Non-pharmacologic Interventions to Alleviate Hot Flash Symptoms Among Breast Cancer Survivors – A Systematic Review

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Abstract: Hot flash symptoms (also known as hot flush symptoms) are a major health issue for breast cancer survivors. Treatments for hot flash symptoms can be both pharmacologic and non-pharmacologic approaches. Although pharmacological interventions can reduce hot flash symptoms in the general population, selecting medications to treat hot flashes for breast cancer survivors is of concern if they can interact with tamoxifen use in these patients. Therefore, it is essential to update the scientific evidence regarding the effectiveness of non-pharmacologic approaches on reducing hot flash symptoms for breast cancer survivors. The purpose of this systematic review was to investigate the scientific evidence on the effectiveness of non-pharmacologic approaches on alleviating hot flash symptoms among this group. A comprehensive literature search was conducted electronically using ScienceDirect, Scopus, PubMed, CINAHL, and Cochrane library. Published papers in English focused on non-pharmacologic approaches and hot flash symptoms in breast cancer survivors were selected. The search reviewed studies from January 2000-December 2020. The literature review was undertaken in February 2021. The definition of non-pharmacological interventions or complementary health approaches based on the National Center for Complementary and Integrative Health was used as a systematic framework for this review. Sixteen studies were included for analysis. The findings showed that acupuncture was considered a possibly effective method for alleviating hot flash symptoms in breast cancer survivors, whereas effectiveness of other non-pharmacologic approaches, including behavioral therapy, yoga, hypnosis, homeopathy, and relaxation techniques, could not be determined because of the small number of included trials.

In conclusion, the evidence showed insufficient data to support effectiveness of non-pharmacologic approaches in reducing hot flashes for breast cancer survivors. More rigorous studies are warranted to examine these interventions. Nurses need to discuss the pro and cons of these interventions with breast cancer survivors who want to use these alternative approaches for their health.

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Introduction

Hot flashes have been reported as a distressing symptom for breast cancer survivors. About 50% of survivors reported at least one hot flash after cancer

treatments such as endocrine therapy or chemotherapy.[1] The incidence rate of hot flashes among these patients is six times greater than in healthy people.[1] In addition, it has been reported that in the first 2-3 months after taking tamoxifen, hot flashes may increasingly occur.[2]

It has been believed that cancer treatments such as endocrine therapy or chemotherapy may lead to dysfunction of thermoregulatory control.[3] Hot flashes may also be related to estrogen decline, leading to changes in the thermoregulatory set point in the anterior hypothalamus. Although the precise mechanism underlying hot flashes remains unclear,[4,5] women with breast cancer experience distress from hot flashes, resulting in sleep disturbances, pain, or other psychological issues.[1,6]

Options for hot flash treatment approaches for breast cancer survivors are more likely to be limited than for women without breast cancer. This is because the long-term risk of cancer recurrence when treated with estrogen therapy or hormone therapy is approximately 30%.[3,7] Therefore, non-hormone pharmacological treatments, such as clonidine, serotonin inhibitors, or gabapentin, may be alternative choices for treating hot flashes in women diagnosed with breast cancer. However, the benefits and risks of these options are still unclear.[3,7] The North American Menopause Society (NAMS) suggests the approach of behavioral modifications for reducing mild hot flashes.[8] These recommendations are maintaining a low core body temperature by wearing looser clothing, drinking cold liquids, or eating cold food.[8]

The non-pharmacologic approaches to modify behaviors, such as yoga, relaxation techniques, or hypnosis, have also been alternative treatment regimens for women with breast cancer suffering from hot flashes.[3] In addition, acupuncture has been reported as a potential treatment for alleviating hot flashes after breast cancer treatments. Many previous scholars focused more on testing the effectiveness of acupuncture on reducing hot flash symptoms women treated for breast cancer than other alternative approaches.[9-14] One systematic review focused on non-hormonal intervention for hot flashes in women diagnosed with breast cancer;[15] however, it was conducted before 2010. Another review included both patients diagnosed with breast cancer and prostate cancer in their review.[16]

Therefore, the goal of this systematic review was to investigate the scientific evidence on the effectiveness of non-pharmacologic approaches on reducing hot flash symptoms among breast cancer survivors from January 2000-June 2020. The broad research question was: *Which types of non-pharmacologic approaches have been reported to alleviate hot flash symptoms of breast cancer survivors?* More specifically we set out to determine in this review: *For breast cancer survivors [P], do non-pharmacologic interventions (i.e., acupuncture, hypnosis, yoga, homeopathy, relaxation technique, medication, cognitive-behavioral therapy, physical therapy or biofeedback) [I], compared to sham intervention or placebo [C], reduce hot flash frequency and/or hot flash severity [O] after treatment [T]?* We expected that this updated review would enable us to summarize beneficial information regarding non-pharmacologic approaches to alleviate hot flash symptoms in breast cancer survivors that may be applied to develop nursing interventions for better quality of life for these women.

After being treated with breast cancer, such as chemotherapy, radiation therapy, or hormone therapy, many breast cancer survivors experience hot flash symptoms due to estrogen deprivation.[8] Hot flash symptoms can affect quality of life in breast cancer survivors, as they reported greater fatigue, poorer sleep, and worse quality of life.[1] Hormone therapy is one option to reduce hot flash symptoms. Unfortunately, this option raises concern about cancer recurrence for breast cancer survivors.[7] The pharmacological approaches, included gabapentin and venlafaxine, were the only therapies rated as likely to be effective for reducing hot flashes.[16] In addition, another issue of concern for selecting medications to treat hot flashes in breast cancer survivors is that the effective pharmacologic hot flash treatments should not interact with tamoxifen use in these patients.[16] Therefore, non-pharmacologic

interventions are other alternative choices in this population, as fewer side effects from non-pharmacological interventions were reported when compared to pharmacologic treatments.[7]

A non-pharmacological intervention refers to any type of health intervention which is non-medication, is science-based, and is a non-invasive intervention to prevent or cure health problems. Its names are known under several designations, such as non-pharmaceutical interventions, non-pharmacological treatments, complementary and alternative medicines, or complementary health approaches.[17] The National Center for Complementary and Integrative Health (NCCIH) in the USA categorized complementary health approaches or non-pharmacological interventions into three types, including: 1) natural products, i.e., herbs, vitamins and minerals, and probiotics; 2) mind-and-body practices, i.e., yoga, relaxation, hypnotherapy, or manipulation; and 3) other complementary health approaches, i.e., ayurvedic medicine, traditional Chinese medicine, homeopathy, or naturopathy.[18] However, in terms of non-pharmacological interventions for reducing hot flash, herbs with the following compounds have been shown that they have possible estrogen-like mechanisms: plant phytoestrogens, black cohosh, or Cimicifuga racemose, tibolone.[15] Therefore, in this systematic review, studies to examine the effects of herbs on reducing hot flashes in breast cancer survivors were excluded.

Hot flashes can be assessed by both subjective and objective methods, as the two measures can be beneficial for each other.[19] Subjective ratings of frequency and severity of hot flashes can be used as two co-primary endpoints in clinical trials for hot flash interventions.[19] Examples of common tools to measure severity and frequency of hot flashes were Daily Hot Flash Diary, Hot Flash Rating Scale, Hot Flash Behavior Scale, Hot Flash Related Daily Interference Scale, and the Kupperman Menopausal Index.[20] In addition, objective measures of hot flashes are invaluable in characterizing the mechanisms and physiology of hot flashes.[19] Objective measures of hot flashes include increases in heart rate, finger blood flow, respiratory exchange ratio, skin temperature, and core body temperature.[21]

A previous systematic review reported that among four non-pharmacological therapies included in the systematic review, only relaxation therapy was more likely to reduce frequency and severity of hot flashes. Other non-pharmacological approaches, including homeopathy, acupuncture, and magnetic therapy show no differences in the number and severity of hot flashes.[15] Another study provided an overview of the intervention to manage hot flashes in patients diagnosed with breast cancer and prostate cancer.[16] The authors concluded that the efficacy of dietary or lifestyle interventions, such as cognitive behavioral intervention, exercise, or yoga, in reducing hot flashes in such could not be confirmed due to limited high-quality evidence.[16]

Methods

Search strategy and eligible criteria: The Cochrane guidelines for conducting systematic reviews were used for this review and the Preferred Reporting for Systematic Reviews (PRISMA) was used to describe the refinement process.[22] Literature was searched from five electronic databases, CINAHL, ScienceDirect, Scopus, PubMed, and Cochrane library, by using the criteria of English language and studies published between January 2000 and December 2020. The literature review was undertaken in February 2021. The definition of non-pharmacological interventions or complementary health approaches based on the National Center for Complementary and Integrative Health[17] was used as a systematic framework for conducting this review. A combination of the following keywords was used: 'non-pharmacologic approaches,' 'non-pharmacological interventions,' 'non-hormonal treatments' and 'psychological interventions,' 'acupuncture,' 'hypnosis,' 'yoga,' 'homeopathy,' 'relaxation techniques,' 'meditation,' 'cognitive behavioral therapy,' 'physical therapy,' 'biofeedback,' and 'hot flash,' 'hot flushes,'

'vasomotor symptom,' 'menopause,' and 'breast cancer patients,' 'breast cancer survivors,' 'women diagnosed with breast cancer,' 'patients with breast tumor,' and 'patients with breast cancer,' For example, the search query for PubMed included: "non-pharmacologic approaches" [MeSH] OR "non-pharmacological interventions" [MeSH] OR "non-hormonal treatments" [MeSH] OR "psychological interventions" [MeSH] AND "hot flash" [MeSH] OR "hot flushes" [MeSH] OR "vasomotor symptom" [MeSH] OR "menopause" [MeSH] AND "breast cancer patients" [MeSH] OR "breast cancer survivors" [MeSH] OR "women diagnosed with breast cancer" [MeSH] OR "patients with breast tumor" [MeSH] OR "patients with breast cancer".

Inclusion criteria: Randomized controlled trials (RCTs) comparing two or more groups of women diagnosed with breast cancer experiencing hot flashes due to breast cancer treatments were included. The study must have had non-pharmacologic approaches categorized by the NCCIH, except for natural products as a previous study proved that some ingredients of herbs had worked as estrogen therapy. Thus, they would be categorized as hormone therapy, not non-pharmacological approaches.[15] Examples of non-pharmacological interventions included in the review were: acupuncture, hypnosis, yoga, homeopathy, relaxation techniques, meditation, cognitive behavioral therapy, physical therapy, or biofeedback. Hot flash frequency and severity served as primary outcome measures.

Exclusion criteria: Study designs such as qualitative, cross-sectional, longitudinal, or case study or studies evaluating herbs or plants, such as soy or black cohosh, were excluded.

Study selection: Two reviewers independently screened the search results. They identified potentially relevant studies from titles and abstracts. When the papers appeared to meet the inclusion criteria, full texts were obtained. If there was disagreement for selection paper, consensus with a third reviewer was applied.

Data extraction and synthesis: Data were extracted from the full-text articles to an Excel spreadsheet designed for this systematic review and research questions. The final data extraction form was addressed in the report for the complete literature table (**Table 1**). The extraction form was pilot-tested before actual data collection was conducted. All papers were double-extracted by authors to assure consistency independently. A third reviewer was involved if there was any disagreement. Extracted data included bibliography, samples, study design, results, and the risk-of-bias score. Data synthesis for the main findings were tabulated from the included studies in line with the PICOS approach to provide a summary of the data.

Assessment of risk of bias in included studies: Two reviewers independently investigated the risk of bias and inconsistencies of assessment was solved with a third expert. We used the Cochrane risk of bias tool.[23] This is composed of seven categories including: 1) generation of allocation sequence; 2) concealment of allocation sequence; 3) blinding (participants and personnel); 4) blinding outcome assessment; 5) incomplete outcome data; 6) selection of reporting; and 7) other sources of bias.[23] The scores of the risk of bias were based on only published material. Therefore, it was not possible to definitively decide if each quality criteria were met or unmet, as many items remained unclear (**Appendix 1**).

The quality of included studies was assessed using the Jadad scale. Two reviewers independently investigated the quality of included studies and inconsistencies of assessment was solved with a third expert. The Jadad scale comprises the following subscales: randomization, double-blinding, description of withdrawals, and dropouts. This validated scale has scores ranging from 0-5: 0-2 referring to low quality and 3-5 referring to high quality.[24] The quality score of each study is reported in **Table 1**.

We did not conduct a meta-analysis in this literature review, as the included studies were too dissimilar in the methods, such as time frame of follow-up, measures to assess outcomes, and types of interventions.[25]

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
Acupuncture					
Deng et al., 2007	2-arm RCT with 72 women with breast cancer who experienced hot flashes (Undergoing breast cancer treatments) Age 48-59 years (mean=55) - Acupuncture group (n=42) - Sham acupuncture group (n=30) Location: New York, US	Acupuncture or sham acupuncture was provided twice a week for 4 weeks.	- Hot flash diary for hot flash frequency - Times of measurement: baseline, 6 weeks, and 6 months after treatment	Hot flash frequency in both groups was reduced over time, but the difference did not reach statistical significance (95% CI, -0.7 to 2.4; p=0.3).	5
Frisk et al., 2008	2-arm with 45 women with breast cancer who experienced hot flashes (Completed breast cancer treatments, ongoing tamoxifen). Age 53.4-56.5 years - Electroacupuncture group (EA) (n=27) - Hormone therapy group (HT) (n=18) Location: Linköping, Sweden	The electro-acupuncture, treatment was given by a physiotherapist for 30 minutes twice a week for the first 2 weeks, and once a week for 10 weeks. The hormone therapy group was given a sequential estrogen/ progesterone combination.	- Hot flash diary for hot flash frequency and distress, Kupperman's index - Time of measurement: baseline, 4, 6, 9, 12, 18, and 24 months after treatment	Significant changes were seen in numbers of and distress due to hot flashes in both groups at all measuring points. In EA group, the hot flashes returned to some degree. At 12 months, 5 participants requested an additional treatment. At 12 months, the HT group significantly had lower number of flushes/24 hours, distress caused by hot flashes and the Kupperman's index (KI) than those in the EA group ($p< 0.001$, $p<0.001$, $p=0.002$, respectively). At 24 month, 12 women reported a decrease in number of hot flash (p=.003).	5
Hervik et al., 2009	2-arm with 59 women suffering from hot flashes following breast cancer surgery and adjuvant oestrogen-antagonist treatment (Completed breast cancer treatments, received tamoxifen) Age 52.3-53.6 years - Acupuncture group (TA) (n=30) - Sham acupuncture group (SA) (n=29) Location: Tønsberg, Norway	Both TA and SA were given as 30 minutes twice a week for the first 5 weeks and once a week for 5 weeks.	- Number of hot flashes at day and night, Kupperman index (KI) - Time of measurement: baseline, during treatment, and at 12 weeks after treatment	During the treatment period, number of hot flashes in the TA group was significantly reduced about 50-60% and was further reduced by 30% during the next 12 weeks. In the SA group, hot flashes numbers per day was reduced by 25% during treatment, but was reversed during the next 12 weeks. No reduction was found in hot flashes at night.	5

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer (Continued)

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
				At the end of treatment, Kupperman index in the TA group was reduced by 44%, and maintained for 12 weeks, but no changes were seen in the SA group.	
Liljegen et al., 2010	2-arm RCT with 84 women with breast cancer received tamoxifen and experienced hot flashes Age 36-80 years - True acupuncture group (n=42) - Superior control group (n=42) Location: Stockholm, Sweden	Both true and control acupunctures were given for 20 minutes twice a week for 5 weeks.	- Hot flushes and sweating frequencies Circulating levels of estradiol, progesterone, testosterone, prolactin, follicle stimulating hormone (FSH), luteinising hormone (LH), and sex hormone binding globulin (SHBG) - Time of measurement: baseline, weeks 6, and 18	Both groups reported improvement of severity and frequencies of hot flushes and sweating, but no statistical difference was found between the groups. Hormonal levels were not changed.	4
Walker et al., 2010	2-arm RCT with 50 women with breast cancer who received antiestrogen hormone therapy (Completed breast cancer treatments, ongoing tamoxifen). Age 35-77 years (mean=55) - Acupuncture group (n=25) - Venlafaxine group (n=25) Location: Michigan, US	Acupuncture was provided twice a week for the first 4 weeks, then once a week for the remaining 8 weeks. Patients took venlafaxine 37.5 mg. at night for 1 week, then 75 mg. for the following 11 weeks.	- Hot flash diary measured the number and severity of hot flashes; the Menopause Specific Quality of Life Questionnaire (MenQOL); the Short Form-12 Item Survey (SF-12) measured general health status; the Beck Depression Inventory-Primary Care (BDI-PC) measured mental health; the National Cancer Institute Common Toxicity Criteria Scale measured adverse effects of treatment - Time of measurement: baseline, 1, 3, 6, 9, and 12 months after treatment	Both groups significantly decreased hot flashes, depression, quality of-life, and mental health ($p<0.05$). At 2 weeks post-treatment, the venlafaxine group significantly increased hot flashes, but the acupuncture group reported hot flashes at low levels. The venlafaxine group had 18 incidences of adverse effects, whereas the acupuncture group had no adverse effects.	3

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer (Continued)

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
Frisk et al., 2012	2-arm with 45 women with breast cancer who experienced hot flashes. (Completed breast cancer treatments, ongoing tamoxifen) Age 47-69 years (mean=54.1) - Electroacupuncture group (EA) (n=27) - Hormone therapy group (HT) (n=18) Location: Linköping, Sweden	The Electroacupuncture, treatment was given by a physiotherapist for 30 minutes twice a week for the first 2 weeks, and once a week for 10 weeks. The hormone therapy group was given a sequential estrogen/progesterone combination.	- The patients recorded daily in log-books the numbers of hot flushes per day and night and distress by flushes, no. of times woken up/night and hours slept The Swedish version of WHQ and Psychological and General Well-Being Index (PGWB) - Time of measurement: baseline, 3, 6, 9, 12, 18, and 24 months after treatment	After intervention, WHQ and PGWB scores in the EA group significantly improved ($p<0.001$, $p=0.002$, respectively). All sleep parameters improved and hot flash score (HFS) decreased by 80%. At 12 months, WHQ, PGWB, and all sleep parameters remained significantly improved (n=14) and HFS score decreased by 65%.	3
Bokmand et al., 2013	3-arm RCT with 94 women with breast cancer who experienced hot flashes after post-surgery and antihormone therapy Age 45-76 years (mean=61) - Acupuncture group (n=31) - Sham acupuncture group (n=29) - No treatment group (n=34) Location: Copenhagen, Denmark	Acupuncture or sham acupuncture in the selected points 15-20 min once a week for five consecutive weeks.	- Subjective Visual Analog Scale (VAS) for nuisance of hot flashes, and sleep disturbance, plasma estradiol - Time of measurement: baseline, 30 minutes after treatment, and 5 weeks later	52% of patients in the acupuncture group and 24% of the patients in the sham group experienced a significant effect such as shot flashes ($p < 0.05$).	4
Bao et al., 2014	2-arm RCT with 51 women with breast cancer who received aromatase inhibitors (AIs). Age 44-85 years (mean=61) - Real acupuncture (n=25) - Sham acupuncture (n=26) Location: Maryland, US	Patients in the real acupuncture group (RA) or sham group (SA) received acupuncture for 8 weeks.	- The National Surgical Adjuvant Breast and Bowel Project (NSABP) menopausal symptoms questionnaire, the Center for Epidemiological Studies Depression (CESD) scale, the Hospital Anxiety and Depression Scale (HADS), the Pittsburgh Sleep Quality Index (PSQI), the hot flash daily diary, the Hot Flash-Related Daily Interference Scale (HFRDI), and the European quality-of-life survey (EuroQol) - Time of measurement: baseline, 4, 8, and 12 weeks	At week 8, the RA group significantly improved on the CESD score ($p=0.022$), hot flash severity ($p=0.006$), hot flash frequency ($p=0.011$), the HFRDI $p=.014$), and NSABP menopausal symptoms ($p=0.022$); whereas the SA arm significantly improved on the EuroQol ($p=0.022$), the HFRDI ($p=0.043$), and NSABP menopausal symptoms ($p=0.005$). No significant difference between arms was found in patient-reported outcomes (PROs). Post-hoc analysis indicated that RA reduced hot flash severity ($p<0.001$) and hot flash frequency ($p<0.001$) more than SA.	4

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer (Continued)

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
Mao et al., 2015	4-arm RCT with 120 women with breast cancer who experienced hot flashes after breast cancer treatments Age 30-79 (mean=52.3) - Electroacupuncture group (EA) (n=30) - Sham acupuncture group (SA) (n=32) - Gabapentin group (GP) (n=30) - Placebo group (PP) (n=28) Location: Philadelphia, US	Electroacupuncture or sham acupuncture was provided twice a week for 2 weeks, then once a week for 6 more weeks. Gabapentin 900 mg. or placebo pills once per day	- Hot flash composites score (HFCS) - Time of measurement: baseline, 4, 8, and 12 weeks	By week 8, the most reduction in HFCS was found in the EA, SA, GP, and PP groups, respectively (-7.4 v -5.9 v -5.2 v -3.4; p ≤0.001). The pill groups had more adverse effects than those in the acupuncture groups (p<0.005). By week 24, the most reduction of HFCS was found in the EA, SA, PP, and GP groups, respectively (-8.5v-6.1v-4.6v-2.8; p=0.002).	4
Lesi et al., 2016	2-arm RCT with 190 women with breast cancer who experienced hot flashes (Ongoing breast cancer treatments- hormone therapy and/or gonadotropin-releasing hormone) Age 31-65 (mean=49) - Acupuncture group (n=85) - Self-care group (n=105) Location: Northern, Italy	The acupuncture group received 10 traditional Chinese medicine acupuncture sessions once per week for 12 weeks combined with self-care recommendations.	- Daily hot flash score (HFS), climacteric symptoms and quality of life measured by the GCS and Menopause Quality of Life (MenQoL) scales - Time of measurement: baseline, 12 weeks, and 3 and 6 months follow-up	At the end of treatment, acupuncture combined with self-care significantly reduced hot flash than those in the self-care group (p<0.001). The low hot flashes still remained at Month 3 and 6 (p=0.0028 and .001, respectively). Acupuncture was also significantly reduced climacteric symptoms and improved quality of life (p<0.05).	5
Other non-pharmacologic approaches					
Jacobs et al., 2005	3-arm RCT with 83 women with breast cancer who experienced hot flashes. (Completed breast cancer treatments) - Single remedy group (n=26) - A homeopathic combination group (n=30) - Placebo group (n=27) Location: Seattle, WA, US	An individualized homeopathic single remedy, a homeopathic combination medicine, or placebo. Patients were seen by homeopathic providers every 2 months for 1 year.	- Hot flash frequency and severity, Kupperman Menopausal Index (KMI), Short Form 36 (SF-36) - Time of measurement: baseline, 3 months, and 12 months	No significant difference found in the hot flash severity score. During the first 3 months of the study, a positive trend in the single remedy group was found (p=0.1). At 1 year, both homeopathy groups showed statistically significant improvement in general health score (p< 0.05).	4

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer (Continued)

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
Ganz et al., 2000	2-arm RCT with 76 women with breast cancer who experienced hot flashes (completed breast cancer treatments, receiving tamoxifen) Age 54.5 years - Intervention group (n=37) - Control group (n=39) Location: LA, US	The intervention group received an individualized plan of education, counseling, pharmacologic and/or behavioral interventions, psychosocial support, referrals, and follow-up tailored to each women's individual needs and preferences. The intervention took 4 months	- Menopausal Symptom Scale Score adapted from the Breast Cancer Prevention Trial Symptom Checklist for severity of hot flashes. Vitality Scale from the RAND 36-Item Health Survey 1.0 (Medical Outcomes Study SF-36) measured QOL. Sexual Summary Scale from the Cancer Rehabilitation Evaluation System - Time of measurement: baseline and 4 months follow-up	Compared to the control group, the intervention demonstrated statistically significant improvement in menopausal symptoms ($p=0.0004$), sexual functioning ($p=0.04$), but not for vitality ($p=0.77$).	3
Mann et al., 2012	2-arm RCT with 96 women with breast cancer and experienced hot flashes (Completed breast cancer treatments, taking endocrine therapy) Age 53.16-54.05 years - Cognitive behavioral group (CBT) (n=47) - Usual group (n=49) Location: London, UK	The group CBT took 90 minutes class once a week for 6 weeks, including: various activities, such as education, group discussion, and homework	- The primary outcome is problem rating of hot flashes and night sweating (HFNS) post-treatment assessment - Time of measurement: baseline, 9 weeks, and 26 weeks after randomization	At 9 weeks, the CBT group had significantly reduced HFNS scores ($p<0.001$) and those scores remained for 26 weeks ($p<0.001$).	4
Fenlon et al. 2008	2-arm RCT with 150 women diagnosed with primary breast cancer, experienced hot flashes (completed breast cancer treatments, taking tamoxifen) Age 51.6-60.3 years - relaxation group (n= 74) - control group (n=76) Location: London, UK	A single 1-hr relaxation training session by an occupational therapist, and continued practice at home following an audiotape for one month	- Hot flashes diary, the Hunter menopause scale, the FACT-ES, and the STAI - Time of measurement: baseline, 3 and 6 months after randomization	Number and severity of hot flashes, and distress from hot flashes significantly reduced over one month in intervention group ($p< 0.001$, $p=0.01$, $p=.01$ respectively). No changes in anxiety and quality of life measures.	3

Table 1. Summary of the effects of non-pharmacologic approaches on reducing hot flashes in women with breast cancer (Continued)

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Jadad Score
Elkins et al., 2008	2-arm with 60 women with primary breast cancer who experienced hot flashes, taking tamoxifen or raloxifene Age 55-58 years - Hypnosis group (n=30) - Control group (n=30) Location: Texas, US	The hypnosis intervention was delivered by a clinician for approximately 50 minutes for each session for 5 weeks.	- The Hot Flash Related Daily Interference Scale (HFRDIS), Center for Epidemiologic Studies Depression Scale (CES-D), Hospital Anxiety and Depression Scale-Anxiety Subscale (HADS-A), and Medical Outcomes Study Sleep Scale (MOS-Sleep Scale) - Time of measurement: baseline and after treatment	At the end of the treatment, the hypnosis group had significantly reduced hot flash scores for about 68% ($p<0.001$). In addition, anxiety, depression, interference of hot flashes on daily activities and sleep were significantly reduced for patients in the hypnosis group ($p< 0.005$).	3
Carson et al., 09	2-arm RCT with 37 women with breast cancer who experienced hot flashes (Completed breast cancer treatments, taking tamoxifen) Age 53.9-54.9 (mean=54.5) - Yoga group (n=17) - Wait-list group (n=20) Location: North Carolina, US	The intervention consisted of eight weekly 120-min group classes (5-10 patients per group).	- Daily diary measurement strategy - Time of measurement: baseline, post-treatment, and 3 months after treatment	At post-treatment, the yoga group had significantly greater improvement for hot-flash frequency/severity, joint pain, fatigue, sleep disturbance, symptom-related bother, and vigour ($p<0.05$). At 3 months, the yoga group still maintained those symptom scores with an additional significant improvement of negative mood, relaxation, and acceptance ($p<0.05$).	4

Results

From a total of 1,056 articles initially retrieved and reviewed, a final 16 papers were included in this systematic review (see **Figure 1**).

Risk of bias and quality of included studies: All 16 included studies were judged at low risk of bias (**Figure 2**). For the quality of the included studies assessed by the Jadad scale, the findings showed that all 16 studies were validated at high quality (scores ranging from 3-5) (**Table 1**).

Type of included studies: Trials included 10 RCTs of acupuncture, two RCTs of behavioral therapy, and one RCT each of: relaxation techniques, hypnosis, yoga, and homeopathy. Most studies were 2-arm RCTs (n=12), followed by 3-arm RCTs (n=3), and a 4-arm RCT (n=1).

Participants: 16 studies involving 1,312 participants (ranging from samples of 37 to 190) from six countries met the inclusion criteria of the systematic review. Their age range was 30-85 years. Eight studies were conducted in the United States, with the rest conducted in Sweden (n=3), the UK (n=2), Norway (n=1), Denmark (n=1), and Italy (n=1). The majority of participants had completed breast cancer treatments of surgery, radiation, or chemotherapy, and had undergone tamoxifen use.

Types of interventions: Based on types of complementary health approaches, as categorized by the NCCIH, the results of the systematic review showed that mind-and-body practice were the most common type of interventions examined among breast cancer survivors who experienced hot flashes. These included:

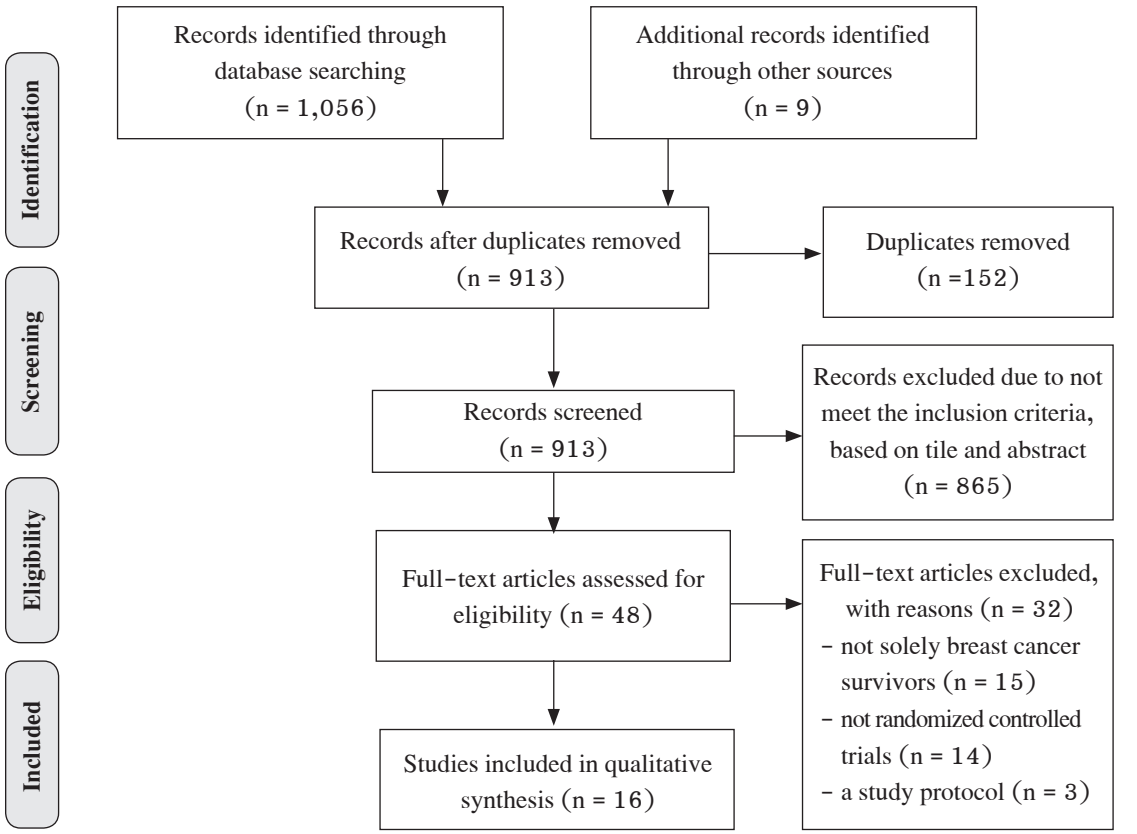

Figure 1. Literature review PRISMA flow diagram

	Adequate sequence generation	Allocation concealment	Adequate blinding–participant and personnel	Adequate blinding–outcome assessor	Incomplete outcome data assessment	Selective reporting bias	Other bias	Overall Judgment for Risk of bias
Deng et al. (2007)	+	+	+	+	+	+	+	+
Frisk et al. (2008)	+	+	?	?	+	+	+	+
Hervik et al. (2009)	+	+	+	+	+	+	+	+
Liljegen et al. (2010)	+	+	+	?	+	+	+	+
Walker et al. (2010)	+	+	?	+	+	+	+	+
Frisk et al. (2012)	+	+	?	?	+	+	+	+
Bokmand et al. (2013)	+	+	+	?	+	+	+	+
Bao et al. (2014)	+	+	+	+	+	+	+	+
Mao et al. (2014)	+	+	+	+	+	+	+	+
Lesi et al. (2016)	+	+	?	?	+	+	+	+
Jacobs et al. (2005)	+	+	+	+	–	+	+	+
Ganz et al. (2000)	+	?	?	?	+	+	+	+
Mann et al. (2012)	+	–	+	+	+	+	+	+
Fenlon et al. (2008)	+	+	+	?	–	+	+	+
Elkins et al. (2008)	+	?	?	?	+	+	+	+
Carson et al. (2009)	+	+	?	+	+	+	+	+

Symbols: – = High risk; + = Low risk; ? = Unclear

Figure 2. Risk of Bias Analysis

acupuncture, cognitive behavioral therapy, hypnosis, yoga, and relaxation, followed by another type of complementary health approach, namely, homeopathy. It was also found that 10 of the 16 studies examined the effects of acupuncture,[26-35] and all reported acupuncture procedures were provided to patients by either trained acupuncturists or physiotherapists who were trained for acupuncture. The majority of included studies used traditional acupuncture. Only two studies tested the electro-acupuncture treatments.[31,34] For the frequency and duration of acupuncture intervention, most studies provided acupuncture twice a week for 4-12 weeks. Only three studies provided acupuncture once a week for 5-12 weeks.[32-35]

In terms of other mind-and-body practices, two studies examined the effects of cognitive behavioral therapy on reducing hot flashes in breast cancer survivors.[37-38] The program included psycho-educational activities either through individual or group activities. The other four studies also examined mind-and-body practices on reducing hot flashes in breast cancer survivors. One study tested yoga that was provided by the trainer for 120 minutes/class for 8 weeks,[41] one study examined hypnosis for 50-minute sessions for 5 weeks,[40] and finally, one study examined the effects of relaxation 1-hour training session by the occupational therapist plus self-practice at home for one month.[39] Only one study conducted an RCT to examine another type of complementary health approach, namely homeopathy provided by homeopathic providers every two months for one year.[36]

Outcome measures: The primary outcome measures reported in the included studies most frequently focused on both hot flash frequency and severity (n= 9 studies, 56.25%).[29-30,33-36,39-41] Five studies (31.25%) focused only on hot flash frequency.[26-28,31,38] Two studies (12.5%) focused only on hot flash severity.[32, 37] Of 16 included studies, 56.25% (n= 9 studies) used hot flash diary;[26,30-31,33-35,39-41] two (12.5%) used a hot flash diary combined with the Kupperman Menopausal Index;[27,36] while one study (6.25%) used only this Index;[28] The rest (25%, n=4)) used other measures, such as a vasomotor symptoms scale,[29] a subjective visual analog scale (VAS)[32] plus plasma estradiol level; a Menopausal Symptom Scale Score adapted from the Breast Cancer Prevention Trial Symptom Checklist,[37] and a Hot Flash Rating Scale.[38]

In addition, other psychological aspects associated with hot flash symptoms, such as quality of life, daily interference, sleep disturbance, anxiety, and depression, were assessed with various tools in eight of 16 studies (50%). Examples of tools to measure quality of life found in this systematic review were: the Psychological and General Well-being Index (PGWB);[31] the European Quality of Life Survey (EuroQoL);[33] the Menopause Quality of Life (MenQoL) Scale;[30,35] the General Health Survey Short Form 36 (SF-36);[37-38] the Women's Health Questionnaire (WHQ);[38] and the Functional Assessment of Cancer Therapy with the endocrine subscale (FACT-ES).[39]

Daily interference related to hot flash symptoms was also measured by the following tool: Hot Flash Related Daily Interference Scale (HFRDIS).[33,40] Similarly, the following tools were used to measure sleep disturbance related to hot flash symptoms of breast cancer survivors: the Women's Health Questionnaire (WHQ);[31] the Pittsburgh Sleep Quality Index (PSQI);[33] and the Medical Outcomes Study Sleep Scale (MOS-Sleep Scale).[40]

Finally, anxiety and depression were other psychological aspects found in this systematic review. Anxiety was measured by two tools, the Spielberger State/Trait Anxiety Index (STAI),[39] and the Hospital Anxiety and Depression Scale-Anxiety Scale (HADS-A).[40] Depression was measured with the following tools, including the Beck Depression Inventory-Primary Care (BDI-PC),[30] the Center for Epidemiologic Studies Depression Scale (CES-D),[33,40] and the Hospital Anxiety and Depression Scale-Anxiety Scale (HADS-A).[33,40]

Reported efficacy of non-pharmacologic approaches for alleviating hot flash symptoms in breast cancer survivors: All included studies showed

that mind-and-body practices were the type of non-pharmacological interventions that had been most investigated for their effectiveness on reducing hot flash frequency and severity, followed by cognitive behavioral therapy, relaxation, hypnosis, and yoga. Another type of non-pharmacological approach was homeopathy.

Mind-and-body practices

Acupuncture: Pooling the data from 10 reviewed studies that investigated the effectiveness of acupuncture on reducing hot flashes among women diagnosed with breast cancer, it was likely that acupuncture was potentially beneficial for reducing both frequency and severity of hot flashes after cancer treatment.

Regarding hot flash frequency, the findings of this systematic review showed that six of nine studies (66.67%) focused on hot flash frequency reporting a positive effect of acupuncture on reducing hot flash frequency among breast cancer survivors.[28,30-35] Only three studies reported a non-significant outcome.[26,27,29] Similarly, for hot flash severity, five of six studies (83.33%) focused on hot flash severity reported a positive effect of acupuncture on reducing hot flash severity of breast cancer survivors.[32-35] Only one study reported a non-significant outcome.[29]

Durations for acupuncture varied from 4 -12 weeks with each session taking approximately 15 - 30 minutes. However, based on the included studies, durations of acupuncture from 8 - 12 weeks [27-28, 30-31, 33-34] were likely to be more effective than durations of 4 -5 weeks[26,29] of treatment for reducing hot flash frequency and severity among women treated for breast cancer. Interestingly, it appeared that acupuncture was still associated with decreasing symptoms of hot flash frequency and severity for about six months after acupuncture treatment ended, [34-3- but not 12 months after treatment ended. Two studies in this review reported that, although reduction of hot flashes was still effective 12 months after treatment, additional treatments for hot flashes were needed for breast cancer survivors.[27,31]

One study compared acupuncture with self-care; the results showed that acupuncture could reduce hot flash frequency and severity for women with breast cancer experiencing hot flashes more than those in the self-care group ($p < .001$).[35] Compared to the pharmacologic treatments, one study reported that acupuncture could reduce hot flash frequency in women with breast cancer significantly less than hormone therapies ($p < .001$).[31] However, two previous studies reported that patients receiving the acupuncture intervention did not report adverse effects, whereas participants treated with venlafaxine and gabapentin reported gastrointestinal and fatigue effects.[30,34]

Finally, most included acupuncture studies compared the effects of real acupuncture with sham acupuncture.[28-29, 32-34] When comparisons were made between these two procedures, three of four studies (75%) that focused on hot flash frequency outcome showed that real acupuncture reduced hot flash frequency significantly more than those in the sham acupuncture groups,[28, 33-34] whereas one study reported that the difference did not reach statistical significance.[29] Similarly, three of four studies that focused on hot flash severity showed that real acupuncture significantly reduced the severity more than those in the sham acupuncture,[32-34] whereas one study reported non-significant difference between these two procedures.[29]

However, due to methodologic issues, such as small sample size,[26-33] no details available to decide whether assessors and participants were blinded,[27,29-32,35] or incomplete outcome data assessment in the included studies,[36,39] whether acupuncture can enhance reduced hot flash symptoms among women diagnosed with breast cancer cannot be definitively confirmed.

Other non-pharmacological approaches: Four mind-and-body therapies (behavioral therapy, relaxation, hypnosis, and yoga) and homeopathy were examined for their effectiveness in enhancing reduction of hot flash symptoms for breast cancer survivors in six trials. In five of these, only one study, namely homeopathy, reported non-significance of

the approach in decreasing hot flash frequency and severity among breast cancer survivors. [36] In contrast, the other interventions (behavioral therapy, relaxation, hypnosis, and yoga) were found to be significantly effective for women with breast cancer experiencing hot flash symptoms in both frequency and severity.[37-41] Unfortunately, only one study was found for each intervention. Therefore, it is difficult to definitively conclude whether these non-pharmacologic approaches effectively reduce distress from hot flash symptoms among breast cancer survivors or not.

Discussion

This review identified a small number of RCTs testing the effective of non-pharmacologic approaches for reducing hot flashes in women diagnosed with breast cancer. Acupuncture was found to be most examined for its effectiveness in reducing hot flashes in both frequency and severity.[26-35]

Regarding hot flash frequency, our found that six of nine studies (66.67%) reported a positive effect of acupuncture on reducing hot flash frequency of breast cancer survivors.[28,30-35] Most studies also reported positive effects of acupuncture on hot flash frequency among breast cancer survivors experiencing hot flashes when compared to sham acupuncture.[28,33-34] The findings of this review concur with a previous systematic review conducted in 2016 reporting that acupuncture was more likely to be an effective therapy for hot flash frequency in breast cancer survivors.[10] However, poor quality research design and the small number of included studies were concerning.[10]

For hot flash severity, this systematic review showed that five of six studies (83.33%) reported a positive effect of acupuncture on reducing hot flash severity of breast cancer survivors.[32-35] Additionally the findings from this systematic review were not consistent with a previous meta-analysis conducted in 2017 that reported no significant effects of acupuncture on frequency and severity of hot flashes among breast cancer survivors.[12] The authors of a previous study explained that acupuncture might had an effect, but the effect was too small due to many factors, such as seasonal changes or use of subjective tools to measure hot flashes, rather than objective measures. The tools to measure hot flash symptoms in breast cancer survivors in the included studies in our review also found that most studies used subjective measures more than objective measures. Therefore, further research may need to use both subjective and objective measures, as the two measures can be mutually beneficial.[19]

In addition, this incongruency with the earlier systematic review might be because of some other factors influencing hot flashes, i.e., different types of adjuvant treatment therapy or stage of breast cancer.[2-3] So, more rigorous research is needed to confirm these findings. Although small sample sizes and various measures are of concern, some previous studies showed that acupuncture had an effect similar to pharmacologic treatments in terms of reducing hot flashes, but with fewer adverse effects.[30,34] Therefore, further studies to confirm these findings are needed because, in patients' perspectives, decision-making about hot flash treatments will be based on both effectiveness and side effects.[7] The findings of this systematic review are consistent with a previous one which showed unproven effectiveness of the acupuncture approach for reducing hot flash symptoms.[11]

Based on this systematic review, in addition to acupuncture, we found that research on other non-pharmacologic approaches for reducing hot flash symptoms in breast cancer survivors is lacking. This may be because our review was conducted using only papers written in English, and not using studies for example in other languages and may have in fact demonstrated otherwise. As reported by WHO, European, America, and Western regions had national policies, offices, programs and research institutes for traditional and complementary and alternative medicines significantly behind the global averages, compared to African, Asia, and Eastern

Mediterranean Regions.[42] Only one paper was reported for each of the other five non-pharmacologic approaches with promising findings. Although some studies showed positive effects in reducing hot flashes for breast cancer survivors,[37-41] more work is needed so that we can better inform women who want to use those non-pharmacologic approaches when suffering from hot flash symptoms.[2] In addition, even though some non-pharmacologic approaches such as homeopathy might not be directly beneficial for reducing hot flash symptoms among women diagnosed with breast cancer,[36] other potential benefits, such as psychological aspects, should be considered for future study.[43] As can be seen from this systematic review, three papers showed that acupuncture could significantly improve quality of life for breast cancer survivors experiencing hot flashes.[30,31,35] In contrast, Fenlon et al.[39] found that quality of life of women who received relaxation techniques was not changed.

Limitations

This systematic review has several limitations that must be considered. First, the included studies in this review were limited only to English language publications and did not include other languages. Consequently, some studies related to non-pharmacologic intervention to reduce hot flash symptoms in breast cancer survivors might not have been reviewed. Secondly, only published materials were used to assess risk of bias and we did not contact authors to seek clarification. The included studies in this systematic review also had some limitations. Small sample size in each study should be noted here. Therefore, more rigorous RCTs with large samples are needed. Although the risk of bias in the studies was at low level, some studies did not provide details on whether participants and assessors were blinded.[27,29-32,35] The randomized double-blind placebo-control studies in which participant, investigator, and data-cleaning persons are blinded are considered as the "gold standard" in intervention studies.[44] However, some situations in clinical setting may not be amenable to blinding health care providers. In this case, single-blind (participant) or double-blind (participant and investigator) may be possible for consideration in future RCTs.[44] Similar to a previous systematic review,[10] most included studies used diary self-report measures as a sole tool for recording hot flash frequency and severity. Therefore, future research using additional well-tested quantitative measures for hot flash symptoms will enhance assessment of evidence for intervention outcomes. Moreover, this systematic review included only two types of complementary health approaches, (mind-and-body practices and another type, homeopathy, not including natural products). Further systematic review may investigate the effectiveness of herbs or natural products used by breast cancer survivors to alleviate hot flash symptoms. Finally, although the effectiveness of non-pharmacological interventions on hot flash symptoms was not warranted, many RCTs measure their effects on psychological aspects of breast cancer survivors. Therefore, a systematic review to examine which types of non-pharmacological interventions can reduce psychological symptoms related to hot flashes among breast cancer survivors will enhance our understanding.

Conclusion and Implications for Nursing

Hot flash symptoms are a major clinical issue for breast cancer survivors after cancer treatment. Therefore, it is essential that nurses be concerned with hot flash symptoms experienced by these women. Based on data currently available in this review, although previous studies regarding non-pharmacologic approaches require further work because of various limitations, acupuncture is a potentially beneficial nonpharmacologic strategy that may be applied in clinical practices for breast cancer survivors suffering from hot flash symptoms. However, due to unclear quality of the included evidence, nurses may need to discuss the

balance of benefits and risks with patients who consider non-pharmacologic approaches as their choices. In the meanwhile, because of the limitations of previous studies regarding other non-pharmacologic approaches, further research using RCTs is needed to confirm the effectiveness of other non-pharmacologic strategies.

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แนวทางการลดอาการร้อนวูบวาบในผู้ป่วยมะเร็งเต้านมโดยไม่ใช้ยา: การสังเคราะห์งานวิจัยอย่างเป็นระบบ

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บทคัดย่อ: อาการร้อนวูบวาบเป็นปัญหาสุขภาพที่สำคัญสำหรับผู้รอดชีวิตจากมะเร็งเต้านม การรักษาอาการร้อนวูบวาบสามารถทำได้ทั้งวิธีการใช้ยาและไม่ใช้ยา แม้ว่าการใช้ยาจะสามารถลดอาการร้อนวูบวาบในบุคคลทั่วไปได้ แต่การเลือกใช้ยาเพื่อรักษาอาการร้อนวูบวาบสำหรับผู้รอดชีวิตจากมะเร็งเต้านมเป็นเรื่องที่น่ากังวลเพราะยาเหล่านี้อาจทำปฏิกิริยากับการใช้ยาต้านฮอร์โมนทาม็อกซิเฟนในผู้ป่วยเหล่านี้ได้ ดังนั้นจึงมีความจำเป็นต้องอัปเดตหลักฐานทางวิทยาศาสตร์เกี่ยวกับประสิทธิผลของวิธีการที่ไม่ใช้ยาในการลดอาการร้อนวูบวาบสำหรับผู้รอดชีวิตจากมะเร็งเต้านม วัตถุประสงค์ของการสังเคราะห์งานวิจัยอย่างเป็นระบบในครั้งนี้เพื่อศึกษาหลักฐานเชิงประจักษ์เกี่ยวกับประสิทธิผลของวิธีการที่ไม่ใช้ยาในการบรรเทาอาการร้อนวูบวาบในกลุ่มผู้รอดชีวิตจากมะเร็งเต้านม การสืบค้นข้อมูลดำเนินการผ่านทางอิเล็กทรอนิกส์จากฐานข้อมูล ScienceDirect, Scopus, PubMed, CINAHL และ Cochrane โดยคัดเลือกเอกสารที่ตีพิมพ์เป็นภาษาอังกฤษตั้งแต่เดือนมกราคม 2543 ถึงธันวาคม 2563 เกี่ยวกับแนวทางที่ไม่ใช่ยาและอาการร้อนวูบวาบในผู้รอดชีวิตจากมะเร็งเต้านม การทบทวนวรรณกรรมดำเนินการในเดือนกุมภาพันธ์ 2564 คำจำกัดความของแนวทางการดูแลโดยไม่ใช้ยาหรือการใช้การแพทย์ทางเลือกของศูนย์การแพทย์ทางเลือกแห่งชาติของสหรัฐอเมริกาได้นำมาใช้เป็นกรอบการศึกษา งานวิจัยทั้งหมด 16 เรื่องได้รับการนำมาวิเคราะห์ในการศึกษาครั้งนี้ ผลการวิจัยพบว่าการฝังเข็มถือเป็นวิธีที่อาจมีประสิทธิผลในการบรรเทาอาการร้อนวูบวาบในผู้รอดชีวิตจากมะเร็งเต้านม ในขณะที่ประสิทธิผลของวิธีการอื่น ๆ ที่ไม่ใช้ยาทั้งการปรับเปลี่ยนพฤติกรรม โยคะ การสะกดจิต โฮมีโอพาธีย์ และเทคนิคการผ่อนคลายไม่สามารถสรุปได้แน่นอนเนื่องจากมีงานวิจัยจำนวนน้อย โดยสรุปจากหลักฐานเชิงประจักษ์แสดงให้เห็นว่ายังมีข้อมูลที่ไม่เพียงพอที่จะสนับสนุนประสิทธิผลของวิธีการที่ไม่ใช้ยาในการลดอาการร้อนวูบวาบสำหรับผู้รอดชีวิตจากมะเร็งเต้านม การศึกษาวิจัยด้วยวิธีการที่มีประสิทธิผลในประเด็นนี้ยังคงมีความจำเป็น พยาบาลจำเป็นต้องอภิปรายข้อดีและข้อเสียของวิธีการไม่ใช้ยาเหล่านี้กับผู้รอดชีวิตจากมะเร็งเต้านมที่ต้องการใช้แนวทางทางเลือกเหล่านี้ในการดูแลสุขภาพของตนเอง

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