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Meta Analysis

Non-pharmacologic intervention to prevent cancer-related fatigue among breast cancer patients: a systematic review and meta-analysis

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ABSTRACT

Cancer-related fatigue (CRF) is a prevalent and debilitating condition among breast cancer patients, significantly impacting their quality of life. Non-pharmacologic interventions have gained attention as potential strategies for managing CRF, but evidence on their efficacy remains fragmented. This study aims to evaluate the effectiveness of non-pharmacologic interventions in preventing and reducing CRF among breast cancer patients through a systematic review and meta-analysis. A comprehensive search of PubMed, Web of Science, Scopus, Medline, Cochrane Library, and Google Scholar was conducted, yielding 741 records. After removing duplicates, 354 records underwent title and abstract screening. A total of 65 studies were assessed for eligibility, of which 12 studies were included in the meta-analysis. The pooled analysis included a total of 990 participants, comprising intervention and control groups. Interventions analyzed included acupuncture, yoga, resistance and aerobic exercises, mindfulness-based stress reduction, and cognitive-behavioral therapy (CBT). Outcomes were assessed using validated fatigue measurement tools. Random-effects models were used to estimate the standardized mean difference (SMD) and 95% confidence intervals (CIs). The pooled analysis demonstrated a significant reduction in CRF among participants receiving non-pharmacologic interventions compared to usual care, with an overall SMD of -1.45 (95% CI: -2.39, -0.51; p=0.003). High heterogeneity was observed (I^2=97%). Subgroup analyses indicated that interventions such as acupuncture, resistance exercise, and mindfulness-based stress reduction yielded the most substantial reductions in fatigue levels. No significant publication bias was detected, as shown in the funnel plot analysis. In conclusion, non-pharmacologic interventions effectively reduce CRF in breast cancer patients, with certain modalities demonstrating superior efficacy. These findings support integrating these interventions into comprehensive cancer care plans to improve patient outcomes. Further research is warranted to address heterogeneity and explore long-term effects.

Keywords: Cancer-related fatigue, Breast cancer, Non-pharmacologic interventions, Meta-analysis, Acupuncture, Exercise therapy

INTRODUCTION

Cancer-related fatigue (CRF) is one of the most distressing and prevalent symptoms experienced by cancer patients, particularly those undergoing treatment for breast cancer. It is a complex, multidimensional syndrome characterized by persistent physical, emotional, and cognitive exhaustion that is disproportionate to the level of recent activity and not alleviated by rest. Unlike ordinary fatigue, CRF significantly interferes with daily functioning and quality of life.[1,2] Breast cancer, the most common malignancy among women worldwide, is associated with high rates of CRF, primarily due to the aggressive nature of its treatment, which often includes surgery, chemotherapy, radiation, and targeted therapies. This symptom is increasingly recognized as a critical issue in continuum of cancer care due to its debilitating impact on patients' physical, psychological well-being.[2-4]

The pathophysiology of CRF is complex and not fully understood. It is believed to involve multiple interacting mechanisms, including inflammation, alterations in

cytokine levels, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, mitochondrial dysfunction, and anemia. Additionally, cancer treatments such as chemotherapy and radiation are known to exacerbate fatigue by causing direct cellular damage, inducing systemic inflammation, and contributing to secondary conditions like neuropathy and depression.[5,6] Psychological factors, including anxiety, depression, and sleep disturbances, also contribute to the burden of CRF in breast cancer patients, creating a vicious cycle that can perpetuate the symptom.[7]

The management of CRF poses significant challenges for clinicians and patients alike, as it is often underdiagnosed and undertreated. Traditional pharmacologic approaches, such as the use of psychostimulants or antidepressants, have shown limited efficacy in mitigating CRF and are associated with potential side effects. As a result, there has been a growing interest in non-pharmacologic interventions as a safer and potentially more effective alternative. These interventions target the multifactorial nature of CRF and aim to address the underlying physiological, psychological, and social factors contributing to fatigue.[3,4,8,9]

Exercise interventions, particularly aerobic and resistance training, have emerged as one of the most studied non-pharmacologic strategies for managing CRF. Evidence suggests that physical activity can reduce inflammation, improve cardiorespiratory fitness, and enhance psychological well-being, thereby alleviating fatigue symptoms. Mindfulness-based interventions, including meditation, yoga, and relaxation techniques, have also gained popularity due to their ability to reduce stress, improve sleep quality, and promote emotional resilience.[10,11] CBT, which focuses on modifying maladaptive thoughts and behaviors, has shown promise in addressing the psychological aspects of CRF, such as depression and anxiety.[10]

Acupuncture, another non-pharmacologic modality, has been explored for its potential role in managing CRF. The practice is thought to regulate energy flow, reduce inflammation, and modulate neurochemical activity, although the mechanisms remain largely theoretical. Nutritional and dietary interventions have also been investigated, with a focus on addressing deficiencies and optimizing energy metabolism. These diverse approaches highlight need for a tailored, patient-centered approach to managing CRF, considering the individual preferences, capabilities, and needs of breast cancer patients.[10,12]

Despite the growing body of evidence supporting non-pharmacologic interventions, the heterogeneity of study designs, intervention protocols, and outcome measures has limited the ability to draw definitive conclusions. Existing studies often vary in terms of intervention type, duration, intensity, and the tools used to assess CRF, making it challenging to establish standardized guidelines for clinical practice. Additionally, most studies are limited by small sample sizes, short follow-up periods, and inadequate reporting of adverse events, further complicating the interpretation of results.[11,13]

Given these limitations, there is a pressing need for a comprehensive synthesis of available evidence to evaluate the effectiveness of non-pharmacologic interventions for CRF in breast cancer patients. Meta-analyses, by pooling data from multiple studies, offer a robust method for generating high-quality evidence and identifying patterns or trends that may not be apparent in individual studies. Such analyses can also provide valuable insights into the comparative effectiveness of different interventions, thereby informing clinical decision-making and guiding future research.

This meta-analysis is timely and essential, given the increasing prevalence of breast cancer and the growing recognition of CRF as a critical survivorship issue. By synthesizing evidence on non-pharmacologic interventions, this study aims to bridge existing knowledge gaps, provide actionable recommendations for healthcare providers, and ultimately improve the quality of life for breast cancer patients struggling with fatigue. Aim of this meta-analysis is to systematically evaluate effectiveness of non-pharmacologic interventions in reducing CRF among breast cancer patients.

METHODS

The meta-analysis adhered to ethical standards by ensuring transparency, rigor, and compliance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[14] It was conducted during the period from January 2025 to May 2025. A systematic and comprehensive search was conducted across multiple databases to identify relevant studies evaluating the efficacy of non-pharmacologic interventions for CRF in breast cancer patients. The databases searched included PubMed, Web of Science, Scopus, Medline, and Cochrane Library, as well as Google Scholar for grey literature. The search strategy combined terms related to CRF, breast cancer, and non-pharmacologic interventions, using Boolean operators AND, OR, and NOT for precision. Medical Subject Headings (MeSH) terms and free-text keywords were tailored for each database. The search was not restricted by publication date to ensure that all potentially relevant studies were captured, but only articles published in English were included. Reference lists of all included studies were manually reviewed to identify additional studies that might have been missed during initial search.

Eligibility criteria

Studies were included in the analysis if they met the following criteria: they involved breast cancer patients of any stage/treatment phase; assessed non-pharmacologic interventions such as exercise, acupuncture, mindfulness-based interventions, or CBT; reported CRF as a primary

or secondary outcome using validated measurement tools; and provided sufficient data for meta-analysis, such as means, standard deviations, or effect sizes. Randomized controlled trials, quasi-experimental studies, and controlled clinical trials were eligible for inclusion. Studies were excluded if they focused solely on pharmacologic interventions, did not involve breast cancer patients, or lacked sufficient outcome data. Studies involving mixed cancer populations were included only if data for breast cancer patients were reported separately.

Study selection

The study selection process was conducted in three stages. Initially, all retrieved records were imported into EndNote software for deduplication. Titles and abstracts were then screened independently by two reviewers to assess their relevance to the research question. Articles that did not meet the eligibility criteria were excluded at this stage. Full-text articles of potentially eligible studies were retrieved and independently reviewed by same two reviewers against inclusion criteria. Any disagreements during selection process were resolved through discussion or consultation with a third reviewer. The final selection of studies was documented using the PRISMA flow diagram, detailing the number of studies included and excluded at each stage, along with reasons for exclusion.

Data extraction

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted information included study characteristics (e.g., author, year, location, study design), participant details (e.g., sample size, age, cancer stage), intervention characteristics (e.g., type, frequency, duration), comparator details (e.g., usual care, placebo), and outcome measures (e.g., CRF assessment tools, baseline and post-intervention fatigue scores). Any discrepancies in data extraction were resolved through discussion. Where data were incomplete, attempts were made to contact the study authors for clarification.

Statistical analysis

Meta-analysis was conducted using review manager (RevMan) software to pool the effect sizes of the included studies. The primary outcome was the reduction in CRF, expressed as a SMD with corresponding 95% confidence intervals (CIs). A random-effects model was used due to expected heterogeneity among studies in terms of populations, interventions and outcome measures. Statistical heterogeneity assessed using I^2 statistic, with values above 50% indicating substantial heterogeneity. Publication bias was assessed using funnel plots.

RESULTS

A comprehensive search across six databases, including PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar, yielded 741 initial records. After removing 387 duplicates, 354 records underwent title and abstract screening, during which 289 studies were excluded based on irrelevance or lack of focus on non-pharmacological interventions for breast CRF.

A total of 65 full-text articles were sought for retrieval, with all successfully obtained. Upon eligibility assessment, 53 studies were excluded for reasons such as insufficient data, non-compliance with the inclusion criteria, or lack of randomized controlled trial design. Final synthesis included 12 studies that met all inclusion criteria, as detailed in PRISMA flow diagram (Figure 1).

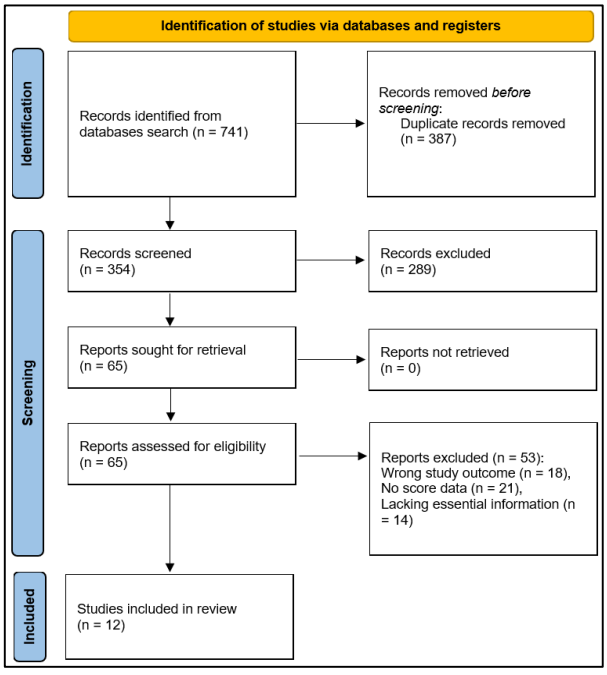

Figure 1: PRISMA flow diagram summarizing the search and screening processes.

Characteristics and findings of included studies

The included studies represented diverse geographic locations, including Germany, Ethiopia, Holland, the United States, Sweden, Japan, Brazil, and China.[15-26] Study populations ranged widely in size, from small trials such as Santagnello et al (11 intervention, 9 control) to larger cohorts like Molassiotis et al (227 intervention, 75 control).[20,23] The average age of participants across studies varied, with the youngest mean age in Getu et al (40.2±10.9 years for intervention) and the oldest in Santagnello et al (59±9.2 years for intervention).[16,23]

Interventions employed were diverse and included acupuncture, CBT, yoga, massage therapy, resistance and aerobic exercise, mindfulness-based stress reduction, high-intensity exercise, and traditional Chinese exercises like Baduanjin and Qigong.[15-26] These interventions were consistently compared against usual care across all studies. Fatigue assessment tools varied, with the functional assessment of cancer therapy-fatigue (FACT-F) used in four studies, the multidimensional fatigue inventory (MFI) in three, and others like the Piper fatigue scale and the brief fatigue inventory (BFI) in the remaining studies.[15,17,18,20,21,24,25]

The studies predominantly focused on middle-aged women undergoing active cancer treatment or post-treatment recovery. Intervention durations were generally short to moderate, with outcomes measured over weeks or months. Despite heterogeneity in intervention types and populations, all studies reported some degree of improvement in fatigue outcomes in the intervention groups compared to controls.

Quantitative data synthesis

Effectiveness of non-pharmacological interventions

The pooled analysis of 12 studies (n=573 intervention, n=417 control) demonstrated a statistically significant reduction in CRF among patients receiving non-pharmacological interventions compared to usual care. The SMD was -1.45 (95% CI: -2.39 to -0.51), indicating a moderate-to-large effect size favoring the intervention group. Substantial heterogeneity was observed across studies (I^2=97%, p<0.00001), suggesting variability in interventions, populations, or the assessment tools (Figure 2).

Individual study results contributed to the overall findings with varying effect sizes. Getu et al reported the largest negative SMD (-5.39, 95% CI: -6.53 to -4.25), reflecting the pronounced effectiveness of CBT.[16]

Similarly, Kinkead et al and Molassiotis et al showed significant reductions in fatigue with SMDs of -3.42 (95% CI: -4.37 to -2.47) and -4.85 (95% CI: -5.37 to -4.34), respectively.[18,20] In contrast, Brinkhaus et al and Myers et al showed smaller effect sizes (SMD: 0.19, 95% CI: -0.13 to 0.51; SMD: 0.58, 95% CI: -0.18 to 1.34).[15,21] These results highlight variability in the magnitude of intervention effects, potentially attributable to differences in intervention type, study populations, or assessment methods.

Assessment of heterogeneity and publication bias

High heterogeneity (I^2=97%) prompted further exploration of study characteristics to explain variability. Differences in intervention types, sample sizes, and assessment tools likely contributed to the observed heterogeneity.

Sensitivity analyses or subgroup analyses, not presented here, would be beneficial to further investigate potential sources of heterogeneity.

The funnel plot (Figure 3) showed a symmetrical distribution of studies, suggesting no substantial publication bias. However, the presence of heterogeneity limits definitive conclusions regarding bias.

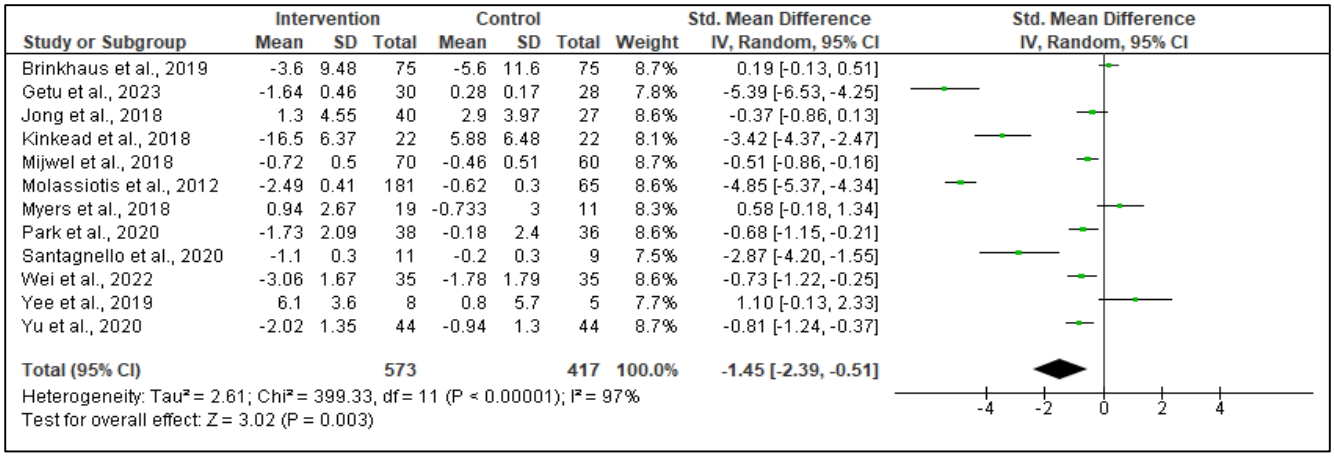

Figure 2: Forest plot of the score differences between non-pharmacological interventions for breast CRF versus controls.

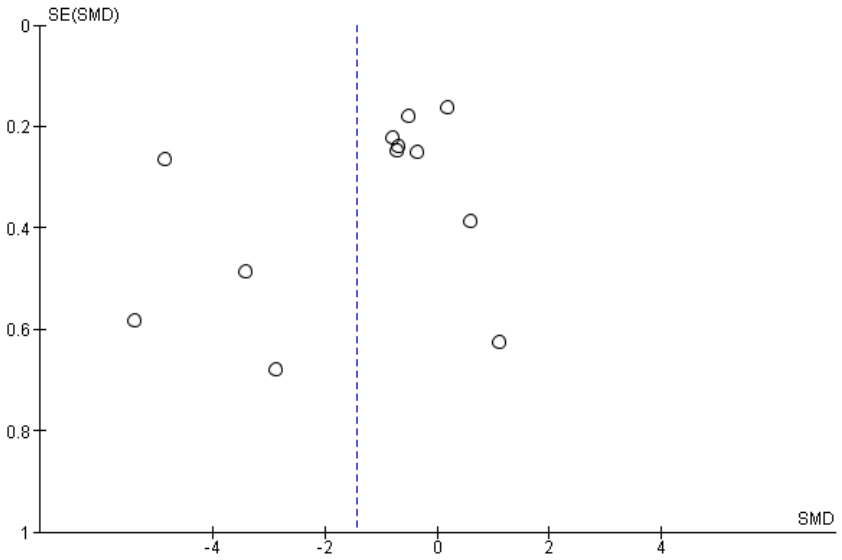

Figure 3: Funnel plot for the assessment of publication bias (symmetrical distribution).

DISCUSSION

CRF is one of the most debilitating and pervasive symptoms experienced by breast cancer patients, significantly impacting their quality of life, physical functioning, and psychological well-being. Unlike normal fatigue, CRF is characterized by a persistent sense of exhaustion that is not alleviated by rest and is not directly proportional to recent activity levels.[1,2] Managing CRF is crucial for enhancing the overall treatment experience and long-term outcomes for breast cancer survivors. While pharmacological treatments have been explored, non-pharmacologic interventions offer promising alternatives with fewer side effects and broader applicability.[6,7] This meta-analysis systematically reviewed and synthesized the evidence on various non-pharmacologic interventions aimed at preventing and alleviating CRF among breast cancer patients, providing a comprehensive understanding of their effectiveness and informing clinical practice.

Our meta-analysis included 12 studies encompassing a total of 573 participants in intervention groups and 417 in control groups. The pooled analysis revealed that non-pharmacologic interventions significantly reduced CRF compared to usual care, with a SMD of -1.45 (95% CI: -2.39 to -0.51). This indicates a moderate to large effect size favoring the intervention groups. However, the analysis also demonstrated substantial heterogeneity (I^2=97%, p<0.00001), suggesting considerable variability in the effect sizes across the included studies.

Among the individual studies, Getu et al reported the most substantial reduction in fatigue with an SMD of -5.39 (95% CI: -6.53 to -4.25) for CBT, followed by Molassiotis et al with an SMD of -4.85 (95% CI: -5.37 to -4.34) for acupuncture.[16,20,25] Conversely, studies such as Yee et al and Myers et al reported smaller or non-significant effects, with SMDs of 1.10 (95% CI: -0.13 to 2.33) and 0.58 (95% CI: -0.18 to 1.34), respectively.[21]

The funnel plot analysis indicated a symmetrical distribution of effect sizes (Figure 3), suggesting an absence of significant publication bias.

The findings of this meta-analysis underscore the efficacy of non-pharmacologic interventions in mitigating CRF among breast cancer patients. Significant overall effect size aligns with existing literature that highlights benefits of integrative and supportive care strategies in cancer management. For instance, systematic review by Mustian et al corroborated effectiveness of exercise interventions in reducing fatigue, echoing our findings on resistance and aerobic exercise.[23,26,27] Similarly, CBT has been widely recognized for its role in managing various cancer-related symptoms, including fatigue, which is consistent with pronounced effect observed Getu et al.[16,28]

Acupuncture, another intervention demonstrating significant efficacy in our analysis[15,20], has been supported by multiple studies for its role in alleviating CRF. A meta-analysis by Lee et al.[29] found acupuncture to be effective in reducing fatigue and improving quality of life in cancer patients, aligning with our findings. The variability in effect sizes across studies, however, highlights the complexity of CRF and the influence of various moderating factors such as intervention type, duration, and patient characteristics.

The high heterogeneity (I^2=97%) observed in our meta-analysis indicates substantial variability among the included studies, which may stem from differences in intervention modalities, study populations, sample sizes, assessment tools, and implementation protocols.

For instance, interventions ranged from physical activities like yoga and resistance exercise to mind-body practices such as Qigong and mindfulness-based stress reduction.[16-26] Each intervention type may operate through distinct mechanisms, contributing differently to fatigue reduction.

Furthermore, diversity in sample sizes, ranging from small trials (e.g., Santagnello et al with 11 intervention participants) to larger cohorts (e.g., Molassiotis et al with 227 intervention participants), may influence stability and generalizability of effect sizes.[20,23] Variation in mean ages of participants, from 40.2-60.1 years, also suggests that age-related factors could modulate effectiveness of interventions.[16,25]

Assessment tools used across studies varied, including the FACT-F, the BFI, the MFI, and the piper fatigue scale (PFS).[15-26] This heterogeneity in measurement instruments could contribute to differences in reported outcomes, as each tool has its sensitivity and specificity in detecting changes in fatigue levels.

Given the high heterogeneity, it is essential to interpret the pooled effect size with caution. Subgroup analyses based on intervention type, study quality, or specific patient populations could provide deeper insights into the sources of variability. Unfortunately, such analyses were beyond the scope of the current meta-analysis but represent important directions for future research.

Getu et al reported an exceptionally large effect size for CBT, suggesting its potent role in managing CRF.[16] CBT likely addresses both the psychological and behavioral aspects of fatigue, helping patients develop coping strategies and modify negative thought patterns that contribute to fatigue perception. This aligns with the theoretical underpinnings of CBT in enhancing self-efficacy and resilience among cancer patients.[28]

Studies by Brinkhaus et al and Molassiotis et al demonstrated significant reductions in fatigue through acupuncture.[15,20] Acupuncture may modulate autonomic nervous system, reduce inflammation, enhance endorphin release, thereby alleviating fatigue symptoms. These findings are consistent with Lee et al found acupuncture effective in improving CRF and overall well-being.[29]

High-intensity exercise, resistance exercise, aerobic exercise, and yoga were among the physical activity-based interventions assessed.[17,19,23,25,26] Exercise is known to enhance physical fitness, reduce inflammation, and improve mood, all of which can contribute to reduced fatigue. Our findings support the broader literature that advocates for tailored exercise programs as a cornerstone in CRF management.[27,30]

Mindfulness-based stress reduction, Qigong, and Baduanjin are examples of mind-body interventions that integrate physical movement with mental focus and relaxation techniques.[21,22,24] These practices may reduce stress and improve psychological well-being, thereby indirectly alleviating fatigue. The positive outcomes observed in studies employing these interventions are in line with evidence suggesting the benefits of mind-body approaches in cancer symptom management.[31]

Kinkead et al reported significant fatigue reduction through massage therapy, which may work by promoting relaxation, improving circulation, and reducing muscle tension.[18]

While massage therapy is less frequently studied compared to other interventions, its effectiveness in this meta-analysis highlights its potential as a complementary therapy in CRF management.

Our meta-analysis findings are largely consistent with existing systematic reviews and meta-analyses that emphasize the effectiveness of non-pharmacologic interventions in managing CRF. For example, a study highlighted the role of exercise in reducing fatigue, mirroring our findings on the efficacy of various exercise modalities.[27] Additionally, another study found that mind-body interventions, including yoga and meditation, significantly alleviate fatigue in cancer patients, supporting our results on mindfulness-based practices and traditional Chinese exercises.[32]

However, our analysis extends the literature by providing more comprehensive synthesis of diverse non-pharmacologic interventions and their comparative effectiveness. While some studies, like Yee et al reported non-significant or adverse effects, our overall findings still favor efficacy of interventions, suggesting that while not all interventions are equally effective, the collective evidence supports their use in clinical practice.[25]

The substantial reduction in CRF through non-pharmacologic interventions highlights their potential integration into standard care protocols for breast cancer patients. Healthcare providers should consider incorporating tailored exercise programs, CBT, acupuncture, and mind-body practices as part of a holistic approach to cancer care. The diversity of effective interventions allows for personalization based on patient preferences, physical capabilities, and cultural contexts, enhancing adherence and overall treatment satisfaction.

Moreover, the significant effect sizes observed, particularly for CBT and acupuncture, suggest that these interventions could be prioritized in clinical settings where resources allow. Given the high heterogeneity, clinicians should also consider individual patient characteristics and intervention-specific factors when selecting appropriate non-pharmacologic strategies.

Future research should aim to address the heterogeneity observed by conducting more standardized and high-quality randomized controlled trials focusing on specific non-pharmacologic interventions. Subgroup analyses

based on intervention types, patient demographics, and cancer treatment stages could elucidate the most effective strategies for different patient populations.

Additionally, exploring the mechanisms underlying the effectiveness of various interventions could provide insights into optimizing CRF management. Integrating objective measures of fatigue, such as physiological markers, alongside subjective assessments could enhance the robustness of future studies.

Lastly, expanding research to diverse geographic and socioeconomic contexts is essential to ensure the generalizability of findings and to develop culturally sensitive intervention protocols that cater to the needs of breast cancer patients globally.

Table 1: Characters of the included studies, (n=12).

Study	Country	Age mean±SD (I) (in years)	Age Mean±SD (C) (in years)	Sample size (I)	Sample size (C)	Intervention	Control	Assessment tool
Brinkhaus et al[15]	German	51.4±10.4	50.6±9.5	75	75	Acupuncture	Usual care	Functional assessment of CTF
Getu et al[16]	Ethiopia	40.2±10.9	42.5±12.3	30	28	CBT	Usual care	Brief fatigue inventory
Jong et al[17]	Netherlands	51±8	51±7.3	40	27	Yoga	Usual care	Multidimensional fatigue inventory
Kinkead et al[18]	Atlanta	54.5±10.4	51.8±9.6	22	22	Massage therapy	Usual care	Multidimensional fatigue inventory
Mijwel et al[19]	Sweden	54.4±10.3	52.3±10.2	146	60	High intensity excise	Usual care	Piper fatigue scale
Molassiotis et al[20]	USA	52±22	53±27	227	75	Acupuncture	Usual care	Multidimensional fatigue inventory
Myers et al[21]	NA	52.89± 11.96	56.18± 11.30	19	11	Qigong	Usual care	Functional assessment of cancer therapy-fatigue
Park et al[22]	Japan	53.21±8.4	54.19± 9.27	38	36	Mindfulness-based stress reduction	Usual care	Brief fatigue inventory
Santagnello et al[23]	Brazil	59.0±9.2	52.1± 10.1	11	9	Resistance excise	Usual care	Brief fatigue inventory
Wei et al[24]	China	52±8	55±5	35	35	Baduanjin	Usual care	Functional assessment of cancer therapy-fatigue
Yee et al[25]	USA	60.1±12.7	65.0±6.9	8	6	Resistance excise	Usual care	Functional assessment of cancer therapy-fatigue
Yu et al[26]	China	44.01± 2.11	44.25± 2.24	44	44	Aerobic excise	Usual care	Piper fatigue scale

I: Intervention group, C: Control group, CI: Confidence interval

CONCLUSION

This meta-analysis provides compelling evidence for the effectiveness of non-pharmacologic interventions in reducing CRF among breast cancer patients. With a pooled SMD of -1.45 (95% CI: -2.39 to -0.51), these interventions offer significant benefits in managing one of the most challenging symptoms associated with breast cancer treatment. Despite the high heterogeneity, the consistent trend favoring non-pharmacologic strategies underscores their value in supportive oncology care. Integrating these interventions into clinical practice can enhance patient outcomes, improve quality of life, and contribute to more holistic cancer care.

Future research should focus on standardizing intervention protocols, understanding the sources of heterogeneity, and expanding the evidence base to diverse populations to further validate and refine these promising approaches.

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