


Acupuncture as an adjuvant therapy for management of treatment-related symptoms in breast cancer patients

Systematic review and meta-analysis (PRISMA-compliant)

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Abstract

Background: Although randomized controlled trials have revealed the considerable effectiveness of acupuncture in breast cancer patients, there have been no studies exploring current acupuncture research trends for treatment induced various symptoms in breast cancer patients. This review evaluated the effectiveness of acupuncture for treatment-induced symptoms in breast cancer patients.

Methods: We performed a systematic review and meta-analysis of the literature regarding acupuncture to treat symptoms associated with breast cancer therapies. The following databases were searched for relevant RCTs published before June 2018: MEDLINE, EMBASE, the Cochrane Library, AMED, CINAHL, OASIS, CNKI, and CiNii.

Results: Among the 19,483 records identified, 835 articles remained after screening titles and abstracts. A total of 19 RCTs were included in this qualitative synthesis. Among the studies, 8 explored climacteric symptoms, 4 explored pain, 2 explored lymphedemas, 2 explored nausea and vomiting and 3 investigated miscellaneous symptoms.

explored miscellaneous symptoms due to cancer treatments. Most of the studies reported that acupuncture can alleviate various symptoms of breast cancer treatment. However, there is a lack of evidence as to whether acupuncture can alleviate chemotherapy associated side effects

Conclusions: Acupuncture may alleviate the treatment-related symptoms of breast cancer; however, further studies are necessary to obtain conclusive evidence of the effectiveness of acupuncture in treating breast cancer.

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Abbreviations: AI = aromatase inhibitor, AT = acupuncture, AVLT = auditory-verbal learning test, BC = breast cancer, BDI = Beck depression inventory, BDNF = Brain-derived neurotrophic factor, BFI = brief fatigue inventory, BPI-SF = brief pain inventory - short form, C = control, CAM = complementary and alternative medicine, CDT = Clock-drawing test, CES-D = center for epidemiological studies depression scale, CRP = C reactive protein, DASH = disabilities of the arm, shoulder and hand score, EA =

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SJ and YK are the co-first author and contributed equally to this work.

All data generated or analyzed during this study are included in this published.

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electro-acupuncture, ESR = Erythrocyte sedimentation rate, EXE = exemestane, F/U = follow-up, FACT-COG = Functional assessment of cancer treatment cognition, FACT-G = functional assessment of cancer therapy-general, FACT-NTX = neurotoxicity component of functional assessment of cancer therapy taxane scale, FACT-TAX = functional assessment of cancer therapy taxane scale, GCS = Greene climacteric scale, HADS = hospital anxiety and depression scale, HAQ-DI = health assessment questionnaire disability index, HFCS = Hot flush composite score, HFS = Hot flush score, HT = hormone therapy, I = intervention, KI = Kupperman's index, MenQoL = menopause specific quality of life, MLN = metastatic lymph node, M-SACRAH = modified score for the assessment and quantification of chronic rheumatoid affections of the hands, MYCaW = measure yourself concerns and wellbeing questionnaire, n.r. = not reported, NPS = neuropathic pain scale, PGWB = psychological and general well-being index, PRISMA = preferred reporting items for systematic reviews and meta-analyses protocols, PSQI = Pittsburgh sleep quality index, RCT = randomized control trial, RoB = Risk of Bias, SDMT = symbol digit modality test, SHBG = sex hormone binding globulin, TAM = tamoxifen, tgAI = third generation of AI, TMT-B = trail-making test part B, TROP = Tropisetron, VAS = visual analog scale, VFT = verbal fluency test, VNF = venlafaxine, W-BQ12 = wellbeing questionnaire, WHQ = Women's health questionnaire, WOMAC = Western Ontario and McMaster Universities osteoarthritis index.

Keywords: acupuncture, complementary and alternative medicine, electro-acupuncture, Korean medicine

1. Introduction

Breast cancer (BC) is the most common type of cancer among women globally. The estimated incidence and the age-standardized incidence rate for female BC patients was 2.4 million and 65.5 per 100,000 women in 2015.^[1,2] The increasing incidence of BC may have an impact on the economic burden of care and productivity of patients.

In general, BC patients experience multiple symptoms related to cancer treatment, including fatigue, pain, sleep disturbances, depression, nausea, and vomiting.^[3] Dong et al reported that these symptoms are often concurrent, with more than 8 symptoms occurring at any given time.^[4] Several studies have used non-pharmacological approaches to treat these symptoms, such as pain, fatigue, sleep disturbance, and quality of life, in a safe and effective manner.^[5–8]

A substantial number of BC patients visit complementary and alternative medicine (CAM) clinics to receive treatment for cancer as well as for treatment-related symptoms, such as psychosocial distress, hot flushes, insomnia, and fatigue.^[9–11] Currently, acupuncture is widely used as a safe and highly accessible adjunctive treatment for various symptoms induced by BC treatment.^[12] Based on the principles of traditional medicine, acupuncture regulates energy pathways and controls the balance of energy circulation to alleviate various symptoms of cancer, as evidenced by the changes in neurophysiologic and neurohormonal activities.^[13]

Previous studies have explored the efficacy of a broad range of CAMs in improving the symptoms of BC treatment-related symptoms.^[14–17] Kim et al. recently reviewed the current clinical evidence of acupuncture for Korean BC survivors and reported that there is a lack of evidence for the benefits of acupuncture in BC patients within Korea.^[18]

There has been no thorough systematic review of various acupuncture treatments for BC treatment-induced symptoms. Thus, we reviewed all relevant studies and conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of acupuncture in relation to the various symptoms induced by BC treatment.

2. Methods

All data of this study analyzed were collected from published trials, so ethical approval is not necessary.

2.1. Search method for identification of studies

2.1.1. Search databases. The following 8 electronic databases were used for the study: MEDLINE, EMBASE, the Cochrane Library, AMED, CINAHL, 1 Korean database (OASIS), 1 Chinese database (China National Knowledge Infrastructure, CNKI), and 1 Japanese database (CiNii). The reference lists of the retrieved articles were manually searched, and previously published review articles were also examined.

2.1.2. Search strategy. Acupuncture and BC were selected as the basic search terms for this study. The keywords used for searching the databases were 'breast cancer', 'breast carcinoma', 'breast neoplasm', and 'acupuncture'. To increase the sensitivity of the search, the terms 'traditional medicine', 'complementary and alternative medicine', 'Chinese medicine', 'Korean medicine', and 'Kampo medicine' were also included as keywords. Language and publication dates were not restricted. Data were searched on June 20, 2018. The search strategy for PubMed is shown in Table 1.

In addition, this review has been registered on PROSPERO (registration number CRD42016049463). The protocol was strictly developed in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P).

2.2. Inclusion criteria for this review

2.2.1. Types of studies. This systematic review included only those RCTs that had been peer-reviewed. Other designs such as

Table 1
Search strategies used in PubMed database.

No	Search Items
1	breast neoplasm[MeSH Terms]
2	breast cancer
3	breast carcinoma
4	acupuncture*[Text Word]
5	traditional medicine[Text Word]
6	complementary and alternative medicine[Text Word]
7	Korean medicine[Text Word]
8	Chinese medicine[Text Word]
9	kampo medicine[Text Word]
10	or/1–3
11	or/5–9
12	4 AND 10 AND 11

observational studies, cohort studies, case reports, case series, non-RCT studies, animal and experimental studies, and these were excluded.

2.2.2. Participants. Participants were women currently being treated for BC. No restrictions were used with respect to the diagnosis criteria for BC and stage of cancer. Both metastatic and non-metastatic BC patients were included. Patients with other types of cancer were excluded.

2.2.3. Types of interventions. We included studies that evaluated the effect of various types of acupuncture in the management of treatment-related symptoms in breast cancer patients. Interventions including manual acupuncture, ear acupuncture, and electro-acupuncture (EA) were included. There were no restrictions on concomitant conventional treatment, such as chemotherapy and hormone therapy, if the study applied concomitant treatment for all groups homogeneously. Studies were excluded if they did not mention penetration of the skin during the procedure of acupuncture, which, for example, occurs with acupressure.

2.2.4. Types of comparisons. There were no special restrictions on comparisons. Sham acupuncture, active-control (such as

conventional medicine and exercise), no-treatment, and wait-list control groups were all permitted.

2.2.5. Outcome measures. There were no designated primary outcomes in this review. Outcomes used for the evaluation of BC-related symptoms were accepted without restriction.

2.3. Data collection, extraction, and assessment

2.3.1. Selection of studies. Two authors (SJ and YK) independently screened the titles and abstracts of the searched studies, after excluding duplicate articles from 8 databases. Then, the full text of the selected articles was reviewed to verify that each article met the inclusion criteria. Another reviewer (BHJ) made the final decision when the earlier two authors had a difference in opinion. This process is summarized in a flow diagram in the PRISMA (Fig. 1).^[19]

2.3.2. Data extraction. One author (SJ) conducted data extraction, and another author (YK) reviewed the extracted document. Extracted items regarding study population, type of symptom, intervention, outcomes, and conclusion were collected from the studies.

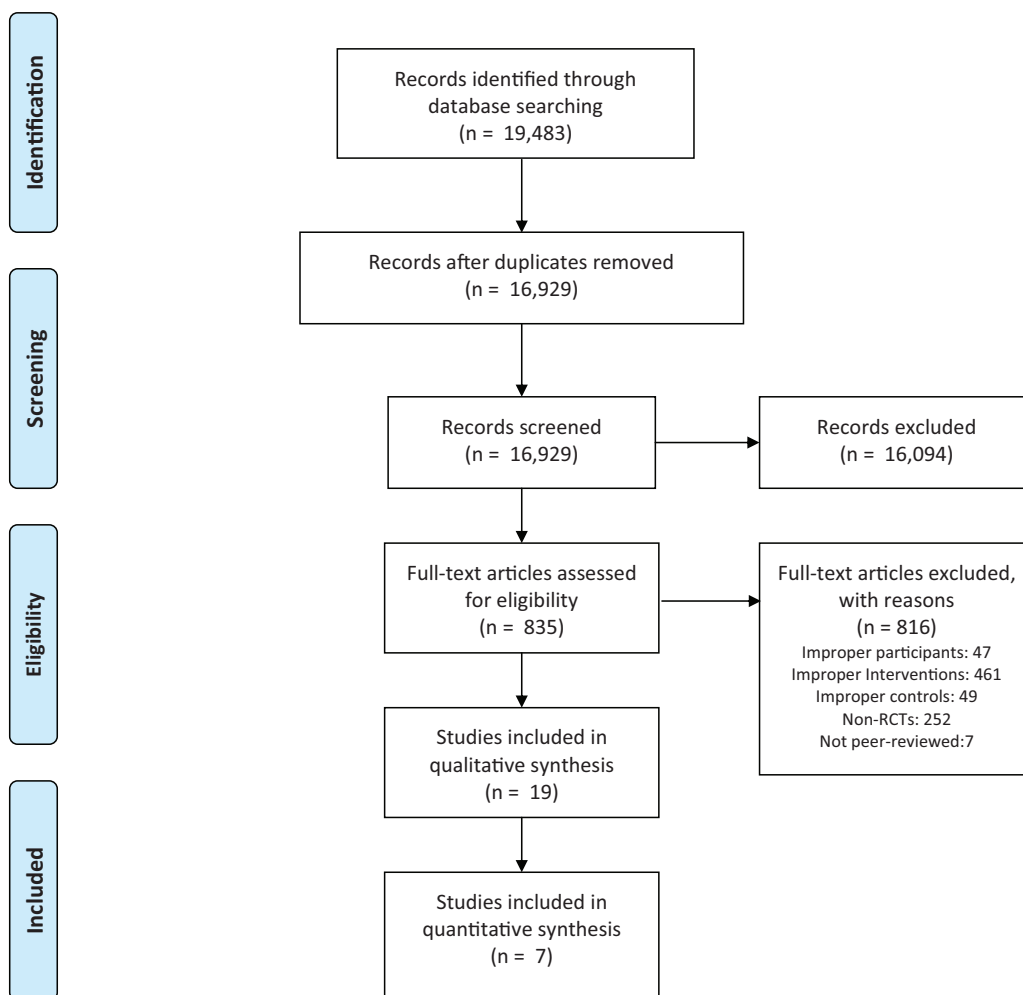


Figure 1. The PRISMA Flow Diagram of Study Selection.

2.3.3. Risk bias assessment. Two reviewers (SJ and YK) assessed the quality of the included studies using the Risk of Bias (RoB) tool developed by Cochrane.^[20] RoB consists of the following seven items:

- 1) random sequence generation,
- 2) allocation concealment,
- 3) blinding of participants and personnel,
- 4) blinding of outcome assessment,
- 5) completeness of outcome data,
- 6) completeness of reporting, and
- 7) other sources of bias.

Each item of every RCT was categorized as “high risk (H),” “unclear (U),” or “low risk (L).” The RoB graph was generated using Review Manager (Cochrane Collaboration Software, RevMan) version 5.3.

2.3.4. Meta-analysis. We planned to perform a meta-analysis if sufficient studies were identified for symptoms or outcome measurements. We used the risk ratio (RR) for dichotomous variables and mean difference (MD) for continuous variables as effect estimates.

3. Results

3.1. Results of the search

In total, 19,483 records were identified from the eight databases. Of these, 16,929 articles remained after eliminating duplicates. After screening titles and abstracts, 835 articles were retained, and finally, through reviewing the full texts, 19 RCTs^[21–40] (described in 20 articles) fulfilled the eligibility criteria for inclusion. The flow chart of the study selection and exclusion criteria is shown in Figure 1. Hervik’s studies were published twice, in 2009^[27] and 2014.^[28] Both were based on the same trial, and the 2014 article was the result of a follow-up study. Therefore, these 2 studies were examined together as 1 study in this review.

3.2. Included studies

A detailed description of the characteristics of the included studies is presented in Tables 2 and 3. The following is a brief overview of the studies.

3.3. Study designs

Data were extracted from the included studies and 19 RCTs^[21–40] were included in the qualitative synthesis of this review.

3.4. Settings

Of the 19 studies, 7^[22,23,26,30,31,37,38] were conducted in the United States, 5^[21,24,25,27–29] in Europe, 2^[32,34] in Australia, 1^[33] in Brazil, and 4^[35,36,39,40] in China. The published year of each trial varied between 2006 and 2018.

3.5. Participants

The number of participants in the trials ranged between 32 and 190. All trials contained women with breast cancer. The mean participant age was distributed between the 40 seconds and 60 seconds. Of the seven trials that targeted women with breast cancer below stage 3,^[23,26,30–32,35,38] two trials enrolled patients

below stage 2,^[34,39] one trial recruited patients with breast cancer higher than stage 2,^[37] one trial^[24] used TNM stage as inclusion criteria, and the remaining 8 trials did not mention specific stages of BC.^[21,22,25,27–29,33,36,40] The symptoms accompanying breast cancer were as follows: climacteric symptoms 8 [21–29], pain 4 [30–33], nausea and vomiting 2,^[34,35] breast cancer-related lymphedema 2,^[36,37] peripheral neuropathy 1,^[38] cognitive impairment 1,^[39] and gastrointestinal symptom 1.^[40] Chemotherapy, aromatase inhibitor (AI) therapy, hormone therapy, surgery, and symptom-specific treatments were mentioned as concurrent treatments during the trial period (Table 2).

3.6. Interventions

Interventions used in all included studies were manual acupuncture and EA. Four trials^[21,24,34,38] used EA, and the remaining 15 trials used manual acupuncture.^[22,23,25–33,35–37,39,40] Among the manual acupuncture trials, one trial^[40] employed a combination of symptomatic therapy, umbilical application with acupuncture, one^[30] applied integrated therapy with acupuncture and auricular acupressure, two trials^[33,36] employed various exercises in addition to acupuncture, and one trial^[29] used a booklet with acupuncture. All of the studies applied manual acupuncture stimulation to treat certain symptoms caused by cancer treatment, of the four studies that used a combination of EA.^[21,24,34,38] Most of the studies mentioned acupuncture points and mostly included a range between 3 and 19 points. However, Crew et al. did not mention specific acupoints other than full body and auricular acupuncture.^[30] fourteen studies applied fixed acupuncture points based on previous studies, textbooks, and expert opinions,^[21,23–28,31–37,40] while the remaining five studies used semi-fixed acupuncture points as indicated by primary patient complaints, pain locations, and pattern identifications.^[22,29,30,38,39]

Acupuncture and EA treatment were administered at least once or twice per week. The treatment period ranged from 3 days to 12 weeks; four trials had periods of 4 weeks or under,^[22,35,36,40] seven trials had periods of 5–8 weeks,^[25,26,30–32,37,39] and 8 had periods of 9 to 12 weeks.^[21,23,24,27–29,33,34,38] The total number of treatment sessions ranged from 4 to 40 sessions. Of the ten studies,^[21–29,31,32] follow-up investigation was conducted in those identified in Tables 2 and 3.

3.7. Comparisons

There were three types of comparisons in this review. Active-control, placebo, and no-treatment groups were included as the control groups. Sham acupuncture was applied as a placebo in 8 trials,^[22,25–28,30–32,35] and sham EA was used in 2 trials.^[34,38] The conventional medicine, venlafaxine (VNF), was used as an active control in one trial.^[23] Hormone therapy,^[24] various exercises,^[33,36] relaxation,^[21] enhanced self-care by clinicians by providing a brochure,^[29] and symptomatic therapy^[40] were also selected for comparisons. Furthermore, no treatment^[39] and wait-list^[37] control groups were also used.

3.8. Outcomes

The outcomes of each trial were used to assess the common accompanying symptoms that were caused by cancer treatment; for example, climacteric symptoms (frequency and severity of hot flush and sweating),^[21–29] pain (severity, functional disability,

Table 2
Basic information of included studies.

Study ID	Characteristics of study					Interventions		Effect estimates (Mean difference after-before treatment, event (n or %))	Conclusion	
	Sample size (enrolled)	Age (mean, SD)	Stage	Main symptoms	Acu-type	Control intervention	Total duration of treatment			Outcomes
Climacteric symptoms (8) Nedstrand (2006) Sweden (21)	38 (I:19, C:19)	53	n.r.	Hot flush	EA	Applied relaxation	12 w + 3 m (F/U)	1. Mood scale 2. SCL 3. Intensity of climacteric symptom (VAS) 4. KI 5. Hot flush FREQ Hot flush FREQ	n.r.	".. improved in both groups, but did not differ significantly."
Deng (2007) US (22)	72 (I:42, C:30)	I: 55 C: 56	n.r.	Hot flush	AT	Sham	4 w + 5 m (F/U)	-0.10 [-0.28, 0.08]	I: 12: slight bleeding or bruising at the needle site	".. cannot exclude the possibility that a longer and more intense acupuncture intervention could produce a larger reduction of these symptoms."
Walker (2010) US (23)	50 (I:25, C:25)	Median 55 (35-77)	0-II	Hot flush	AT	VNF	12 w + 9 m (F/U)	1. Hot flush FREQ 2. Severity of Hot flush 3. MenQoL (total) 4. BDHPG*	C: 18: nausea, headache, difficulty sleeping, dizziness, etc.	".. a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with BC." "EA should be further evaluated as treatment for women with BC and climacteric complaints, since HT no longer can be recommended for these women."
Frisk (2009) Sweden (24)	45 (I:27, C:18)	I: 54.1 C: 53.4	T1 or T2 with max 4 MLN, T3 without metastasis	Climacteric symptoms	EA	HT	12 w + 21 m (F/U) (AT) - 24 m (HT)	1. Hot flush FREQ (No of hr sleep/night; Times woken up/night; No of flushes/night; Distress flushes/night) 2. HFS (Reduction rate) [†] 3. WHQ (total, sleep) 4. PGWB	none	
Liljegren (2012) Sweden (25)	84 (I:42, C:42)	I: 58 ± 6.8 C: 58 ± 9.3	n.r.	Climacteric symptoms	AT	Sham	5 w + 12 w (F/U)	1. -0.10 [-0.60, 0.40] 2. -0.90 [-1.02, -0.78] 3. no statistical significant (data not shown)	n.r.	"..shows that both true and CTRL reduce vasomotor symptoms in BC patients treated with adjuvant tamoxifen." "EA and SA were both associated with improvement in PPOs in BC patients taking AIs and detected no significant difference between arms."
Bao (2014) US (26)	51 (I:25, C:26)	Median I: 61 (44-82) C: 61 (45-85)	0-II	Aromatase inhibitor-induced Musculo-skeletal Symptoms	AT	Sham	8 w + 4 w (F/U)	1. 1.50 [-4.01, 7.01] 2. -5.50 [-17.79, 6.79] 3. 1.50 [-1.30, 4.30] 4. 1.50 [0.43, 2.57] 5. -1.00 [-7.11, 5.11] 6. -0.50 [-1.34, 0.34] 7. 2.00 [7.82, 11.82] 8. -1.00 [-12.13, 10.13]	none	
Hervik (2009) (27) & Hervik (2014) Norway (28)	59 (I:30, C:29)	I: 52 ± 8.4 C: 52 ± 9.5	n.r.	Hot flush	AT	Sham	10 w + 2 y (F/U)	-5.69 [-5.71, -5.67]	n.r.	"Acupuncture seems to have a positive effect on health related quality of life for up 3 months post-treatment, but no significant effect 2 years FU." ".. is an effective integrative intervention for managing hot flashes
Lesi (2016) Italy (29)	190 (I:85, C:105)	I: 50 ± 9 C: 49 ± 8.5	n.r.	Hot flushes	AT + Enhanced self-care based on Brochure	Enhanced self-care based on Brochure	12 w + 6 m (F/U)	1. -11.4 [-16.4, -6.3] 2. -6.8 [-9.4, -4.2] 3. -1.6 [-2.1, -1.1] -0.8 [-1.3, -0.3]	I: 12 mild adverse events (muscle pain, headache, menstrual bleed)	

(continued)

Table 2
(continued).

Study ID	Characteristics of study				Interventions			Effect estimates (Mean difference after-before treatment, event (n or %))	Adverse events	Conclusion
	Sample size (enrolled)	Age (mean, SD)	Stage	Main symptoms	Acu-type	Control intervention	Total duration of treatment			
PAIN (4) Crew (2010) US (30)	43 (I:23, C:20)	Median I: 58 (44–77) C: 57 (37–77)	I–III	Joint pain or stiffness	AT + Auricular AT	Sham	6 w	Psychosocial, Physical, Sexual 1. WOMAC (pain, stiffness, function, normalized) 2. M-SACRAH (pain, stiffness, function, normalized) 3. BPI-SF (worst pain, pain severity, pain related interference) 4. FACT-G (physical, social/family, emotional, functional)	I: 2: pain from needling C: 1: pain from needling	and improving QoL in women with BC." "Acupuncture is an effective and well-tolerated strategy for managing this common treatment-related side effect."
Bao (2013) US (31)	51 (I:25, C:26)	Median I: 61 (44–82) C: 61 (45–85)	0–III	Musculo-skeletal Symptoms	AT	Sham	8 w + 4 w (FU)	1. HAQ-DI* 2. VAS* 3. LAB	none	"...did not observe a significant changes in AIMSS between real and sham acupuncture."
Oh (2013) Australia (32)	32 (I:16, C:16)	n.r.	I, II or IIIa hormone receptor-positive BC	Joint pain or stiffness	AT	Sham	6 w + 6 w (FU)	1. BPI-SF* 2. WOMAC* 3. FACT-G 4. Handgrip strength test 5. CRP, ESR 1. BDI* 2. DASH* 3. ROM (FL, EL, AD, AB, IR, ER)	I: 5: minor bruising	"...suggest that acupuncture is feasible and safe in patients with BC with joint pain caused by AI."
Giron (2016) Brazil (33)	50 (I:25, C:25)	53.7 ± 11.1	n.r.	Pain in scapular girdle and upper limb region	AT + Kinesiotherapy	Kinesiotherapy	10 w	1. -1.70 [-3.06, -0.34] 2. 6.10 [4.59, 7.61] 3. 9.00 [5.45, 12.55] -3.90 [-5.94, -1.86] 2.30 [1.36, 3.24] 10.00 [4.38, 15.62] -2.00 [-6.37, 2.37] -3.00 [-7.13, 1.13]	n.r.	"Both groups showed statistically significant improvement and there was no difference between them."
Cancer treatment induced Nausea & Vomiting (2) Beth (2012) Australia (34)	32 (I:16, C:17)	I: 42 ± 8.4 C: 52 ± 9.5	0–II	Nausea & Vomiting	EA	Sham EA	3 cycles of chemo (9 w)	1. 9/11; 10/11 (p > 0.05) 2. 2/1; 1/0 (P > .05) 3. P = .01, P = .01, P = .19	none	"... EA during chemotherapy is a promising option for controlling side-effects of chemo."
He (2017) China (35)	64 (I:32, C:32)	I: 42.1 ± 4.29 C: 42.2 ± 4.11	I–IIIa	Nausea & Vomiting	AT	Sham	1 w	1. Severity of NIV (MCGSF) CTC 4.0, ≥ III) 2. TCM symptoms (loss of appetite; fatigue; bloating) 3. HADS (anxiety, depression)	n.r.	"...could help BC patients relieving NIV, improving the symptoms of poor appetite and body tired fatigue, and reducing HADS."

(continued)

Table 2
(continued).

Study ID	Characteristics of study				Interventions		Outcomes	Effect estimates (Mean difference after-before treatment, event (n or %))	Adverse events	Conclusion
	Sample size (enrolled)	Age (mean, SD)	Stage	Main symptoms	Acu-type	Control intervention				
Lymphedema (2) Zhan (2017) China (36)	60 (I:30, C:30)	n.r.	n.r.	BC related upper limb lymphedema	Abdominal acupuncture + Upper limb exercise	Upper limb exercise	4 w	1. Pain (VAS)* 2. Arm circumference* 3. Incidence of severe edema†	n.r.	"... is of better curative effect in eliminating edema and improving pain in phantom, which is worthy of promotion." "... did not significantly reduce BCRL in pre-treated patients receiving concurrent lymphedema treatment."
Bao (2018) US (37)	82 (I:40, C:42)	I: 65 C: 58	≥ II	BC-related lymphedema	AT	Wait-list	6 w	1. Arm circumference* 2. Bio-impedance*	1: 45/buises 2: hematoma, 2: pain, 1: skin infection	
Miscellaneous Symptoms (3) Greenlee (2016) US (38)	63 (I:31, C:32)	I: 51.8 ± 10.7 C: 48.3 ± 12.0	I-III	Taxane-induced peripheral neuropathy	EA	Sham EA	12 w	1. BPI-SF* 2. FACT-NTX 3. FACT-TAX 4. NPS*	I: 1: minor swelling and bruising at needle site	"... there were no differences in pain or neuropathy between groups . . ." "... is effective in the treatment of CRCL in BC patients through a mechanism that may be related to an increase of BDNF."
Tong (2018) China (39)	80 (I:40, C:40)	I: 43.1 ± 4.23 C: 42.3 ± 4.42	0-II	Chemo-related cognitive impairment	AT	No treatment	8 w	1. FACT-COG 2. AVLT (immediate recall, delayed recall, recognition) 3. VFT 4. SDMT 5. CDT 6. TMT-B* 7. BDNF	n.r.	"... can effectively relieve the symptoms of diarrhea, constipation, NVV, and improve clinical efficacy."
Zhang (2018) China (40)	70 (I:35, C:35)	I: 49.9 ± 3.20 C: 50.5 ± 3.16	n.r.	Chemo-induced gastro-intestinal symptoms	AT + Umbilical application + Symptomatic therapy	Symptomatic therapy (Granisetron loperamide, Sino decoction)	3 d	Response rate† (diarrhea, constipation, NVV) 91.4%/82.9% 94.3%/80.0% < .05	n.r.	

AI = aromatase inhibitor, AT = acupuncture, AVLT = Auditory-verbal learning test, BDI = Beck depression inventory, BDNF = Brain-derived neurotrophic factor, BFI-SF = Brief fatigue inventory, BPI-SF = Brief pain inventory - short form, C = control, CDT = Clock-drawing test, CES-D = Center for epidemiological studies depression scale, CRP = C reactive protein, DASH = Disabilities of the arm, shoulder and hand score, EA = electroacupuncture, ESR = Erythrocyte sedimentation rate, EXE = Exemestane, F/U = follow-up, FACT-COG = Functional assessment of cancer treatment cognition, FACT-G = Functional assessment of cancer therapy-general, FACT-NTX = Neurotoxicity component of functional assessment of cancer therapy taxane scale, FACT-TAX = Functional assessment of cancer therapy taxane scale, GCS = Greene climacteric scale, HADS = Hospital anxiety and depression scale, HAQ-DI = Health assessment questionnaire disability index, HFCS = Hot flush composite score, HFS = Hot flush score, HT = hormone therapy, I = intervention, KI = Kupperman's index, MenQoL = Menopause specific quality of life, MLN = metastatic lymph node, M-SACRAH = Modified score for the assessment and quantification of chronic rheumatoid affections of the hands, M/CaW = Measure yourself concerns and wellbeing questionnaire, n.r. = not reported, NPS = Neurotoxicity pain scale, PGWB = Psychological and general well-being index, PSQI = Pittsburgh sleep quality index, SDMT = Symbol digit modality test, SHBG = Sex hormone binding globulin, TAM = tamoxifen, tGAI = third generation AI, TMT-B = Trail-making test part B, TROP = Tropisetron, VAS = Visual analog scale, VFT = Verbal fluency test, VNF = Venlafaxine, W-BQ12 = Wellbeing questionnaire, WHOQ = Women's health questionnaire, WOMAC = Western Ontario and McMaster Universities osteoarthritis index.

* Higher score indicates severe symptoms.
† Dichotomous variables.

Table 3
Details of Characteristics of Acupuncture.

Study ID	Acupuncture rationale	Acupoint selection principle	Acupuncture points used	Acupuncture features				Frequency of acupuncture treatment	Concurrent treatment
				Number of needles	Needle stimulation	Number of sessions			
Climacteric Symptoms (8) Nedstrand (2006) Sweden (21)	n.r.	Fixed acupoints	BL23, BL32	4	Manual stimulation+EA	14	Twice a week for the first 2 w + once a week for remaining 10 w	n.r.	
Deng (2007) US (22)	derived from previous reports & standard acupuncture textbooks	Semi-fixed acupoints according to symptoms	GV14, GB20, BL13, PC7, HT6, KI7, ST36, SP6 Ear AT (Shenmen, Sympathetic)	19	Manual stimulation	8	Twice a week, 4w	SERMs, GnRH or AI	
Walker (2010) US (23)	n.r.	Fixed acupoints	KI3, BL23, SP6, GB20, GV14, GV20, ST36, LR3, HT7, PC7, CV6, LU9	12	Manual stimulation	16	Twice a week for the first 4 w + once a week for remaining 8 w	hormone therapy with Tamoxifen or Arimidex	
Frisk (2012) Sweden (24)	Based on earlier studies	Fixed acupoints	BL15, BL23, BL32, GV20, HT7, PC6, LR3, SP6, SP9	12	Manual stimulation+EA	14	Twice a week for the first 2 w + once a w for remaining 10 w	n.r.	
Liljgren (2012) Sweden (25)	According to previous reports and from expert opinion, as found in standard acupuncture textbooks	Fixed acupoints	LI4, HT6, LR3, ST36, SP6, KI7	8	Manual stimulation	10	Twice a week, 5 w	Tamoxifen	
Bao (2014) US (26)	Based on our clinical experience suggesting that AIMSS resulted from Qi deficiency	Fixed acupoints	CV4, CV6, CV12, LI4, MH6, GB34, ST36, KI3, BL65	15	Manual stimulation	8	Once a week, 8w	AI therapy	
Hervik (2009) (27) & Hervik (2014) Norway (28)	n.r.	Fixed acupoints	LI3, GB20, LU7, KI3, SP6, CV4, PC7, LI8	8	Manual stimulation	15	Twice a week for the first 5 w + once a week for remaining 5 w	AI therapy (anastrozole, letrozole, or exemestane)	
Lesi (2016) Italy (29)	According to Maciocia's recommendations	Semi-fixed acupoints according to pattern identification	SP6, LI11, CV4 + additional points according to TCM syndrome	≥3	Manual stimulation	10	Once a week, 10w	Cisplatin + chemotherapy	
PAIN (4) Grew (2010) US (30)	based on a standard TCM point prescription to treat musculoskeletal pain	Semi-fixed acupoints according to pain location (max.3 points)	full body + auricular acupuncture + 3 most painful areas	≥3	Manual stimulation	12	Twice a week, 6w	tgAI (anastrozole, letrozole, or exemestane)	
Bao (2013) US (31)	Based on our clinical experience suggesting that AIMSS resulted from Qi deficiency.	Fixed acupoints	CV4, CV6, CV12, LI4, MH6, GB34, ST36, KI3, BL65	15	Manual stimulation	8	Once a week, 8w	tgAI	
Oh (2013) Australia (32)	derived from standard acupuncture textbooks	Fixed acupoints	Day1: LI4, LI11, GB34, ST40, LR3, GV20, EX-HN1, EX-UE9 Day2: GB21, TE5, ST36, SP6, LR3, GV20, EX-HN1, EX-UE9	12	Manual stimulation + EA	12	Twice a week, 6w	tgAI	
		Fixed acupoints		12	Manual stimulation	10	Once a week, 10w		

(continued)

Table 3
(continued).

Study ID	Acupuncture rationale	Acupoint selection principle	Acupuncture points used	Acupuncture features				
				Number of needles	Needle stimulation	Number of sessions	Frequency of acupuncture treatment	Concurrent treatment
Giron (2016) Brazil (33)	in accordance with the recommendations of Standards for Reporting of Controlled Trials in Acupuncture (RCTA)		CV3, SP9, ST36, K7, LR3, GB21, LI15, HT14, LU5, LI4, ST38, BL60					Adjuvant or neo-adjuvant Paclitaxel
Treatment Induced Nausea & Vomiting (2)								
Beith (2012) Australia (34)	n.r.	Fixed acupoints	PC6 (left), LI4 (right), ST36 (both)	3	Manual stimulation	4	2 hr prior to chemo; on day 1 & 2 of the first two cycles	AC or FEC; Antiemetics
He (2017) China (35)	Based on the expert opinion Prof. Wang from Capital Medical University Beijing Hospital of Traditional Chinese Medicine	Fixed acupoints	CV12, LRI3, CV6, ST25, PC6, ST36	6	Manual stimulation	4	Every other day, 8d	ODT
Lymphedema (2)								
Zhan (2017) China (36)	Based on the theory of meridians	Fixed acupoints	CV12, CV10, CV6, CV4, ST24, ST26	6	Manual stimulation	28	Once a day, 28d	n.r.
Bao (2018) US (37)	based on previous pilot study	Fixed acupoints	CV12, CV3, TE14, LI15, LU5, LI4, ST36, SP6	8	Manual stimulation	12	Twice a week, 6w	Common standard dose chemotherapy regimens
Miscellaneous Symptoms (3)								
Greenlee (2016) US (38)	Developed based on a standard TCM protocol for qi and xue deficiency and stagnation and informal practitioner query.	Semi-fixed acupoints according to pain location	GB34, ST36, LI4, LI10, LU3, LU5, GV14	4-8	Manual stimulation + EA	12	Once a week, 12w	Hormonal treatment
Tong (2018) China (39)	n.r.	Semi-fixed acupoints according to symptoms	GV20, EX-HN1, GV24, ST36, KI13, KI14, GB39	3-10	Manual stimulation	40	Once a day for 5 days, 2 days of rest/w, 4w/cycle, 3d rest between cycle, 2 cycles	Chemotherapy
Zhang (2018) China (40)	n.r.	Fixed acupoints	RN4, RN6, RN10, RN12, ST24, ST25, SP15	8	Manual stimulation	9	30 min/ session, twice a day, 3 d	Granisetron hydrochloride

quality of life including sleep and emotional status),^[30–33] nausea and vomiting (frequency, severity, and WHO grading),^[34,35] lymphedema (level of edema, arm circumference),^[36,37] neuropathic pain (severity and function),^[38] cognitive impairment (functional assessment and neuropsychological tests),^[39] and gastrointestinal symptoms (overall response rate).^[40] The details of the effectiveness of acupuncture for the management of treatment-induced discomfort of the main problematic symptoms indicated in each study were as follows:

In patients experiencing climacteric symptoms, Hervik et al reported that general climacteric symptoms after treatment significantly reduced in the acupuncture group compared to the sham group using Kupperman's Index,^[27,28] but Nedstrand et al. reported a significant effect in the applied relaxation group compared to the EA group.^[21] Walker et al reported that the acupuncture group had a significant decrease in the daily frequency and severity of hot flushes after treatment compared to the Venlafaxine group ($P < .05$).^[23] Frisk et al reported that compared to hormone therapy, the EA group demonstrated a significantly lower frequency of hot flushes (MD -0.5; 95%CI -0.9, -0.1).^[24] Assessing the reduction rate of hot flushes with the Hot Flush Score, Lesi et al. reported that acupuncture with an enhanced self-care group had a higher reduction rate than did the single self-care group (64.9%/16.9%, $P < .05$).^[29] However, Frisk et al showed that the hormone therapy group had a higher reduction rate than the EA group (100%/80%).^[24] Two studies reported a significant effect of the intervention with respect to menopause-specific quality of life ($P < .05$).^[23,29]

In patients experiencing pain induced by cancer treatment, Crew et al. demonstrated significant differences after treatment between acupuncture and sham groups using the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Brief Pain Inventory-short form (BPI-SF), and Functional Assessment of Cancer Therapy-General (FACT-G), except the pain domain in the WOMAC and the social/family domain in the FACT-G ($P < .05$).^[30] However, in Oh et al, none of the outcomes that Crew reported significant differences for showed any significant differences.^[32] Giron et al showed significant differences in functional measures of flexion (MD 9.0; 95%CI 5.45, 12.55), adduction (MD 2.30; 95%CI 1.36 3.24), and abduction (MD 10.0; 95%CI 4.38 15.62), and significant reduction in depression measures (MD -1.7; 95%CI -3.06, -0.34).^[33]

Of the 4 studies that assessed the effect of acupuncture on cancer treatment-induced nausea and vomiting. Beith et al. reported a higher incidence of acute (9/11) and delayed (10/11) nausea in the sham group, but there were no significant differences between groups ($P > .05$).^[34] Incidence vomiting also resulted in a higher incidence of acute (2/1) and delayed (1/0) vomiting in the EA group ($P > .05$).^[34] The incidence of severe nausea and vomiting after treatment was reported in one study using the US National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0 (NCI-CTC 4.0) and showed a significantly higher incidence of severe nausea and vomiting in the control group (2/4, $P < .05$).^[35] The concomitant symptoms associated with treatment induced nausea and vomiting, such as anxiety, depression, loss of appetite, abdominal bloating, and fatigue, were measured using the Hospital Anxiety and Depression Scale and TCM symptom grading scale. He et al. showed a significant reduction in the severity of anxiety (MD -1.46; 95%CI -1.94, -0.98), depression (MD -1.14; 95%CI -1.26 -1.02), fatigue (MD -1.21; 95%CI -1.33, -1.09), and loss of appetite (MD -1.27; 95%CI -1.31 -1.23) in acupuncture with ondansetron group compared to controls.^[35]

In patients experiencing lymphedema, Zhan et al. reported a significant decrease in the change of arm circumference compared to upper limb exercises (MD -1.47; 95%CI -1.62, -1.32),^[36] but Bao et al did not show any significant difference compared to the wait-list group (MD -0.38; 95%CI -0.89, 0.12).^[37] The intensity of joint-related pain using the *Visual Analog Scale* was statistically significant after acupuncture and upper limb exercise treatment compared to the upper limb exercises group (MD -1.22; 95%CI -1.48, -0.96).^[36]

Taxane-induced peripheral neuropathy was assessed over time in one study. Greenlee et al. assessed symptoms or concerns associated with chemotherapy and pain by using the Neurotoxicity Component of Functional Assessment of Cancer Therapy (FACT-NTX), Functional Assessment of Cancer Therapy Taxane Scale (FACT-TAX), BPI-SF, and neuropathy pain scale (NPS), but there were no significant differences between groups.^[38]

In patients experiencing chemotherapy-related cognitive impairment, Tong et al. reported a greater improvement in the Functional Assessment of Cancer Treatment Cognition (FACT-CTOG) (MD 3.43; 95%CI 3.15, 3.71), recognition of Auditory-Verbal Learning Test (MD 0.55; 95%CI 0.46, 0.64), Clock-Drawing Test (MD 0.51; 95%CI 0.39, 0.63), and serum brain-derived neurotrophic factor (BDNF) (MD 3.65; 95%CI 3.53, 3.77) in the acupuncture group.^[39]

In patients complaining of chemo-induced gastrointestinal symptoms, Zhang et al reported greater improvement in diarrhea (91.4%/82.9%), constipation (94.3%/80.0%), as well as nausea and vomiting (91.4%/77.1%) in the acupuncture group, with significant differences between groups.^[40] Due to the heterogeneity of assessment measurements, we could not thoroughly analyze this section. Table 2 summarizes the details of the outcomes.

3.9. Adverse events

Adverse events were assessed in 11 trials.^[22–24,26,29–32,34,37,38] Four studies^[24,26,31,34] reported no incidence of adverse events. Five studies^[22,30,32,37,38] reported mild adverse events such as, pain, bleeding or bruising from the needles. In one study, various adverse reactions (i.e., nausea, headache, dizziness, and sleeping difficulty) were reported in the control group treated with VNF,^[23] and the remaining study showed muscle pain, headache, or menstrual bleeding in the treatment group.^[29]

3.10. RoB in the included studies

The methodological quality of the included studies was assessed using the RoB tool, which evaluated 7 areas. In the performance bias category, only three studies used participant and assessor blinding and were assessed as 'low-risk'.^[22,30,38] Seven studies did not report random sequence generation^[23,27–29,34,35,39,40] and 14 studies did not mention an allocation concealment method.^[21–25,27–29,31,33–36,39,40] Thus, the category of selection bias was largely assessed as 'unclear'. The detection bias was high because self-reporting questionnaires were generally used. The majority of studies reported what they mentioned in the methodology section and thoroughly collected outcome results. Thus, attrition bias and reporting bias were assessed as low-risk. Additionally, the category of other bias was assessed as unclear, since 9 studies did not adequately describe the baseline data.^[22,23,27,28,30–32,34,39,40] The details of the RoB assessment are presented in Figure 3.

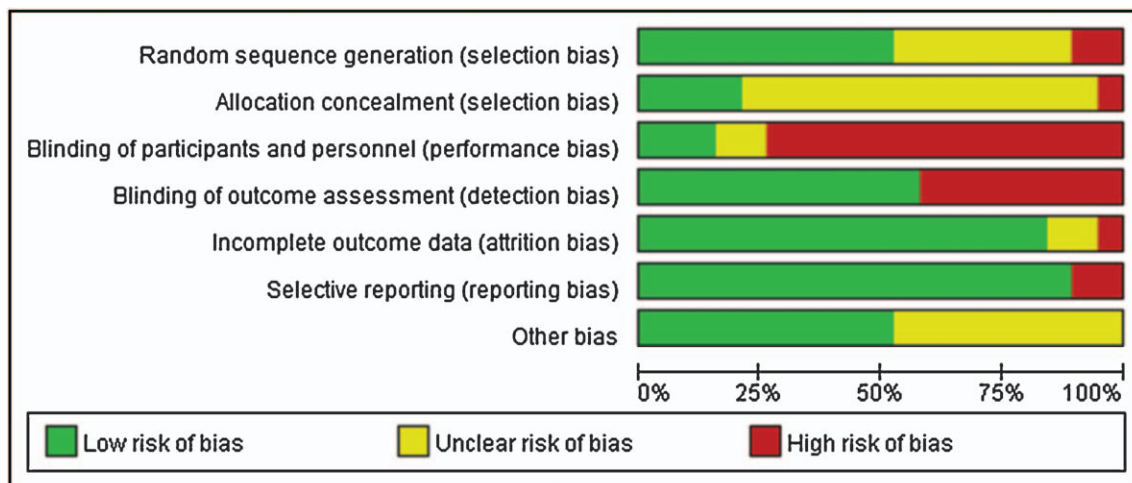


Figure 2. Risk of Bias Graph: Reviewer’s assessments about each risk of bias item presented as percentages of all included studies.

3.11. Meta-analyses

Due to the variety of outcomes, we only included 7 studies in the quantitative synthesis.^[21,22,24,25,27,28,36,37] Overall, acupuncture was significantly effective for improving arm circumference due to cancer-related lymphedema and quality of sleep. On the other hand, menopausal symptoms such as hot flashes and KI did not improve compared to the control group (Fig. 2). The following is a brief overview of the meta-analysis results.

3.11.1. Hot flash frequency (overall, nighttime time). Five trials were suitable for meta-analysis.^[21,22,24,25,27,28] The mean differences in daily hot flash frequency between the acupuncture and sham acupuncture or relaxation therapy groups (MD 0.3; 95%CI -0.84, 1.44; $P = .61$; $I^2 = 47%$; 177 participants; 3 trials) (Fig. 4) and night time frequency between the acupuncture and wait-list groups (MD -0.83; 95%CI -1.94, 0.28; $P = .14$; $I^2 = 95%$; 96 participants; 2 trials) were not statistically significant (Fig. 5).

3.11.2. Menopausal symptoms. Sufficient data on menopausal symptom assessments by KI were reported in two studies.^[21,27,28] There were no statistically significant differences in the total KI score between the acupuncture and wait-list or relaxation therapy groups (MD -2.61; 95%CI -7.35, 2.14; $P = .28$; $I^2 = 99%$; 126 participants; 2 trials) (Fig. 6).

3.11.3. Arm circumference. Two trials compared mean differences in arm circumference between the acupuncture and waitlist or exercise therapy groups (MD -1.61; 95%CI -1.92, -1.31; $P < .00001$; $I^2 = 72%$; 133 participants; 2 trials), which were statistically significant, in favor of the control group^[36,37] (Fig. 7).

4. Discussion

The purpose of this review was to provide an overview of previous studies which investigated symptoms induced by BC treatments and to investigate the overall effectiveness of

acupuncture. Nineteen studies were included in this review, and 7 studies were suitable for meta-analysis. The sample size of the included studies varied between 32 and 190, with 1,216 participants overall. These studies mentioned possible positive effects of acupuncture on BC treatment induced various symptoms, such as climacteric symptoms, pain, lymphedema, nausea, and miscellaneous symptoms. However, most of the authors suggested further confirmatory trials with conclusive evidence were needed, which indicates that there is still a lack of sufficient trials on acupuncture treatment as adjuvant therapy for BC. Overall, sixty distinct outcomes were measured in this review; the most frequently assessed outcomes were climacteric symptoms, pain, lymphedema, nausea and vomiting.

This study has several strengths. First, this study aimed to examine all of the acupuncture trials concerning the symptoms induced by BC treatment, in order to identify the efficacy of acupuncture treatment. Thus, we determined that the climacteric symptoms, pain, nausea, vomiting, lymphedema, cognitive impairment, gastrointestinal symptoms, and neuropathy were the main complaints in BC patients. Second, we reviewed a number of studies which were identified by a rigorous literature search strategy and we used standardized tools for reporting reviews and assessing bias.

Through this review, we learned that most of the studies were conducted in the United States, Europe, and China, while no studies have been published from Korea. In Korea, breast cancer is the second-most common cancer with a rapidly increasing incidence in Korean women. However, we identified a lack of evidence for the management of concomitant symptoms during BC treatment.

We also learned that most interventions have focused on manual acupuncture or EA. Interventions included enhanced self-care, auricular acupuncture, kinesio-therapy, exercises, symptomatic therapy, and umbilical application. However, due to the heterogeneity across the studies, they differed widely in terms of participant characteristics, duration, frequency of the interventions, and outcome measurement tools. Thus, we could not thoroughly evaluate the effectiveness of outcomes for measuring the benefit on certain symptoms. Only the change in affected arm

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bao 2013	+	?	?	-	+	+	?
Bao 2014	-	+	?	+	?	+	+
Bao 2018	+	+	-	+	+	+	+
Beith 2012	?	?	-	+	+	+	?
Crew 2010	-	-	+	+	-	-	?
Deng 2007	+	?	+	+	+	+	?
Frisk 2012	+	?	-	+	+	+	+
Giron 2016	+	?	-	-	+	+	+
Greenlee 2016	+	+	+	+	+	+	+
He 2017	?	?	-	+	+	+	+
Hervik 2009&2014	?	?	-	+	+	+	?
Lesi 2016	?	?	-	-	+	+	+
Liljegren 2012	+	?	-	+	+	+	+
Nedstrand 2006	+	?	-	-	?	+	+
Oh 2013	+	+	-	+	+	-	?
Tong 2018	?	?	-	-	+	+	?
Walker 2010	?	?	-	-	+	+	?
Zhan 2017	+	?	-	-	+	+	+
Zhang 2018	?	?	-	-	+	+	?

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. "+": low risk, "?": unclear risk, and "-": high risk.

circumference due to lymphedema was significantly different before and after treatment, which contradicts previous studies.^[41,42] Such differences may be due to variations between measurement tools. With regard to climacteric symptoms, most of the studies reported a significant effect on general menopausal symptoms, but there was no improvement in the frequency and severity of hot flush, which is consistent with the results of previous studies.^[43,44] Our findings with respect to musculoskeletal symptoms indicate that acupuncture may or may not alleviate pain and improve the function of the affected region. Conflicting with our data, a study on arthralgia previously reported that acupuncture reduced the pain and stiffness, but this was not statistically significant.^[45] This difference may be due to the musculoskeletal symptoms which were not classified into body regions. Regarding nausea and vomiting, we found that acupuncture was associated with a statistically significant increase appetite and reduce the level of fatigue, anxiety, and depression. Further, studies on cognitive impairment and gastrointestinal symptoms demonstrated significant effects of acupuncture, including in cognitive function, levels of BDNF, incidence of diarrhea, constipation, nausea, and vomiting. However, there are no published studies to which these studies can be compared.

Despite the beneficial results of acupuncture treatment on various symptoms induced by BC treatment, most studies had a low level of reporting quality and a high heterogeneity in methodological quality. Furthermore, there are few studies in which specific symptoms are treated by acupuncture and subsequently evaluated.

This review has some limitations. First, there was no specific restriction on the study selection characteristics for breast cancer, such as stage of cancer, size of tumor, type of surgery, type of chemotherapy. Therefore, these findings only provide preliminary evidence for BC and further studies with a systematic methodology will be needed. Second, acupuncture points were not discussed because there was no similarity among the included trials. Our research team will analyze this topic using network meta-analysis in the near future. Third, although we searched all published studies concerning acupuncture for symptoms induced by BC treatment, we could not identify any studies in the Korean population. Thus, ethnic differences between countries should be examined in future comparative trials for appropriate planning in Korea. Despite these limitations, none of the studies reported severe adverse effects other than minor events, such as slight bleeding and/or bruising due to needle puncture.

This systematic review and meta-analysis of women being treated for breast cancer confirmed that acupuncture had no significant effect on the frequency and severity of hot flushes, but was associated with a significant reduction in general climacteric symptoms and an increase in quality of life. We conclude that acupuncture is not inferior, with respect to safety, to hormone therapy or other applied relaxation therapies in alleviating the symptoms of menopause.

5. Conclusions

There is currently insufficient evidence to conclude that acupuncture is of any benefit to patients suffering from symptoms caused by cancer treatment. Therefore, more rigorous studies are needed to clearly reveal the effectiveness of acupuncture in symptoms induced by BC treatment.

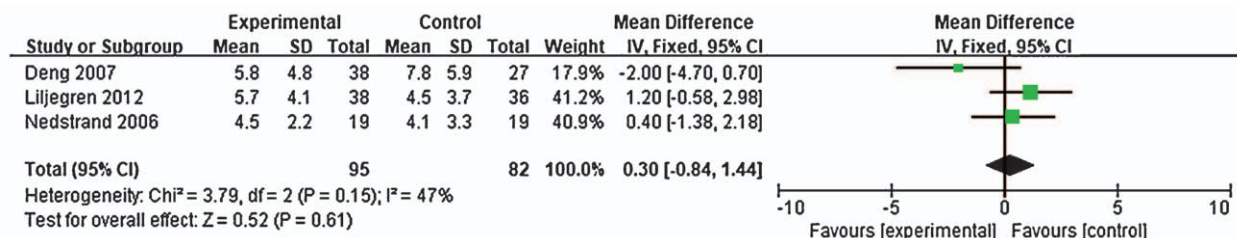


Figure 4. Forest plot of the effect of acupuncture on the frequency of hot flush (Overall).

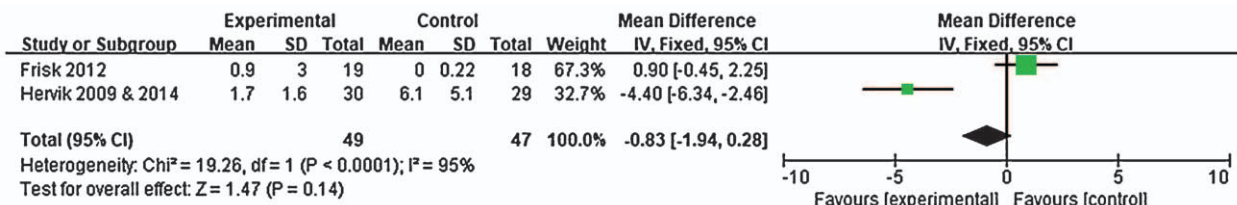


Figure 5. Forest plot of the effect of acupuncture on the frequency of hot flush (Night time).

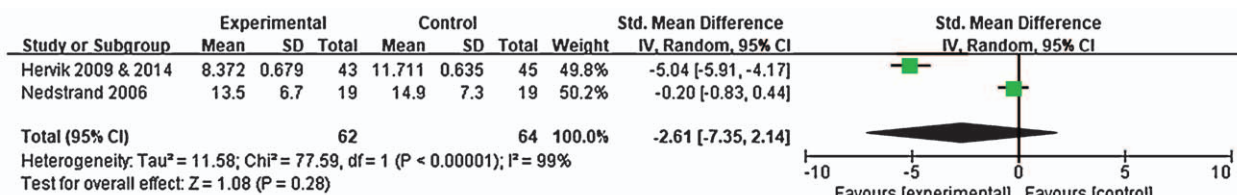


Figure 6. Forest plot of the effect of acupuncture on menopausal symptoms (Kupperman's Index).

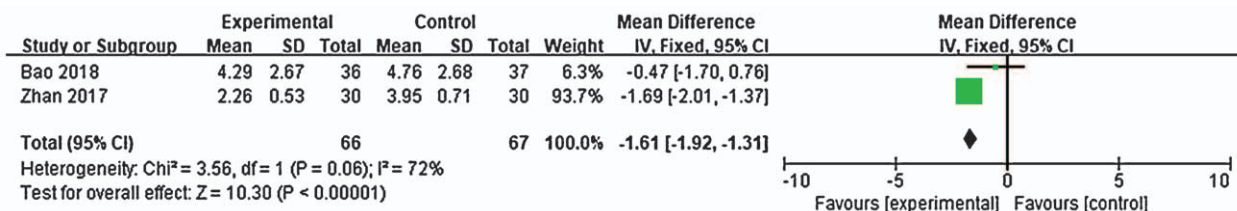


Figure 7. Forest plot of the effect of acupuncture on lymphedema (Arm circumference).

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Author contributions

BHJ and DSH designed the entire study. SJ and YK wrote the manuscript. All authors have read and consent to the publication of the manuscript.

Correction

The corresponding author has been changed from Bo-Hyoung Jang to Deok-Sang Hwang.

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