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A systematic review association of reflexology in managing symptoms and side effects of breast cancer treatment

Ausanee Wanchai [a,*], Jane M. Armer [b]

[a] Deputy Director for Academic Services and Research, Boromarajonani College of Nursing Buddhachinaraj, Muang, Phitsanulok, Thailand
[b] Sinclair School of Nursing, University of Missouri, T32 Health Behavior Science Research Training Program, Nursing Research, Ellis Fischel Cancer Center, American Lymphedema Framework Project, Columbia, MO, USA, 65211

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ABSTRACT

Background: Reflexology is one of complementary approaches most used by patients with breast cancer. The purpose of this article was to evaluate the effects of reflexology on managing symptoms and side effects of breast cancer treatment.
Methods: Data sources included PubMed, CINAHL, ScienceDirect, and Scopus. The criteria were applied to 224 articles and only six articles met the criteria.
Results: Four studies were randomized control trials and two were quasi-experimental designs. Sample sizes varied from 60 to 385 participants. All reflexology programs were taught by certified reflexologists. The results showed that reflexology is associated with benefits for both psychological and physical aspects. Reflexology was reported to improve quality of life, but not for depression or anxiety. It was also beneficial for reducing fatigue, nausea, and vomiting, but not for peripheral neuropathy.
Conclusions: enough high-level evidence has not been reported to confirm the effectiveness of reflexology on breast cancer symptom management.

1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide. There were over 2 million new cases worldwide in 2018 [1]. Breast cancer can also be found in men, although the incidence is less than 1% or only one in a thousand men may be diagnosed with breast cancer [2]. At present, there are many ways to treat breast cancer. Breast cancer patients with stage I to stage III disease have been treated by surgery, followed by radiation therapy or chemotherapy [1]. On the one hand, these treatments help eliminate cancer cells; on the other hand, these treatments may cause negative side effects. For example, radiation therapy may lead to skin irritation and redness, breast tenderness, and lymphedema [3]. Some side effects of chemotherapy may include hair loss, fatigue, nausea vomiting, diarrhea, and pain [4]. The side effects after surgery in breast cancer patients may include pain and discomfort, infection, seroma, and lymphedema [5]. So it is common that patients around the world seek out other treatments called "complementary and integrative health," outside the approaches or in combination with conventional treatments, for their health practices, as they prefer holistic or natural remedies to support their own healing [6].

According to the National Center for Complementary and Integrative Health (NCCIH), the following terms have been clarified [7]. If patients use a non-mainstream practice in addition to conventional medicine, it is called "complementary." If patients combine traditional and non-traditional as part of their care, the term "integrative" will be used. Finally, if a non-mainstream practice is used instead of conventional therapy, it is called "alternative" [7]. Types of complementary and integrative health approaches used by breast cancer patients include herbal medicine, homeopathy, acupuncture, music therapy, hypnosis, Qi Gong, yoga, and reflexology [6,8,9].

However, one aspect to be aware of is that patients who use these complementary and integrative health approaches may not be aware of the potential risks of using these methods, such as the potential interaction of herbal medicine with modern medicine. Many complementary and integrative health approaches still lack high-level scientific evidence to support their safety and effectiveness for cancer patients [6]. This calls for systematic evidence about the effectiveness of using complementary and integrative health approaches in breast cancer patients, so that women with breast cancer can thoughtfully decide

* Corresponding author. Boromarajonani College of Nursing Buddhachinaraj, Muang, Phitsanulok, 65000, Thailand.
E-mail address: wausanee@hotmail.com (A. Wanchai).

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whether or not to include complementary and integrative health approaches in their treatment.

Reflexology is a complementary and integrative health field in which practitioners have been interested in using it to manage symptoms of cancer patients, such as reducing pain from cancer, reducing nausea and vomiting from chemotherapy, and reducing constipation [10]. One theory proposed that the mechanisms of reflexology worked because direct pressure on a specific nerve ending of the foot stimulates the corresponding area of the body for symptomatic relief [11]. Others purported that reflexology helped to activate receptors to release oxytocin; to improve circulation through pressure; and to reduce symptoms through the complex inputs and processes in the neuro matrix of the central nervous system [12]. These theories still needed to be clarified. Therefore, further studies of the mechanisms of reflexology in symptom management among breast cancer patients are needed.

It is also possible that the active "doing" of a regularly applied complementary and integrative health approach such as reflexology provides a psychological comfort beyond the effects of the conventional cancer treatment of surgery, chemotherapy, and radiation. This potential psychological comfort may be considered by some a placebo effect, but further investigation in RCTs and physiological studies may help clarify this role. However, some patients reported experiencing side effects after using reflexology, such as fatigue, chills, dizziness, and fever [13]. These symptoms may come from the nocebo effects, defined as negative physical or emotional responses to reflexology from patient's expectations. Reflexologists need to provide evidence-based information, and maintain good relationship with patients to reduce these nocebo effects [14].

In 2010, one previous paper reported the effectiveness of reflexology on the management of patient symptoms through use of a systematic review [15]. In that paper, the authors reported that reflexology could help to reduce pain and reduce nausea and vomiting in breast cancer patients. However, due to the passage of time and the limitations of the included studies, only four papers were included at that times. Moreover, as only one systematic review paper focused on the effect of reflexology on symptomatic treatment of breast cancer [15], we conducted this systematic review to update the data from RCTs on the application of reflexology for managing symptoms and side effects of breast cancer treatment. Our research question was: What is the association of reflexology with reduction of symptoms and side effects of breast cancer treatments, both psychological and physical aspects? We expect that our conclusion from this update systematic review will enhance health care providers' provision of evidence-based health education to breast cancer patients who are interested in appropriately using reflexology as a complementary and integrative health approach.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

Randomized controlled trials (RCTs) and two-group experimental designs.

2.1.2. Types of participants

Patients with all stages of breast cancer.

2.1.3. Types of interventions

Reflexology intervention. The comparison arm could have been placebo, an alternative intervention, or usual care.

2.1.4. Type of outcome measures

The primary outcomes for this systematic review were self-reported symptom or side effects of breast cancer treatment using validated measures. Adverse events were also recorded in the studies.

2.2. Search methods for identification of studies

The Cochrane guidelines for conducting systematic reviews were used for this review [16]. The Preferred Reporting for Systematic Reviews (PRISMA) was used to describe the refinement process of this systematic review [17]. The following databases were searched from their inception to June 2019: PubMed, CINAHL, ScienceDirect, Scopus, and Cochrane library. The search terms were "reflexology', "reflex therapy", "massage", "foot massage", "zone therapy" combined with "breast cancer", "symptom management", "side effect". For example, search query for PubMed included: "reflexology" [MeSH] OR "reflex therapy" [MeSH] OR "massage" [MeSH] OR "foot massage" [tiab] OR "zone therapy" [MeSH] AND "breast cancer" [MeSH] OR "symptom management" [MeSH] OR "side effect" [MeSH]. Additionally, reference lists of electronically-retrieved manuscripts were hand-searched to retrieve additional relevant citations within the search timeframe.

2.3. Data collection and analysis

2.3.1. Inclusion criteria

Randomized controlled trials or two-group experimental research of women with breast cancer where symptom or side effects of cancer treatment were included as primary or secondary outcome measure and had reflexology as an intervention met inclusion criteria.

2.3.2. Exclusion criteria

Studies were excluded if they were cross-sectional studies, qualitative studies, case-studies, reviews, and expert-opinion papers. Non-refereed articles, abstracts, and dissertations were also excluded.

2.3.3. Study selection

Two review authors independently screened the search results. They identified potentially relevant studies from titles and abstracts. When the papers appeared to meet the inclusion criteria, they obtained the full text. If there was disagreement for selection paper, it was resolved by consensus with a third reviewer.

2.3.4. Data extraction and management

Data from each study were extracted into the literature review form created by the authors, including: intervention (characteristics and duration), details of the participants' health status, assignment to study arm, outcome measures, timing of measurements, adherence to intervention and control, and sample size. One author extracted data and these were checked by another. Disagreements were resolved by consensus with a third reviewer to ensure appropriate and accurate representation of the material.

2.3.5. Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study by using the modified Cochrane Collaboration tool [16]. Any disagreement was resolved by discussion or by involving a third reviewer. This tool has seven domains including: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other sources of bias. It should be noted that only published material was used to assess risk of bias and authors were not contacted to seek clarification. Therefore, a number of items remained unclear and it could not be decided whether the quality criteria were met or unmet. However, based on those information, four studies [18–20,23] were assessed as low risk of bias and two studies [21, 22] were assessed as uncertain risk of bias, as there was insufficient information about the sequence generation and allocation concealment (See Table 1 and Appendix 1).

Table 1
Risk of bias Analysis.

Study	Adequate sequence generation	Allocation concealment	Adequate blinding-participant and personnel	Adequate blinding-outcome assessor	Incomplete outcome data assessment	Selective reporting bias	Other bias	Risk of bias
Wyatt et al., 2012 [18]	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Sharp et al., 2012 [19]	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Kurt et al., 2016 [20]	Low	Unclear	Unclear	Unclear	High	Low	Low	Low
Özdelikara et al., 2017 [21]	High	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Özdelikara et al., 2017 [22]	High	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Wyatt et al., 2017 [23]	Low	Low	Unclear	Unclear	Low	Low	Low	Low

3. Results

The main search results yielded 518 articles and four additional articles were retrieved from references of included studies; these 522 articles underwent initial screening. After checking for duplication, the inclusion and exclusion criteria were applied to 224 articles; 186 articles were excluded based on title and abstract. Of the 39 articles that underwent further detailed inspection, 32 were excluded due to a single-group design or samples were not breast cancer patients. The remaining six articles were included in the final review (Fig. 1). The data were extracted and synthesized into a summary table (Table 2) [18–23].

3.1. Study characteristics

3.1.1. Type of included studies

Among six selected studies, four studies [18–20,23] were RCT (66.67%) and two studies [21,22] were quasi-experimental designs (33.33%).

3.1.2. Participants

The sample size of the studies varied from 60 to 385 participants. Most studies were conducted in women diagnosed with breast cancer [18–22]. Only one study was conducted with patient-caregiver dyads [23]. The mean age of participants fell mainly within the fifth decade (mean of age = 55.50). Three studies included participants with stage I –

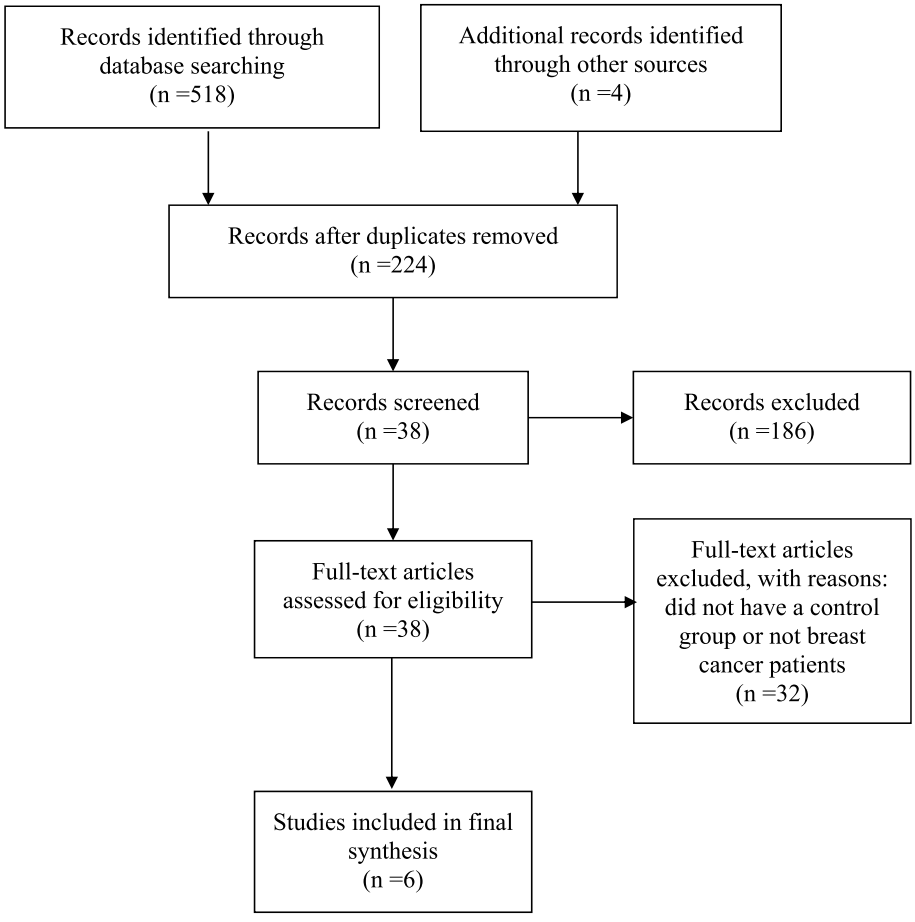

Fig. 1. Literature review flow diagram.

Table 2
Summary of the effects of Reflexology on symptom management.

Study	Design and Sample	Intervention	Outcome Assessment	Findings	Risk of Bias
Wyatt et al., 2012 [18]	Longitudinal RCT with 385 women with advanced-stage breast cancer receiving chemotherapy and/or hormonal therapy - Reflexology (n = 95) - Lay foot manipulation (LFM) (n = 95) - Conventional care (n = 96) Two preliminary – reflexology (n = 51) – LFM (n = 48)	4 weeks 30-min sessions with certified reflexologists	The Physical function subscale of the SF-36; The Functional Assessment of Cancer Therapy-Breast (FACT-B); The Brief Fatigue Inventory (BFI); The Brief Pain Inventory-Short Form (BPIS); The Centre of Epidemiologic Studies-Depression (CES-D); The State-Trait Anxiety Inventory	- Significant improvements in physical functioning, severity of dyspnea, and fatigue for the reflexology group compared to the control group and the LFM group ($p < .05$). - No differences were found on breast cancer–specific HRQOL, depressive symptomatology, state anxiety, pain, and nausea. - No adverse events were reported.	Low risk of bias
Sharp et al., 2012 [19]	RCT with 183 women with early breast cancer. - Self-initiated support (SIS) (n = 62) - SIS plus reflexology (n = 60) - SIS plus scalp massage (n = 61).	Reflexology and massage comprised eight sessions at weekly intervals.	The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy (FACT-B) – breast cancer version. The Hospital Anxiety and Depression Scale (HADS) and the Mood Rating Scale (MRS).	- At primary end-point, massage, but not reflexology, was significantly better than SIS on the TOI. Reflexology and massage were both better than SIS for MRS relaxation. - Massage was better than reflexology and SIS for MRS easygoingness. At secondary end-point: Reflexology, but not massage, was better than SIS on the TOI and MRS relaxation. - There were no significant differences between reflexology or massage. - There were no significant differences between group differences in HADS anxiety and depression.	Low risk of bias
Kurt et al., 2016 [20]	RCT with 60 patients who had chemotherapy-induced peripheral neuropathy - Experimental group (n = 30 - Control group (n = 30)	6 weeks 20-min, twice- a-day, with certified reflexologists or relatives (educated by researcher)	The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy (EORTC-CIPN-20) form, and BPI (used for related chemotherapy-induced peripheral neuropathy symptoms).	- Peripheral neuropathy severity and incidence were not different between 2 groups ($p > 0.05$). - There were no significant differences between 2 groups for QOL functions related to CIPN ($p > 0.05$).	Low risk of bias
Özdelikara et al., 2017 [21]	An experimental research with 60 patients with stage I-III breast cancer - The control group (n = 30) - The experimental group (n = 30).	Reflexology was applied in 3 sessions (one in each 3 chemotherapy cycles), and a posttest was applied to the patients over the phone 24 h. Each reflexology session took approximately 30–40 min	The European Organization for Research and Treatment of Cancer Core QoL Questionnaire (EORTC-QLQ-C30)	After the reflexology treatment: - Symptom total scores in the experiment group decreased. - The general health and functional total scores in the treatment group increased ($p = 0.000$). - Symptom total scores of the patients in the treatment group were significantly lower than that of the patients in the control group ($p = 0.001$).	Unclear
Özdelikara et al., 2017 [22]	An experimental research with patients diagnosed with stage I–III breast cancer sixty patients - The control group (n = 30) - The experimental group (n = 30).	Each reflexology session took approximately 30–40 min. Sessions were applied in a special room within the chemotherapy unit on ergonomic and position-changeable beds.	The Brief Fatigue Inventory (BFI); The Rhodes index of nausea, vomiting, and retching (INVR)	- The BFI mean scores of patients in the experimental group gradually decreased in the first, second, and third measurements ($P < 0.05$). - The difference between the total mean scores of INVR in the experimental and control groups was significant on the onset and first and second measurements.	Unclear
Wyatt et al., 2017 [23]	RCT enrolled 256 patient-caregiver dyads	4-week, home-based reflexology Intervention, delivered by caregiver trained by the reflexologist	The M.D. Anderson Symptom Inventory (MDASI); Patient-Reported Outcomes Measurement Information System (PROMIS); Quality of Life Index (QLI); Multidimensional Scale of Perceived Social Support (MSPSS); Quality of Relationship	- Significant reductions in symptom severity and interference over 11 weeks were found in the reflexology group compared with control. - No group differences in functioning, social support, quality of relationship, or satisfaction with life at weeks 5 and 11.	Low risk of bias

III cancer [18,21,22] and two additionally included participants with stage III and IV [19,23] and one study did not report cancer stage [20].

3.1.3. *Interventions*

All reflexology interventions were taught by certified reflexologists [18–23]. Although one study reported the reflexology intervention was delivered by caregivers, those caregivers were trained by the certified

trainers before doing reflexology for patients [23]. Durations for reflexology intervention varied from 3 weeks to 8 weeks. Each reflexology session took approximately 20 min–40 min.

3.1.4. Outcome measures

The primary outcome measures reported in the included studies most frequently focused on quality of life as measured by using the Short-Form Health Survey (SF-36) [18], the Functional Assessment of Cancer Therapy-Breast (FACT-B) [18,19], the Breast Cancer-Specific Health-Related Quality of Life (HRQOL), the European Organization for Research and Treatment of Cancer Core QoL Questionnaire (EORTC-QLQ-C30) [21], and the Quality of Life Index (QLI) [23]. Other psychological aspects, such as anxiety and depression were also evaluated, using the State-Trait Anxiety Inventory [18], the Hospital Anxiety and Depression Scale (HADS) [19], and the Center of Epidemiologic Studies-Depression (CES-D) [18]. In addition, other symptoms-related to breast cancer treatments, such as fatigue, peripheral neuropathy, and nausea/vomiting were assessed with various tools, including: the Brief Fatigue Inventory-Short Form (BFI) [18,22], the European Organization for Research and Treatment of Cancer QoL Questionnaire Chemotherapy-Induced Peripheral Neuropathy (EORTC-CIPN-20) [20], and the Rhodes Index of Nausea, Vomiting, and Retching (INVR) [22].

3.2. Reported efficacy of reflexology for symptom management in patient with breast cancer

Pooling the data from the six reviewed studies, it may be concluded that reflexology may be more beneficial for psychological effects than physical side effects for patients suffering from cancer treatment. More details are presented throughout this article.

3.2.1. Psychological symptom outcomes

3.2.1.1. Quality of life. Based on the six included studies, there were four studies which explored the association of reflexology on quality of life of women with breast cancer. Two studies found a positive relationship with reflexology on improving quality of life of these women [19,21]. In the first study, the researchers evaluated the effects of reflexology on quality of life in women with early-stage breast cancer (N = 183) [19]. The finding of the study reported that reflexology plus self-initiated support was associated with improved quality of life of patients at the 24th week after surgery, but not at the 18th week after surgery. The intervention was provided by the certified trainers one -hour sessions for 8 weeks [19] In a second study, the researcher applied foot reflexology while patients (N = 60) were receiving the chemotherapy infusion cycle for three sessions, each session lasting 30–40 min. The researcher reported to have received reflexology training through the reflexology course at the reflexology school before conducting research [21].

On the other hand, different findings regarding the quality of life of women with breast cancer were reported in two studies. One study compared reflexology with two other interventions, including lay foot manipulation and conventional care, as to whether they were associated with improved quality of life of patients with advanced-stage breast cancer (N = 385) [18]. In this study, the reflexology intervention was comprised of four sessions, with 30-min sessions for 4 weeks provided by certified reflexologists. Although researchers reported no adverse events were reported, nor was a difference found on health-related quality of life outcome in these patients [18]. Another study reported that reflexology was not associated with improved satisfaction with life as measured by the Quality Life Index in patients with stage III or IV breast cancer (N = 256) [23]. However, in this study, the reflexology intervention was performed by caregivers trained by a certified reflexologist in a 30-min for 4 weeks [23].

It is difficult to conclude from this systematic review the association of reflexology with improved quality of life for breast cancer patients, since the included studies were equal in showing the significant (n = 2)[19,21] and not significant (n = 2)[18,23] effects of reflexology in terms of the number of studies. Other important issues which should be considered here are risk of bias and sample size of each study. As can be seen, one study that reported positive outcome for improving quality of life of these patients was determined at uncertain risk of bias, had small sample sizes (N = 60), and used a quasi-experimental design [21]. On the other hand, two studies that did not report positive outcomes of reflexology in association with improved quality of life among these patients had greater sample sizes (N = 385, 256, respectively), more rigorous study design (RCT), and were determined as having low risk of bias [18,23]. These findings may beg for further studies to confirm the results.

3.2.1.2. Depression and anxiety. Two included studies conducted RCT to evaluate the effect of reflexology on depression and anxiety among women with early and advanced-stage breast cancer (N = 358,183, respectively) [18,19]. The first study, the reflexology intervention was comprised of four sessions, with 30-min sessions for 4 weeks provided by certified reflexologists [18]. On the other hand, the reflexology intervention in the second study was comprised of eight sessions, with one-hour sessions for 8 weeks provided by certified therapists [19]. Symptoms were assessed through use of the Center of Epidemiologic Studies-Depression (CES-D), the State-Trait Anxiety Inventory, and the Hospital Anxiety and Depression Scale (HADS) tools. Similar results were found in these two studies. Depression and anxiety scores were not improved from receiving reflexology intervention. Although these two studies were determined as low risk of bias and used the rigorous study design with the RCT, the number of included studies is still questionable, as inclusion of only two papers does not provide a sound conclusion for this association.

3.2.2. Physical symptom outcomes

3.2.2.1. Fatigue, nausea and vomiting. There were two studies focused on the effect of reflexology on fatigue, nausea and vomiting [18,22]. One study conducted a longitudinal, RCT with 385 predominantly-Caucasian women with advanced-stage breast cancer receiving chemotherapy and/or hormonal therapy [18]. Another study conducted an experimental research with 60 patients diagnosed with stage I–III breast cancer [22]. These two studies used the same tool to measure fatigue, namely the Brief Fatigue Inventory (BFI) [18,22]. Interestingly, both studies confirmed the positive association of reflexology with decreased fatigue of women treated for breast cancer ($p < 0.01$; $p < 0.05$, respectively) [18,22]. In addition, these two studies also examined the effects of reflexology on nausea and vomiting symptoms of women treated for breast cancer. The results were different on this dimension. Whereas the former study reported no difference was found on nausea symptom [18], the latter study reported the positive effect of reflexology in nausea and vomiting [22]. However, as only two papers reported such outcomes, more rigorous studies are needed before confirming these results. Furthermore, the limitations of one study, including use of a quasi-experimental research design, uncertain risk of bias, and small sample sizes (N = 60) [22], supports the need for more rigorous studies to examine the effectiveness of reflexology on decreasing such symptoms.

3.2.2.2. Peripheral neuropathy. Only one study evaluated the effect of reflexology on the management of chemotherapy-induced peripheral neuropathy in cancer patients [20]. In this study, the researcher compared reflexology with the standard of care in patients who had chemotherapy-induced grade II-IV peripheral neuropathy (N = 60). The reflexology intervention was composed of six weeks, twice daily. Each session lasting 20 min. This protocol was performed by the certified reflexologist or relatives (educated by researcher). Unfortunately, the

results of the study showed that peripheral neuropathy severity and incidence were not different between the two groups. One issue which should be pointed out here is that the reflexology intervention in this study was not provided only by certified reflexologists, but also patient's relatives who were educated by the researcher. So, although the risk of bias was scored as low-level risk, this may be the influencing factor related to the results of study.

4. Discussion

This systematic review revealed that, at the present, high-level evidence does not strongly demonstrate reflexology to be effective for any cancer symptom management. Even though some previous studies in this systematic review reported positive effects of reflexology on psychological aspects, such as quality of life and physical aspects, such as nausea and vomiting, the limited numbers of studies and small sample sizes are a concern. This is consistent with previous systematic reviews which reported insufficient high-level evidence demonstrated the effectiveness of reflexology for any medical condition [24,25].

Interestingly, although we cannot explain clearly how reflexology works to reduce symptoms, it has been used as complementary to the main treatment to manage symptoms related to cancer and its treatment by breast cancer patients and many scholars remain interested in testing its effectiveness for symptom management among breast cancer patients [22,23]. We may note here that there have been many excluded studies in breast cancer patients reporting the positive effects of reflexology, such as improved quality of life, reduced pain, increased range of motion, reduced secondary lymphedema, reduced peripheral neuropathy, increased workplace productivity, or reduced hospital visits [22,26–28]. Unfortunately, they were one group quasi-experimental designs. So, their conclusions were not strong enough to convincingly support the positive effects of reflexology. In addition, many reflexology practitioners have reported that reflexology is an effective complementary way for improving general health and well-being, rather than for curing a specific symptom [29,30]. Therefore, these perspectives support the continuing need for further randomized control trials to confirm the benefits of reflexology in breast cancer patients. So, in conclusion, until stronger evidence is demonstrated, for patient safety, reflexology intervention should be delivered by certified reflexologists or persons who are trained by certified trainers. Any adverse events should be reported to health care providers. More importantly, reflexology should be used as a complementary approach, not as a main treatment or used instead of the conventional cancer treatment.

5. Conclusions

This systematic review finds that reflexology has not yet accrued sufficient high-level evidence to support its effectiveness in managing symptoms related to breast cancer treatments, in large part due to the limited numbers of included studies. More studies to confirm the effectiveness of reflexology in managing symptoms and side effects of cancer treatments are needed in order to recommend its wide use among breast cancer survivors. However, no adverse effects are reported among those receiving the reflexology intervention. Also of positive note is the breast cancer survivors are willing to participate in studies in complementary and integrative therapies, supporting the opportunity for further research in this area. The authors acknowledge that the final studies selected were published from 2012 to 2018.

Authorship

All authors made significant contributions to the study design, searching data, drafting of the article, and final approval of the article.

Author contribution

Ausanee Wanchai: Study conception & design, Literature review, Data synthesis, Drafting of the article.

Jane M. Armer: Data synthesis, Critical revision of the article.

Declaration of competing interest

None.

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Appendix C. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ctcp.2019.101074.

Appendix 1

Characteristics of included studies

Wyatt et al., 2017 [23].

Methods	RCT: 3 arms	
Participants	Women with advanced-stage breast cancer receiving chemotherapy and/or hormonal therapy.	
Interventions	Reflexology comprised 4 weekly 30-min sessions, provided by the certified reflexologists.	
Outcomes	The Physical function subscale of the SF-36; The Functional Assessment of Cancer Therapy-Breast (FACT-B); The Brief Fatigue Inventory (BFI); The Brief Pain Inventory-Short Form (BPIS); The Centre of Epidemiologic Studies-Depression (CES-D); The State-Trait Anxiety Inventory	
Exclusions	Receiving hospice care, residing in a nursing home, being bedridden, regularly using CAM similar to those used in the protocol, and participating in an experimental chemotherapy protocol.	
Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	Low	Using computerized minimization technique
Allocation concealment	Low	Using computerized minimization technique
	Unclear	No details provided for clinician blinding.

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Risk of bias	Authors' judgement	Support for judgement
Adequate blinding-participant and personnel		
Adequate blinding-outcome assessor	Unclear	Interviewers were blinded to group assignment, but no details provided.
Incomplete outcome data assessment	Low	3 women in the intervention group and 5 women in the control group dropped out and these women were not assigned.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

Sharp et al., 2012 [19].

Methods	RCT: 3 arms
Participants	Women with early breast cancer received breast surgery.
Interventions	Reflexology comprised 8 weekly one-hour session, provided by the trained therapists.
Outcomes	The Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy (FACT-B) – breast cancer version. The Hospital Anxiety and Depression Scale (HADS) and the Mood Rating Scale (MRS).
Exclusions	History of cancer, participating in another trial, cognitive impairment

Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	Low	Using a permuted blocks randomization
Allocation concealment	Low	Sequences were stored in sealed, opaque, numbered envelops.
Adequate blinding-participant and personnel	Unclear	No details provided for participant and clinician blinding.
Adequate blinding-outcome assessor	Unclear	No details provided for assessor blinding.
Incomplete outcome data assessment	Low	Intention to treat.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

Kurt et al., 2016 [20].

Methods	RCT: 2 arms
Participants	Patients who had chemotherapy-induced peripheral neuropathy.
Interventions	Reflexology comprised 6 weekly 20-min session, provided by certified reflexologist or relatives (educated by researcher).
Outcomes	The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy-Induced Peripheral Neuropathy (EORTC-CIPN-20) form, and BPI (used for related chemotherapy-induced peripheral neuropathy symptoms).
Exclusions	Any condition that could interfere with reflexology, such as bone or vertebra metastasis

Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	Low	Using a computer.
Allocation concealment	Unclear	No details provided for allocation concealment.
Adequate blinding-participant and personnel	Unclear	No details provided for participant and clinician blinding.
Adequate blinding-outcome assessor	Unclear	No details provided for assessor blinding.
Incomplete outcome data assessment	High	15 patients in the control group loss of 2nd follow up. 6 patients in the intervention group did not do massage regularly.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

Özdelikara et al., 2017 [21].

Methods	Two-group experimental research
Participants	Patients with stage I-II-III breast cancer.
Interventions	Reflexology comprised 3 sessions, 30–40 min in each session, provided by trained reflexology researcher.
Outcomes	The European Organization for Research and Treatment of Cancer Core QoL Questionnaire (EORTC-QLQ-C30)
Exclusions	Haemorrhage, epilepsy or fever, paraplegia or thrombosis, gall-kidney stone, leg foot disease, psychiatric disorder.

Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	High	Sequence generated by some rule on day of application.
Allocation concealment	Unclear	No details provided for allocation concealment.
Adequate blinding-participant and personnel	Unclear	No details provided for participant and clinician blinding.
Adequate blinding-outcome assessor	Unclear	No details provided for assessor blinding.
Incomplete outcome data assessment	Low	Intention to treat.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

Özdelikara et al., 2017 [22].

Methods	Two-group experimental research	
Participants	Patients with stage I-III breast cancer.	
Interventions	Reflexology session took 30–40 min in chemotherapy unit and provided by researcher who received training in the reflexology course.	
Outcomes	The Brief Fatigue Inventory (BFI); The Rhodes index of nausea, vomiting, and retching (INVR)	
Exclusions	Haemorrhage, epilepsy or fever, paraplegia or thrombosis, gall-kidney stone, leg foot disease, psychiatric disorder.	
Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	High	Sequence generated by patient first application day of the week to clinic.
Allocation concealment	Unclear	No details provided for allocation concealment.
Adequate blinding-participant and personnel	Unclear	No details provided for participant and clinician blinding.
Adequate blinding-outcome assessor	Unclear	No details provided for assessor blinding.
Incomplete outcome data assessment	Low	Intention to treat.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

Wyatt et al., 2017 [23].

Methods	RCT: 2 arms	
Participants	Patients with stage III or IV breast cancer undergoing chemotherapy and/or hormonal therapy and their caregivers.	
Interventions	Reflexology comprised 30-min sessions. Caregiver was trained by a study reflexologist at home in the first session. Then the two additional weeks of one or more sessions per week were delivered by the caregiver to the patient without the reflexologist.	
Outcomes	The M.D. Anderson Symptom Inventory (MDASI); Patient- Reported Outcomes Measurement Information System (PROMIS); Quality of Life Index (QLI); Multidimensional Scale of Perceived Social Support (MSPSS); Quality of Relationship.	
Exclusions	Mental illness, residing in a nursing home, bedridden, deep thrombosis or foot neuropathy.	
Risk of bias	Authors' judgement	Support for judgement
Adequate sequence generation	Low	Using minimization technique
Allocation concealment	Low	Using minimization technique
Adequate blinding-participant and personnel	Unclear	No details provided for clinician blinding.
Adequate blinding-outcome assessor	Unclear	No details provided for assessor blinding.
Incomplete outcome data assessment	Low	7 women dropped out and these women were not assigned.
Selective reporting bias	Low	No evidence of selecting reporting.
Other bias Risk of bias	Low	No evidence of other bias identified.

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