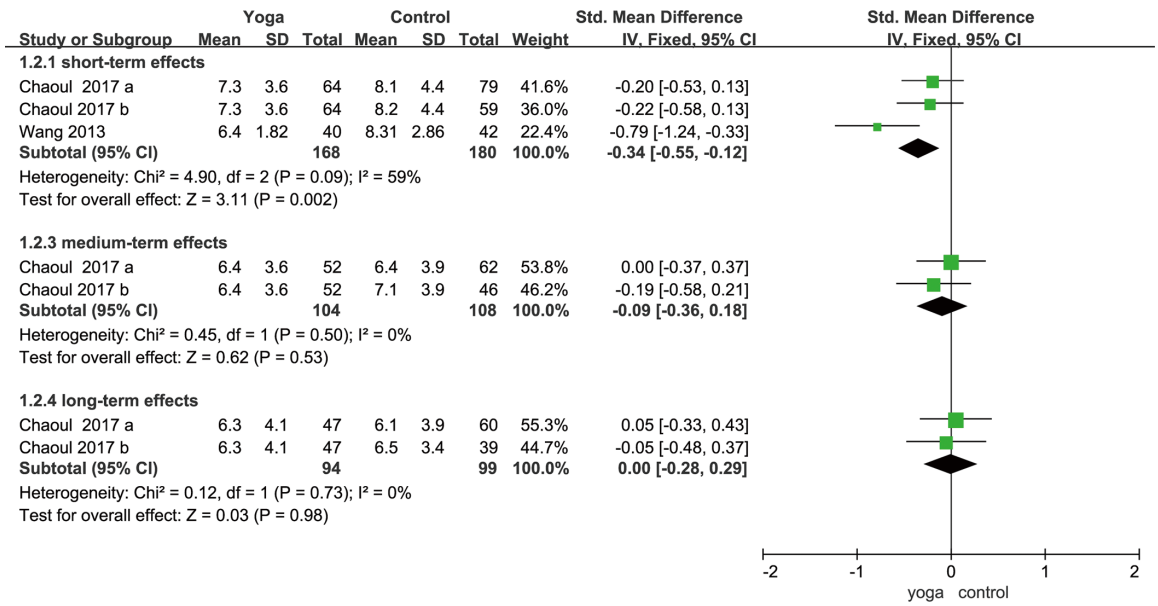

Figure 5 Meta-analysis of sleep disturbance.

Safety

Across the 7 included studies, in roughly half studies (32-34,38) provided the safety-related data. However, those numerical data cannot be used in meta-analysis. Thus, we took a descriptive analysis to summarize all information. The first one (32) was conducted by Danhauer *et al.* elaborated on this outcome: of the 21 participants in the yoga group, 4.76% (1 patient) experienced serious AE and 52.38% (11 patients) experienced minor AEs; of the 17 participants in the educational wellness group, 5.88% (1 patient) experienced serious AE, 47.06% (8 patients)

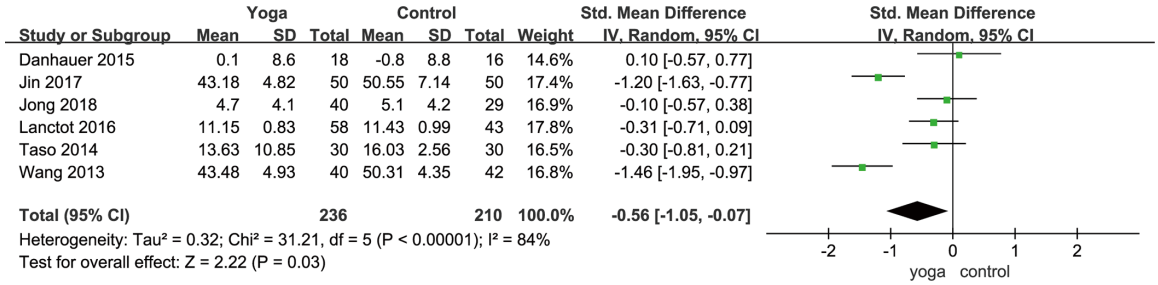

Figure 6 Meta-analysis of depression.

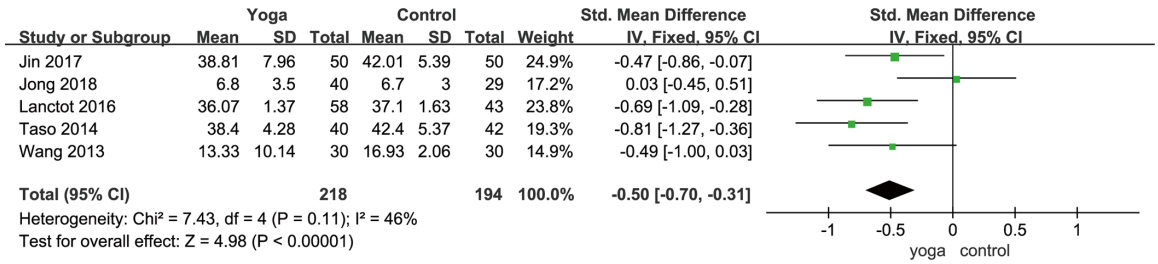

Figure 7 Meta-analysis of anxiety.

experienced minor AEs. The second trial (34) showed that a total of 57 AEs occurred by 81% (25 out of 31) women in the yoga group and 45 AEs occurred by 80% (20 out of 25) women in the control groups. The authors also clearly stated that none of the AEs was caused by yoga practice. Moreover, the remaining studies (33,38) found no remarkable side effects was collected in both groups.

Publication bias

In this review, the small number of studies (n<10) were included in our quantitative analysis, and thus we decided not to perform a publication bias test based on a funnel plot.

Discussion

Yoga is an ancient Indian philosophy and science which emphasizes the mind, body and spirit flowing in perfect harmony with nature, and considers practitioners' spirituality as an essential addition for disease management (25,47-49). It seems to yield positive effect in diverse medical conditions such as diabetes (50,51), asthma (52,53), AIDS (54), heart failure (55,56), immune function (57), serum cortisol levels (58) and Lymphoma (59). Previous researches (59-61) have also demonstrated that participants practicing yoga regularly have a substantial reduction in their natural killer cells and less DNA damage while undergoing chemotherapy (62).

Breast cancer, a leading cause of death in women between 35 and 54 years of age (2), is often treated with chemotherapy to reduce risk of distant recurrence (63). In this process, nevertheless, a myriad of undesired side effects ranging from physical (e.g., pain, fatigue, dry mouth, insomnia, nausea, vomiting) to psychological (e.g., emotional distress, anxiety, depression) (7,9,64,65), all of which may impact substantially on QoL and activities of daily living, challenged breast cancer survivors to cope with. A trial conducted in breast cancer participants who are receiving chemotherapy found that 46% of them reported self-perceived cognitive impairments and 82% of them were subjected to cancer-related fatigue in at least one dimension (66). It is now widely acknowledged that exercise can significantly maintain physical fitness and function and mitigate sleep dysfunction and mood disturbance for women with breast cancer during chemotherapy (12-14,67). However, cancer-related pain and severe fatigue condition discouraged women with breast cancer from taking part in purely gymnastic exercise (19,68). In comparison to other forms of physical activity, yoga's slow, gentle movements are easy to be adjusted to individual's medical conditions and the degree of activity limitation on the premise of guaranteeing

safe (20,69). Despite few published studies exclusively recruited breast cancer survivors receiving chemotherapy, information on the safety and efficacy of yoga practices is limited and inconsistent. Moreover, those results haven't been recur. In light of these findings and yoga's increasing popularity in this target population, to further confirm whether yoga is beneficial becomes paramount.

Summary of main results

To our knowledge, this is the first systematic review and meta-analysis to assess the strength of the evidence for yoga as a positive intervention for women with breast cancer receiving chemotherapy alone. A majority of studies only focused on short-term effects. The result indicated that yoga has an immediate effect on relieving fatigue and sleep disturbances, attenuating depression and anxiety and enhancing overall health-related QoL during chemotherapy compared to the control group. According to Cohen's categories (70), all comparisons indicated either a medium or a large effect size for yoga group over control conditions which suggested group differences might be clinically relevant. Nonetheless, most of the analyses had considerable heterogeneity which could not be reduced by subsequent subgroup analyses. So this likely affected the interpretation of the effect size. Besides, a total of 2 RCTs from an identical study investigated medium-term and long-term effects of yoga on sleep disturbance and fatigue, which stated no statistically significant effects. Given the lack of evidences from more researches and small sample, the results on the basis of these data pieces must be cautiously interpreted. Furthermore, we found no evidence of effects favoring yoga group over control group for increasing the incidence of minor or serious side effects.

Based on the published evidences, the mechanisms proposed to explain how yoga can exert short-term physical and psychological benefits involved the following aspects: (I) yoga has the capability of altering activity of the hypothalamic-pituitary-adrenal axis in response to stress (26,71), thus decreasing the secretion of cortisol and suppressing the stress-induced physiological arousal (72-74). Ultimately, it may lead to the decrease in the anxiety and depression levels (74,75); (II) under stressful conditions, yoga can increase parasympathetic dominance involving deepen breath amplitude and reduced heart rate and blood pressure—all of which lighten the mood (76). (III) Yoga stimulates the human body to lower levels of cytokines [e.g., interleukin-6 (77), lymphocyte-1B (78)] to prevent the impairment of cellular immunity under high-stress situation (79-84). Several studies have found that changes in levels of interleukin-6 (IL-6) are significantly correlated with changes in fatigue (13,79,80); (IV) through the progression of a series of static physical postures, yoga adopted stretching resulting in the increased muscular strength and endurance, which may have achieve invigorating effects on mental and physical energy when facing stress (85), and thereby may reduce fatigue and sleep disturbance (34,86,87). When the severity of one of these symptoms is moderate or above, they often co-occur (88,89). And these changes often have directly or (and) indirectly impact on health-related QoL (90,91)

However, the present study failed to find medium- and long-term effects of yoga on fatigue and sleep disturbance during chemotherapy. But for all this, it is still worthwhile to explore possible reasons contributing to the findings. The effectiveness of yoga may be associated to the treatment status (during active cancer treatment *vs.* completion of active treatment) (92), a previous meta-analysis revealed evidence of efficacy only for yoga when participants are undergoing active cancer treatment but not when they completed active treatment (93). Secondly, the severity level of fatigue and sleep disturbance were low when assessed at 6 and 12 months. Therefore, there was not much room for improvement, which may be a reason for the non-significant findings (94). Thirdly, the frequency of practice may be also an influence factor of treatment outcome (86). If the frequency of training was too poor, it is hard to produce observable effects (95). The only one included article (38) reported that breast cancer patients who practiced yoga ≥2 times per week during their chemotherapy treatment were less likely to experience sleep problems at 6 months.

Limitations of the present study

Several limitations in our study warrant comment. The safety of yoga practice undergoing chemotherapy has been questioned. Although several randomized trials (32-35,38) found no evidence of increased risk of AEs associated with yoga for women with breast cancer under chemotherapy. But reporting standards have not been unified yet, some studies not only minored intervention-related side effects, but also recorded follow-up toxicity data (32) or chemotherapy-associated data (32,34,35). These evidences can't specially embody the safety of yoga. Besides, as only one trial (38) included a follow-up assessment 12 months post intervention, medium- and long-term effects could

not be assessed for all pre-specified outcome indicators and quantitative analyses were unable to implement. Thus, it is unclear how sustainable the benefit of yoga would be beyond the active intervention period. Furthermore, there still remain some variability in yoga interventions (i.e., yoga styles and their components; the length and intensity of yoga), patient groups (i.e., stage of cancer; accepted or accepting treatments) and instruments used to assess the outcome. This may be reflected by the high heterogeneity (I^2>59%) among some comparisons. Because the trails included were randomized, there is a high probability that they would have been evenly distributed across all intervention arms. These limitations have hindered researchers from determining the true benefits of a yoga regimen to treat all outcomes of breast cancer.

Implications for practice and further research

In our review, only two RCTs (32,38) have included an active control group, relying instead on nonactive control conditions such as a waiting list or usual care condition. While class frequency or duration in the control intervention cannot be tailored and matched to that in the yoga intervention, I wonder whether this factor influences intervention efficacy since chemotherapy. A previous studies done by Pan *et al.* (96) revealed that any such yoga effects are probably larger among individuals with breast cancer who had a yoga practice over longer periods of time. But American Cancer Society guidelines recommended that participants using chemotherapy and (or) radiotherapy who already take exercise may need to lower the intensity and duration of exercise sessions during treatment (97). Thereby, after confirming optimum practice duration criterion, future studies should examine whether a similarly time-intensive physically oriented approach (e.g., stretching) is efficacious when applied to breast cancer survivors under chemotherapy.

Conclusions

Based on limited data, yoga can be deemed as a supportive intervention for improving short term fatigue, sleep disturbance, depression, anxiety and health-related QoL in women with a diagnosis of breast cancer who are currently undergoing chemotherapy. But yoga may not produce any medium- and long-term benefits in reduction of sleep disturbance and fatigue. Given that evidence showing the safety of yoga is promising but preliminary, further studies are warranted to closely minoring and reporting intervention-related safety information.

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