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Systematic review

The effectiveness of moxibustion for cancer-related fatigue: An updated systematic review and meta-analysis

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ABSTRACT

Introduction: Cancer-related fatigue is a common and debilitating symptom in cancer patients. Moxibustion is frequently used in cancer and its complications. However, evidence that moxibustion can improve cancer-related fatigue is insufficient. We systematically reviewed existing clinical randomized controlled trials to investigate whether moxibustion can improve cancer-related fatigue.

Methods: We used three methods to search for relevant studies. Thirteen electronic databases were searched. Adult patients diagnosed with cancer were included in our study. Intervention group patients received moxibustion only or a combination of moxibustion with other co-interventions. Patients in the control group used no moxibustion intervention. The primary outcome was fatigue. RevMan version 5.3 was used to analyze all data. This study was reported based on the PRISMA statement.

Results: A total of 22 studies with 1628 cancer patients were included in this review. The included studies had methodological limitations of varying degrees. The results of the meta-analysis indicate that moxibustion can significantly reduce fatigue regardless of the type—sensory fatigue, behavioral fatigue, affective meaning fatigue, cognitive fatigue, physical fatigue, or total score of fatigue.

Conclusions: The study findings suggest that moxibustion can improve cancer-related fatigue and most aspects of quality of life (except for economic difficulty and insomnia). Moxibustion is relatively safe as treatment for cancer patients. Owing to the small number, short intervention duration and methodological drawbacks of the included studies, more rigorously designed large randomized controlled trials with satisfactory intervention durations and follow-up periods are required to provide more reliable evidence.

1. Introduction

Fatigue is a common symptom observed in cancer patients with an incidence range of 60%–90% [1]. The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." [2] Patients consider CRF as the most painful symptom of cancer or its treatment. Compared with pain, nausea, and vomiting, which can be improved by interventions, CRF causes more distressing problems [3]. Long-term CRF prevents patients from devoting themselves to activities of daily living, thus reducing their quality of life (QOL) [4–6]. Compared with fatigue in non-tumor patients, CRF is more severe, more painful, and cannot be alleviated by rest [2].

The CRF interventions recommended by NCCN can be classified into two broad categories: pharmacologic interventions (psychostimulants such as methylphenidate) and nonpharmacologic interventions (physical activity, physically based therapies, psychosocial interventions, nutrition consultation, sleep therapy, et al.) [2]. Acupuncture,

Abbreviations: AMED, allied and complementary medicine; BFI, brief fatigue inventory; CBMdisc, China biology medicine disc; CENTRAL, cochrane central register of controlled trials; CFS, cancer fatigue score; CINAHL, cumulative index to nursing and allied health literature; CNKI, China national knowledge infrastructure; CRF, cancer-related fatigue; Embase, excerpta medica database; EORTC QLQ-C30, European organization for research and treatment of cancer quality of life questionnaire; NCCN, national comprehensive cancer Network; PFS-R, piper fatigue Scale; PSQI, Pittsburgh sleep quality index; QOL, quality of life; RCTs, randomized controlled trials; SMD, standardized mean difference; WMD, weighted mean difference

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acupressure and massage are regarded as physical therapies in the NCCN guidelines, and massage as category 1 (NCCN consensus based on high-level evidence determined that the intervention is appropriate.) was recommended for CRF in patients on active treatment [2]. However, moxibustion as a widely used technique in traditional Chinese medicine has not been mentioned in the guidelines. The current systematic review [7,8] is outdated because numerous randomized controlled trials (RCTs) on moxibustion for CRF have been conducted in recent years. So the aim of this systematic review was to evaluate RCTs on the effectiveness of moxibustion as a treatment for CRF and determine the role and safety of moxibustion in improving CRF.

2. Methods

We reported this study on the basis of the PRISMA statement.

2.1. Inclusion criteria for determining eligibility studies

2.1.1. Types of studies

Randomized controlled trials (RCTs).

2.1.2. Types of participants

Adult cancer survivors (aged 18 years and older) were included, regardless of sex, type of cancer diagnosis, tumor grade, clinical status (e.g., active cancer treatment, post-treatment, end of life), or anticancer treatment protocols.

2.1.3. Types of interventions

Moxibustion treatment included any of the widely used forms (in Fig. 1), but not limited to these. Patients received moxibustion only or a combination of moxibustion with other co-interventions, which were consistent with the control groups.

2.1.4. Types of comparisons

Patients in the control groups used no moxibustion intervention, such as exercises, sham moxibustion, psychosocial therapy, or standard methods of care.

2.1.5. Types of outcome measures

The primary outcome for this systematic review was CRF, as determined using valid measurements, such as the Brief Fatigue Inventory (BFI), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the Revised Piper Fatigue Scale (PFS-R). The secondary outcomes were QOL and potential adverse events associated with the interventions. Adverse events refer to any harm caused by the moxibustion interventions to participants, such as scalding. All included studies were required to report the primary outcome—CRF.

2.2. Search methods for identification of studies

We used three methods to search for relevant studies: electronic searching, manual retrieval and citation snowballing. The following 13 electronic databases were searched (from their respective inceptions to November 2018): China National Knowledge Infrastructure (CNKI), Wanfang, VIP, China Biology Medicine disc (CBMdisc), PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica Database (Embase), Allied and Complementary Medicine (AMED), Science Direct, Thomson Reuters Web of Science, PsyclNFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and ALT HealthWatch. Mesh terms and key words used in this study included: “moxibustion”, “moxa”, “warming needle moxibustion”, “neoplasm”, “cancer”, “tumour” and so on. PubMed (Appendix 1) and CNKI database retrieval strategies were developed, and other databases in the same language were retrieved after appropriate adjustments. Unpublished and published data were manually retrieved from our university library. In addition, published reference lists of existing reviews and all included studies were checked for further eligible publication. Retrieval results were not restricted by language.

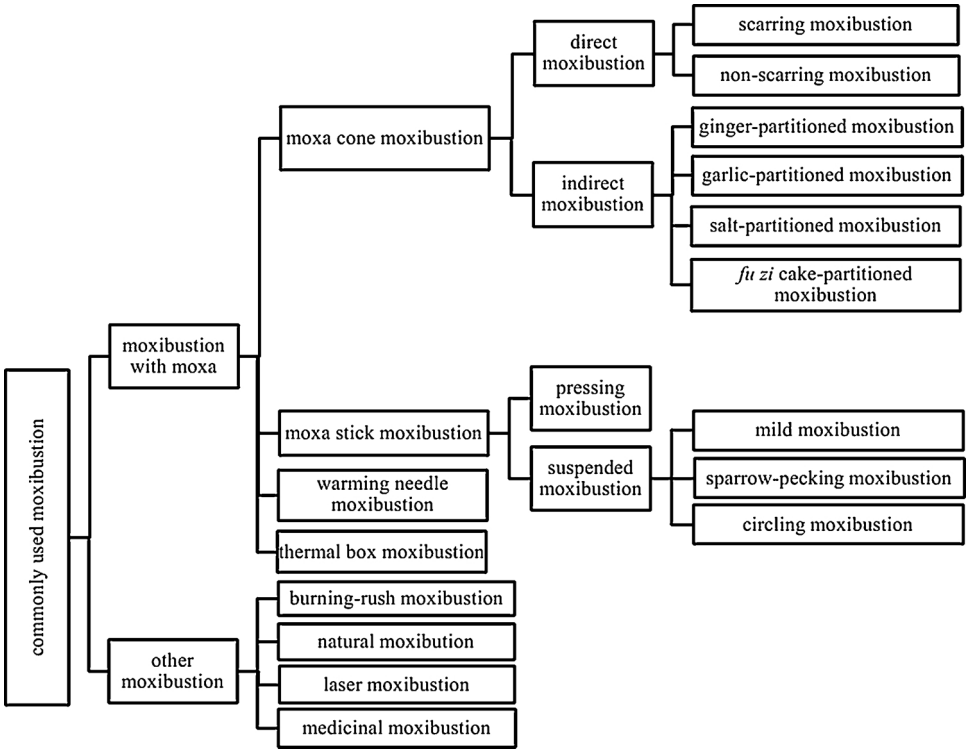

Fig. 1. The commonly used moxibustion.

2.3. Selection of studies

Titles and abstracts of all search results were screened by two reviewers (Ma and Lou) for eligibility. The same two reviewers re-examined the full-text versions of the articles to determine whether to include them in the study. Disagreements between the two reviewers were resolved by discussion or with the involvement of a third reviewer (Sun).

2.4. Data extraction and assessment of risk of bias

The two reviewers independently extracted data from all included studies by using a standardized data extraction form, which contained general information (name of the first author, publication year, and ethnicity), patient characteristics (sex, mean age, sample size, cancer diagnosis, clinical status and tumor grade), interventions methods (style, intensity, and duration), control groups, and outcome data. Risk of bias was evaluated based on the quality assessment method of the 2011 Cochrane Handbook; parameters of the risk of bias were graded as high, low, or unclear [9]. Disagreements between the two reviewers were resolved by discussion or with the participation of a third reviewer (Sun). Reviewers needed to contact the authors of the articles that provided no quantitative data to obtain the missing data; otherwise, the missing data was estimated from other available statistics.

2.5. Data synthesis

RevMan version 5.3 was used to analyze all data. One reviewer (Ma) entered the data into RevMan 5.3, and another reviewer (Lou) checked data for inputting. If the same measures or scales were used to quantify the outcomes, the weighted mean difference (WMD) was used; otherwise, the standardized mean difference (SMD) was used. For differences of the scale direction, "If some scales increase with disease severity whilst others decrease it is essential to multiply the mean values from one set of studies by -1 to ensure that all scales point in the same direction" [9]. We used the chi-squared and I^2 tests to check for statistical heterogeneity between trials. When significant heterogeneity was demonstrated by a statistically significant chi-squared test or $I^2 > 50\%$, we investigated sources of heterogeneity by conducting subgroup analysis (according to patients characteristics, cancer type, clinical status, intensity, duration among trials, control group comparisons, etc.) or sensitivity analysis. Random-effects model was used to pool all trials as a rough synthesis. Stability of outcomes was tested by sensitivity analysis.

3. Results

3.1. Trial characteristics

A total of 123 relevant references were retrieved, 11 of which were removed because of duplication, and 90 were excluded for failing meet to the eligibility criteria. A total of 22 studies were ultimately included in the qualitative synthesis [10–31], among which, 21 studies were included in the quantitative synthesis [10–26,28,11–31] (Fig. 2). A two-arm parallel group design was adopted in 20 trials [10–25,27,28,30,31], and a three-arm parallel group design was used in the 2 remaining trials [26,29]. Sample sizes ranged from 24 to 180. All included studies were performed in China. The characteristics of all included studies are listed in Table 1.

3.2. Participant characteristics

Our research included 1628 patients; 812 were assigned to the intervention groups and 816 were assigned to the control groups. Patients with breast cancer were included in 4 trials [15–17,28]; patients with lung cancer were recruited in 3 trials [11,20,21]; patients with gastric cancer [13], cervical carcinoma patients [12], esophageal cancer [23] and liver cancer [31] respectively participated in 1 trial; and patients with different type of cancer were included in the remaining 11 trials [10,14,18,19,22,24–27,29,30] (Table 1).

3.3. Intervention protocols

Different interventions were adopted in different numbers of trials: grain-sized moxibustion in 5 trials [11,14,21,28,30]; ginger-partitioned moxibustion in 4 trials [22,26,29,31]; moxa stick moxibustion in 3 trials [17,23,25]; thermal box moxibustion in 3 trials [12,19,24]; moxa cone moxibustion in 2 trials [13,15]; laser moxibustion in 2 trials [10,18]; medicinal moxibustion in 1 trial [16]; thermal moxibustion in 1 trial [20]; thermal box moxibustion combined with ginger-partitioned moxibustion in 1 trial [27]. Comparison interventions were also used: conventional therapy in 19 trials [11–17,19–21,23–31]; sham laser moxibustion in 2 trials [10,18]; and sham ginger-partitioned moxibustion in 1 trial [22]. With regard to the three-armed parallel group design [29], its three groups used daily ginger-partitioned moxibustion, every-other-day ginger-partitioned moxibustion, and conventional therapy. Only 2 groups (daily ginger-partitioned moxibustion group and conventional therapy group) were included in our analysis. Treatment frequency varied from 3 to 7 times per week and lasted for 10–30 min or 3–20 ZHUANG every time, while the duration of treatments lasted from 8 days to 6 months.

3.4. Risk of Bias of the included studies

Each risk of bias item for all included trials is presented in Fig. 3. Randomization was mentioned in all 22 studies, and random sequence generation methods (low risk of bias) were described in 13 studies (68.2%) [10–15,17–21,28,29]. Only 6 studies (27.3%) [10–12,18,22,29] clearly reported on allocation concealment methods (low risk of bias); 5 studies (22.7%) [10,12,18,22,29] reported on blinding of patients and personnel (low risk of bias). Blinding of outcome assessment (unclear risk of bias) was not reported in any of the included studies. Among the 22 studies, 1 trial [10] (4.5%) provided incomplete outcome data (high risk of bias), and all the remaining trials provided complete outcome data (low risk of bias). None of the studies selectively reported outcomes (low risk of bias).

3.5. Effects of the interventions

All included trials supported the positive effects of moxibustion in the control of CRF and improvement of QOL. The included studies measured outcomes using different assessment instruments. With differences in intervention method considered, the outcomes of meta-analysis need to be interpreted charily. Table 2 presents a summary of the meta-analysis.

3.5.1. Fatigue

Fatigue was measured in 21 studies by using BFI [10,14,16–18,21,26,28], EORTC QLQ-C30 scores [11,13,22,24,29,31], PFS-R [15,19,20,25,27,30], and Cancer Fatigue Score (CFS) [12]. The remaining 1 study did not report measurement method [23]. In accordance with the classification of fatigue in these assessment scales, the results were reported from five aspects (sensory fatigue, behavioral fatigue, affective meaning fatigue, cognitive fatigue, physical fatigue, total score of fatigue). The results of the meta-analysis indicate that moxibustion can significantly reduce fatigue regardless of the type—-sensory fatigue (SMD -1.12; 95% CI [-1.65, -0.58]; $P < 0.0001$), behavioral fatigue (SMD -2.93; 95% CI [-4.32, -1.54]; $P < 0.00001$), affective meaning fatigue (SMD -1.01; 95% CI [-1.65, -0.38]; $P = 0.002$), cognitive fatigue (SMD -1.05; 95% CI [-1.52, -0.58]; $P = < 0.0001$), physical fatigue (SMD -1.61; 95% CI [-2.38, -0.85]; $P < 0.0001$), or total score of fatigue (SMD -1.17; 95% CI [-1.44, -0.90];

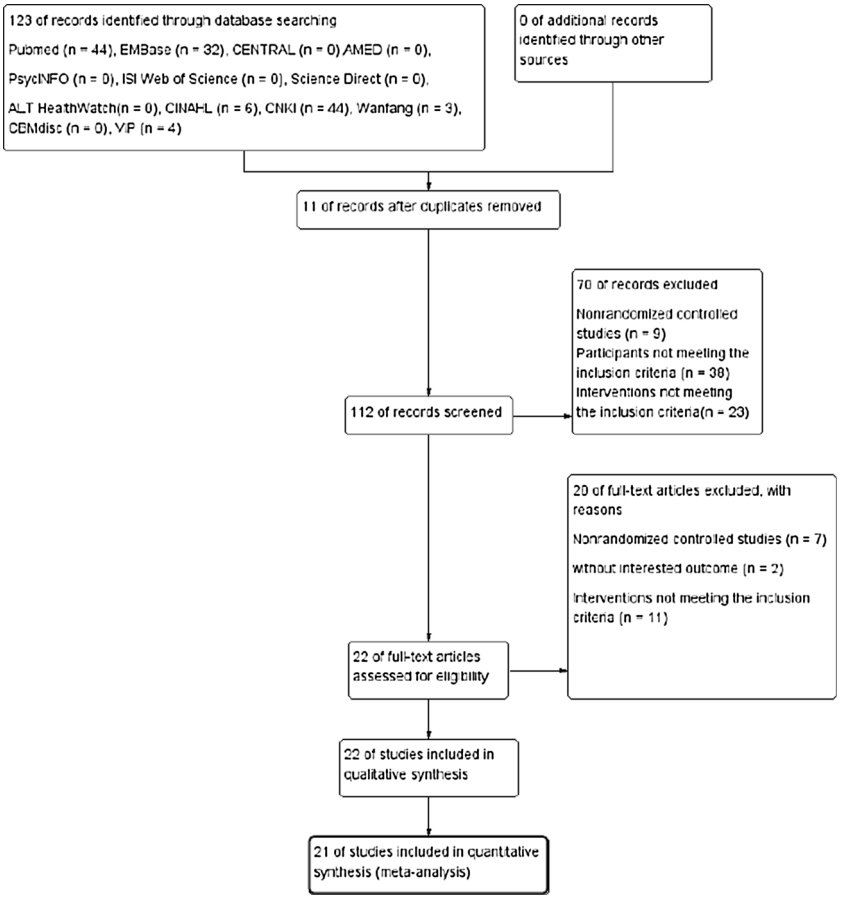

Fig. 2. Flow chart of study selection.

$P <$ 0.00001). One study was not included in the meta-analysis because of insufficient number of studies [14], and its results showed that moxibustion exerted a positive effect on relieving CRF. Three trials [17,26,27] reported results using hierarchical data. Although their results could not be analyzed in our meta-analysis, their outcomes indicated an improvement in CRF.

3.5.2. Quality of life

The majority of the included trials used EORTC QLQ-C30 to measure QOL. The instrument measures 15 aspects of QOL (astriction, nausea and vomiting, diarrhoea, role function, economic difficulty, anhelation, emotional function, physical function, cognitive function, social function, insomnia, loss of appetite, pain, a global QOL scale); thus, we also reported results based on these 15 aspects. One trial measured insomnia by using Pittsburgh sleep quality index (PSQI), hence the inclusion of the results for this outcome in our meta-analysis. The meta-analysis showed that moxibustion can improve the majority of the aspects of the QOL; however, for economic difficulty (MD -5.11; 95% CI [-10.66, 0.44]; $P =$ 0.07) and insomnia (SMD -0.31; 95% CI [-0.72, 0.10]; $P =$ 0.14), moxibustion was invalid. Other results of meta-analysis are shown in Table 2.

3.5.3. Adverse events

Five studies [10,19,21,24,25] reported adverse events associated with moxibustion: 1 study [25] reported no adverse events; 3 studies [19,21,24] reported mild blisters in 1 or 2 patients, and 1 study [10] reported erythema and slight itching in 1 patient.

3.5.4. Other findings

In addition, there are some findings in these included studies. The results of Jiang, 2018 [15] showed that the decrease in CRF accompanied with the change of the biochemical index (interleukin-1, tumor necrosis factor-α, transforming growth factor-β and C-reactive protein decreased; cortisol in serum increased). Xu, 2017 [25] showed that moxibustion could improve the number of T-lymphocytes, T helper cells and natural killer cells. Zhang Mengxue, 2016 [11] showed that moxibustion could significantly reduce the proportion of neutral granule-lymphocyte. Yang, 2012 [26] showed that moxibustion could significantly improve the percentage of CD3, CD4 and natural killer cells. In order to observe whether moxibustion treat CRF by improving the nutritional status, Li, 2013 [16] measured the serum albumin content of the patients before intervention and after 2 weeks, 4 weeks, 8 weeks after moxibustion. They found no significant fluctuations in serum albumin in the moxibustion group, which suggested that the mechanism of moxibustion therapy for CRF may not be directly related to nutritional status. Li, 2013 [16] found that moxibustion for 4 weeks can significantly improve the level of mononuclear cell count in patients, so they speculated that the improvement of CRF in patients may be related to the improvement of immune function in patients with moxibustion. Zhang Min, 2014 [28] found that the decrease of appetite and CRF was often accompanied by each other, and in the process of moxibustion, CRF and appetite were often improved to different degrees simultaneously. With the increase of the treatment time of grain-sized moxibustion, the improvement of fatigue and appetite was synergistic [28]. Zhang, 2008 [29] found that ginger-partitioned moxibustion could reduce the bone marrow inhibition and the decline of white blood cells, hemoglobin, platelets and neutrophils caused by chemotherapy caused by chemotherapy, which was a safe and effective method to prevent the toxic and side effects of chemotherapy. Furthermore, the effect of daily moxibustion was better than that of every

Table 1
Characteristics of the included studies.

Trials	Cancer diagnosis & tumors grading	Participants	Intervention	Acupoint	Outcome measures & results
Shen, 2018 [18]	Various cancer, –	Randomized = 100, Completed = 100 T (n = 50): M/F = -, Age (yr.) = -, C (n = 50): M/F = -, Age (yr.) = -	T = laser moxibustion Length = 4 weeks Duration =20 min/session Frequency = 3 session/week C = Sham laser moxibustion	*Guanyuan* RN4, *Qihai* RN6, *Zusanli* ST36 (bilateral)	Fatigue (BFI)▲
Mao, 2016 [10]	Various cancer, I–IV	Randomized = 78, Completed = 61 T (n = 39): M/F = 19/20, Age (yr.) = 59.1 ± 7.1, C (n = 39): M/F = 17/22, Age (yr.) = 59.7 ± 7.8	T = laser moxibustion Length = 4 weeks Duration =20 min/session Frequency = 3 session/week C = Sham laser moxibustion	*Zusanli* ST36 (bilateral), *Guanyuan* RN4, *Qihai* RN6	Fatigue (BFI)▲ Adverse events
Yu, 2012 [27]	Various cancer, I–IV	Randomized = 146, Completed = 146 T (n = 73): M/F = -, Age (yr.) = -, C (n = 73): M/F = -, Age (yr.) = -	T = Thermal box moxibustion + ginger-partitioned moxibustion Length = 20 times Duration =20 min/session Frequency = Once a day C = Conventional therapy	*Qihai* RN6, *Guanyuan* RN4, *Zhongwan* RN12, *Shenque* RN8, *Zusanli* ST36, *Mingmen* DU4 (Unilateral or bilateral cannot be judged.)	Fatigue (PFS-R)▲
Li, 2013 [16]	Breast cancer, III–IV	Randomized = 168, Completed = 158 T (n = 79): M/F = 0/79, Age (yr.) = 62.61 ± 12.25, C (n = 79): M/F = 0/79, Age (yr.) = 62.61 ± 12.25	T = Medicinal moxibustion Length = 2 months Duration = 10–15 min/session Frequency = - C = Conventional therapy	*Guanyuan* RN4	Fatigue (BFI)▲
Enkh, 2010 [13]	Gastric cancer, III	Randomized = 24, Completed = 24 T (n = 12): M/F = 7/5, Age (yr.) = 61.6 ± 11.4, C (n = 12): M/F = 6/6, Age (yr.) = 61.6 ± 11.4	T = Moxa cone moxibustion Length = 2 months Duration = 10–15 min/session Frequency = - C = Conventional therapy	*Guanyuan* RN4	Fatigue (EORTC QLQ-C30)▲ QOL (EORTC QLQ-C30)▲
Xu, 2017 [24]	Various cancer, I–IV	Randomized = 60, Completed = 60 T (n = 30): M/F = 17/13, Age (yr.) = -, C (n = 30): M/F = 19/11, Age (yr.) = -	T = Thermal box moxibustion + traditional Chinese medicine Length = 12 weeks Duration =10 min/session Frequency = Once a day C = Conventional therapy + traditional Chinese medicine	*Shenque* RN8, *Zusanli* ST36 (Unilateral or bilateral cannot be judged.)	Fatigue (EORTC QLQ-C30)▲ Adverse events
Yang, 2012 [26]	Various cancer, III–IV	Randomized = 180, Completed = 180 T (n = 60): M/F = 29/31, Age (yr.) = 65-85, C_1 (n = 60): M/F = 32/28, Age (yr.) = 65–84 C_2 (n = 60): M/F = 31/29, Age (yr.) = 65-82	T = Ginger-partitioned moxibustion + traditional Chinese medicine Length = 4 weeks Duration = 10-20 min/session Frequency = Once a day C_1 = Ginger-partitioned moxibustion C_2 = Conventional therapy	*Qihai* RN6,*Guanyuan* RN4, *Zhongwan* RN12, *Shenque* RN8	Fatigue (BFI)▲
Xu Xiaozhou, 2017 [25]	Various cancer, III–IV	Randomized = 80, Completed = 80 T (n = 40): M/F = -, Age (yr.) = 58.10 ± 12.50, C (n = 40): M/F = -, Age (yr.) = 60.00 ± 11.69	T = Moxa stick moxibustion Length = 4 weeks Duration = 10–20 min/session Frequency = Once a day C = Conventional therapy	*Zusanli* ST36, *Xuehai* SP10, *Taixi* KI3, *Xuanzhong* GB3, *Qihai* RN6,*Guanyuan* RN4 (Unilateral or bilateral cannot be judged.)	Fatigue (RFS-R)▲ QOL (EORTC QLQ-C30)▲ Adverse events
Cao, 2017 [12]	Cervical carcinoma, Ib–IVa	Randomized = 80, Completed = 80 T (n = 40): M/F = -, Age (yr.) = 49.93 ± 8.10, C (n = 40): M/F = -, Age (yr.) = 50.13 ± 9.78	T = Thermal box moxibustion Length = 4 weeks Duration =20 min/session Frequency = Once a day C = Conventional therapy	*Guanyuan* RN4,*Qihai* RN6, *Zusanli* ST36 (bilateral), *Sanyinjiao* SP6 (bilateral)	Fatigue (CFS)▲ QOL (PSQI)▲
Qin, 2012 [19]	Various cancer, III–IV	Randomized = 30, Completed = 30 T (n = 15): M/F = 8/7, Age (yr.) = -, C (n = 15): M/F = 9/6, Age (yr.) = -	T = Thermal box moxibustion Length = 2 weeks Duration =30 min/session Frequency = Once a day C = Conventional therapy	*Qihai* RN6,*Guanyuan* RN4,*Zhongwan* RN12, *Shenque* RN8, *Zusanli* ST36,*Tianshu* ST25, *Yongquan* KI1 (Unilateral or bilateral cannot be judged.)	Fatigue (PFS-R)▲ Adverse events
Xu, 2013 [22]	Various cancer, –	Randomized = 54, Completed = 50 T (n = 27): M/F = 14/13, Age (yr.) = 47.80 ± 8.32, C (n = 27): M/F = 15/12, Age (yr.) = 50.95 ± 9.74	T = Ginger-partitioned moxibustion Length = 9 weeks Duration =20 min/session Frequency = 3 session/week C = Sham Ginger-partitioned moxibustion	*Guanyuan* RN4, *Zusanli* ST36 (bilateral), *Pishu* BL20 (bilateral)	Fatigue (EORTC QLQ-C30)▲ QOL (EORTC QLQ-C30)▲

(*continued on next page*)

Table 1 (*continued*)

Trials	Cancer diagnosis & tumors grading	Participants	Intervention	Acupoint	Outcome measures & results
Zhang, 2008 [29]	Various cancer, II–IV	Randomized = 90, Completed = 90 T (n = 30): M/F = 29/31, Age (yr.) = 65–85, C_1 (n = 30): M/F = 32/28, Age (yr.) = 65-84 C_2 (n = 30): M/F = 31/29, Age (yr.) = 65-82	T = Ginger-partitioned moxibustion Length = 2 weeks Duration = 10–20 min/session Frequency = Once a day C_1 = Ginger-partitioned moxibustion Frequency = Every other day C_2 = Conventional therapy	*Dazhui* DU14,*Pishu* BL20 (bilateral) *Weishu* BL21(bilateral), *Geshu* BL17(bilateral), *Shenshu* BL23(bilateral)	Fatigue (EORTC QLQ-C30)▲ QOL (EORTC QLQ-C30)▲
Zhu, 2017 [31]	Liver cancer, –	Randomized = 60, Completed = 60 T (n = 30): M/F = 23/7, Age (yr.) = 47.47 ± 6.59, C (n = 30): M/F = 21/9, Age (yr.) = 48.20 ± 6.00	T = Ginger-partitioned moxibustion Length = 8 days Duration =30 min/session Frequency = Once a day C = Conventional therapy	*Yongquan* KI1(bilateral), *Zusanli* ST36 (bilateral)	Fatigue (EORTC QLQ-C30)▲ QOL (EORTC QLQ-C30)▲ Adverse events
Xu Mengna, 2018 [23]	Esophageal cancer, -	Randomized = 40, Completed = 40 T (n = 20): M/F = 15/5, Mean age (yr.) = 62.4, C (n = 20): M/F = 15/5, Mean age (yr.) = 64.4	T = Moxa stick moxibustion Length = 6 months Duration = - Frequency = 5 session/week C = Conventional therapy	*Gaohuang* BL43(bilateral), *Zusanli* ST36 (bilateral)	Fatigue (-)▲ QOL (-)▲
Lu, 2018 [17]	Breast cancer,-	Randomized = 60, Completed = 60 T (n = 30): M/F = 0/30, Mean age (yr.) = 48.9 ± 9.5, C (n = 30): M/F = 0/30, Mean age (yr.) = 50.5 ± 8.5	T = Moxa stick moxibustion Length = 2 weeks Duration =30 min/session Frequency = 5 session/week C = Conventional therapy	*Pishu* BL20 (bilateral), *Weishu* BL21(bilateral), *Sanjiaoshu* BL22(bilateral), *Qihai* RN6	Fatigue (BFI)▲
Zhang Xue, 2016 [30]	Various cancer, I–IV	Randomized = 46, Completed = 44 T (n = 22): M/F = 12/10, Mean age (yr.) = 55 ± 11, C (n = 22): M/F = 10/12, Mean age (yr.) = 62 ± 8	T = Grain-sized moxibustion Length = 10 days Duration = 7 *ZHUANG* Frequency = Once a day C = Conventional therapy	*Zusanli* ST36 (bilateral)	Fatigue (PFS-R)▲ QOL (EORTC QLQ-C30)▲
Zhang Mengxue, 2016 [11]	Lung cancer, I–IV	Randomized = 70, Completed = 65 T (n = 33): M/F = 21/12, Mean age (yr.) = 57 ± 11, C (n = 32): M/F = 21/11, Mean age (yr.) = 54 ± 10	T = Grain-sized moxibustion Length = 6 weeks Duration = 9 *ZHUANG* Frequency = Once a day C = Conventional therapy	*Zusanli* ST36, *Feishu* BL13 (Unilateral or bilateral cannot be judged.)	Fatigue (EORTC QLQ-C30)▲ QOL (EORTC QLQ-C30)▲
Zhang Min, 2014 [28]	Breast cancer, I–III	Randomized = 60, Completed = 54 T (n = 26): M/F = 0/26, Mean age (yr.) = 51.31 ± 9.73, C (n = 28): M/F = 0/28, Mean age (yr.) = 54.46 ± 8.67	T = Grain-sized moxibustion Length = 2 weeks Duration = 18 *ZHUANG* Frequency = Once a day C = Conventional therapy	*Dazhui* DU14, *Zusanli* ST36 (bilateral)	Fatigue (BFI)▲
Xie, 2017 [21]	Lung cancer, IIIb–IV	Randomized = 60, Completed = 53 T (n = 26): M/F = 14/12, Mean age (yr.) = 57.46 ± 6.33, C (n = 27): M/F = 15/12 Mean age (yr.) = 59.19 ± 5.83	T = Grain-sized moxibustion Length = 2 weeks Duration = 9 *ZHUANG* Frequency = Once a day C = Conventional therapy	*Dazhui* DU14, *Zusanli* ST36 (bilateral)	Fatigue (BFI)▲ Adverse events
Huo, 2016 [14]	Various cancer, III–IV	Randomized = 66, Completed = 66 T (n = 32): M/F = 21/11, Mean age (yr.) = 47.9 ± 7.1, C (n = 34): M/F = 23/11 Mean age (yr.) = 49.2 ± 7.8	T = Grain-sized moxibustion Length = 3 months Duration = 20 *ZHUANG* Frequency = 1 session/week C = Conventional therapy	*Zusanli* ST36 (bilateral)	Fatigue (BFI)▲
Jiang, 2018 [15]	Breast cancer, II–IV	Randomized = 70, Completed = 70 T (n = 35): M/F = 0/35, Mean age (yr.) = 51.3 ± 9.14, C (n = 35): M/F = 0/35, Mean age (yr.) = 52.1 ± 8.57	T = Moxa cone moxibustion Length = 3 weeks Duration = 3 ZHUANG Frequency = Once a day C = Conventional therapy	*Geshu* BL17 (bilateral), *Danshu* BL19 (bilateral)	Fatigue (PFS-R)▲

(*continued on next page*)

Table 1 (*continued*)

Trials	Cancer diagnosis & tumors grading	Participants	Intervention	Acupoint	Outcome measures & results
Wu, 2016 [20]	Lung cancer, IIIa–IV	Randomized = 120, Completed = 120 T (n = 60): M/F = 48/12, Mean age (yr.) = 52.6 ± 6.2, C (n = 60): M/F = 39/21, Mean age (yr.) = 53.3 ± 5.6	T = Thermal moxibustion Length = 3 weeks Duration = the sensation of heat vanished Frequency = Once a day C = Conventional therapy	*Shenque* RN8, *Yongquan* KI1 (bilateral), Qihai RN6, *Feishu* BL13 (bilateral)	Fatigue (PFS-R)▲

T: intervention group; C: control group; C_1: control group of one; C_2: control group of two; -: not reported; QOL: quality of life; ▲: Statistically significant; BFI: Brief fatigue Inventory; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PFS-R: The Revised Piper Fatigue Scale. PSQI: Pittsburgh sleep quality index.

other day [29]. Zhang, 2008 [29] also suggested that ginger-partitioned moxibustion was performed on the back, for some patients, a long period of the prone position was quite laborious, which had a certain impact on the compliance of the patients, so it would reduce the quality of the study [29]. Xu, 2013 [22] proposed that the selected acupoints were mainly in the waist and abdomen, which were closely related to the spleen and stomach, and may be more conducive to the improvement of digestive system function. In future studies, control groups of different acupoints can be set up to observe whether the curative effect is affected by acupoints [22]. Shen, 2018 [18] found that laser moxibustion made up for the shortcomings of traditional moxibustion methods (inconvenient operation, smoke stimulation and pollution, etc.) and greatly improved CRF.

3.6. Sensitivity heterogeneity

Statistical heterogeneity was found in the majority of our meta-analysis outcomes, thus, sensitivity analysis were performed to identify the possible source of heterogeneity and investigated the stability of the results. All outcomes of the sensitivity analysis are presented in Table 3. After dubious studies were removed, the values of heterogeneity markedly decreased, and the study results became relatively reliable. The five trials (Xu, 2013; Zhu, 2017; Zhang Mengxue, 2016; Huo, 2016; Jiang, 2018) [11,14,15,22,31] were the most frequently identified sources of heterogeneity.

4. Discussion

Our study consisted of 22 trials with 1628 cancer patients. The study findings suggested that moxibustion can improve CRF and most aspects of QOL (except for economic difficulty and insomnia) and that moxibustion is relatively safe as treatment for cancer patients. However, the small samples size and varying degrees of methodological limitations in most of the included studies limited the strength of evidence of the study results.

Traditional Chinese medicine holds that the effect of moxibustion is achieved by warming acupoints and regulating *qi* and blood [32]. Supplementing energy (*qi*) is an important function of moxibustion; consequently, it has been often adopted to patients with fatigue or similar conditions [32]. Modern scientific studies also suggest that moxibustion can relieve chronic fatigue [33–35], and its mechanism maybe related to reduction in oxidative damage [33,34,36], activation of the vagus nerve [33], improvement of inflammation [37], upregulation of hippocampal progranulin [38], and regulation of the hypothalamic-pituitary-adrenal axis [38].

A systematic review and meta-analysis of moxibustion in CRF patients [7] found that moxibustion can improve fatigue, and that it could safely treat CRF. Another systematic review and meta-analysis of moxibustion in CRF patients [8] also suggested that moxibustion provides relatively significant improvement in severe fatigue. Our systematic review confirms that moxibustion significantly alleviates fatigue.

This study includes several limitations. First, small samples, short intervention times, single test country and different degrees of methodological limitations in most of the included trials may have led to the results less convincing. Second, the various types of cancer and moxibustion and different lengths of intervention duration may be the main sources underlying the observed heterogeneity. We performed no subgroup analysis because of the small number of studies included in each comparison, number of included trials, and variation in data. Third, owing to the inadequate number of studies (< 10) in each comparison, funnel plots could not be used to explore publication bias.

This study has several implications for future research and practices. First, advanced-stage cancer and chemotherapy predict severe fatigue, prompting researchers to conduct subgroup analysis based on cancer stage and its treatment methods. Second, to ensure baseline balance, factors contributing to fatigue (e.g. pain, emotional distress, poor sleep hygiene, sleep disturbance, anemia, nutrition, medication side effect profiles.) should be compared between the intervention groups and the control groups prior to intervention. Third, long-term interventions and follow-ups need to be conducted to verify the effectiveness of moxibustion for CRF. Finally, Different interventions and subjects may produce different results. No studies exist on different moxibustion methods and race in the treatment of CRF; future, relevant studies may be conducted to determine the various effects of different moxibustion techniques and race.

5. Conclusions

Current evidence demonstrates that moxibustion can improve CRF and most aspects of QOL (except for economic difficulty and insomnia). Moxibustion is relatively safe as treatment for cancer patients. Owing to the small number, short intervention duration and methodological drawbacks of the included studies, more rigorously designed large RCTs with satisfactory intervention durations and follow-up periods need to be conducted to provide more reliable evidence.

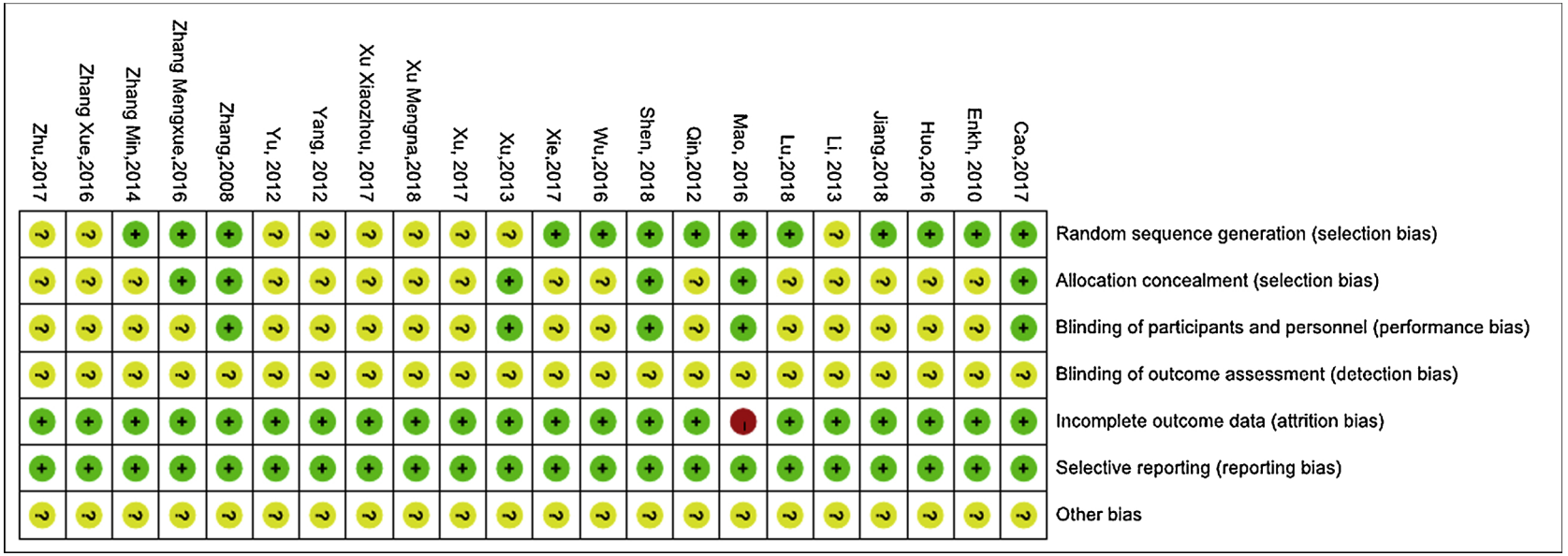

Fig. 3. Risk of bias summary.

Table 2
Summary of meta-analysis.

Outcome	No. of trials	No. of participants	Heterogeneity (I^2)	Statistical Method	Effect estimate	Test for overall effect		Favours moxibustion
						Z	*p*	
Sensory fatigue	6	410	83%	Std. Mean Difference (IV, Random, 95% CI)	−1.12 [-1.65, -0.58]	4.08	< 0.0001	Yes
Behavioral fatigue	5	344	88%	Mean Difference (IV, Random, 95% CI)	−2.93 [-4.32, -1.54]	4.14	< 0.00001	Yes
Affective meaning fatigue	7	490	90%	Std. Mean Difference (IV, Random, 95% CI)	−1.01 [-1.65, -0.38]	3.12	0.002	Yes
Cognitive fatigue	6	424	79%	Std. Mean Difference (IV, Random, 95% CI)	−1.05 [-1.52, -0.58]	4.37	< 0.0001	Yes
Physical fatigue	8	469	92%	Std. Mean Difference (IV, Random, 95% CI)	−1.61 [-2.38, -0.85]	4.13	< 0.0001	Yes
Total score of fatigue	10	780	67%	Std. Mean Difference (IV, Random, 95% CI)	−1.17 [-1.44, -0.90]	8.36	< 0.00001	Yes
Effective rate of fatigue	1	103	–	–	–	–	–	
QOL								
Astriction	5	258	0%	Mean Difference (IV, Fixed, 95% CI)	−10.00 [-16.43, -3.57]	3.05	0.002	Yes
Nausea and vomiting	6	302	87%	Mean Difference (IV, Random, 95% CI)	−15.53 [-26.69, -4.38]	2.73	0.006	Yes
Diarrhoea	5	226	0%	Mean Difference (IV, Fixed, 95% CI)	−12.05 [-18.12, -5.98]	3.89	< 0.0001	Yes
Role function	6	322	73%	Mean Difference (IV, Random, 95% CI)	9.39 [2.22, 16.56]	2.57	0.01	Yes
Economic difficulty	6	302	38%	Mean Difference (IV, Fixed, 95% CI)	−5.11 [-10.66, 0.44]	1.80	0.07	No
Anhelation	6	302	72%	Mean Difference (IV, Random, 95% CI)	−7.45 [-14.79, -0.11]	1.09	0.05	Yes
Emotional function	8	447	85%	Mean Difference (IV, Random, 95% CI)	11.71 [4.41, 19.01]	3.14	0.002	Yes
Physical function	7	387	85%	Mean Difference (IV, Random, 95% CI)	10.46 [4.41, 16.52]	3.39	0.0007	Yes
Cognitive function	7	382	60%	Mean Difference (IV, Random, 95% CI)	7.96 [3.08, 12.85]	3.20	0.001	Yes
Social function	7	382	8%	Mean Difference (IV, Fixed, 95% CI)	11.01 [7.46, 14.56]	6.07	< 0.00001	Yes
Insomnia	8	422	77%	Std. Mean Difference (IV, Random, 95% CI)	−0.31 [-0.72, 0.10]	1.47	0.14	No
Loss of appetite	9	449	92%	Std. Mean Difference (IV, Random, 95% CI)	−0.80 [-1.54, -0.07]	2.15	0.03	Yes
Pain	5	242	84%	Std. Mean Difference (IV, Random, 95% CI)	−0.70 [-1.37, -0.03]	2.05	0.04	Yes
A global QOL scale	9	471	67%	Std. Mean Difference (IV, Random, 95% CI)	0.88 [0.54, 1.22]	5.11	< 0.00001	Yes

Table 3
Sensitivity analysis.

Outcomes	Before sensitivity analysis				Method for sensitivity analysis	No. of trials	Afore sensitivity analysis		
	No. of trials	(Model)SMD/MD 95%CI	p	I^2			(Model) SMD/MD 95%CI	p	I^2
Sensory fatigue	6	(Random) -1.12 [-1.65, -0.58]	< 0.0001	83%	Removing Huo, 2016 and Jiang, 2018	4	(Fixed) -0.69 [-0.94, -0.45]	< 0.00001	3%
Behavioral fatigue	5	(Random) -2.93 [-4.32, -1.54]	< 0.00001	88%	Removing Wu,2016 and Zhang Xue, 2016	2	(Fixed) -1.46 [-1.74, -1.19]	< 0.00001	0%
Affective meaning fatigue	7	(Random) -1.01 [-1.65, -0.38]	0.002	90%	Removing Huo, 2016 and Jiang, 2018	5	(Fixed) -0.50 [-0.71, -0.28]	< 0.00001	0%
Cognitive fatigue	6	(Random) -1.05 [-1.52, -0.58]	< 0.0001	79%	Removing Qin, 2012, Wu, 2016 and Jiang, 2018	3	(Fixed) -0.85 [-1.14, -0.57]	< 0.00001	0%
Physical fatigue	8	(Random) -1.61 [-2.38, -0.85]	< 0.0001	92%	Removing Huo, 2016 and Zhang Mengxue, 2016	6	(Fixed) -0.95 [-1.18, -0.73]	< 0.00001	49%
Total score of fatigue	10	(Random) -1.17 [-1.44, -0.90]	< 0.00001	67%	Removing Xu Mengna 2018 and Zhang Min, 2014	8	(Fixed) -1.06 [-1.24, -0.87]	< 0.00001	22%
Nausea and vomiting	6	(Random) -15.53 [-26.69, -4.38]	0.006	87%	Removing Xu, 2013	5	(Fixed) -8.49 [-12.33, -4.65]	< 0.0001	41%
Role function	6	(Random) 9.39 [2.22, 16.56]	0.01	73%	Removing Zhang Xue, 2016	5	(Fixed) 6.01 [2.16, 9.86]	0.002	43%
Anhelation	6	(Random) -7.45 [-14.79, -0.11]	0.05	72%	Removing Xu, 2013 and Zhang, 2008	4	(Fixed) -2.26 [-3.87, -0.65]	0.006	0%
Emotional function	8	(Random) 11.71 [4.41, 19.01]	0.002	85%	Removing Zhang, 2008, Zhu, 2017 and Zhang Mengxue, 2016	5	(Fixed) 9.50 [5.05, 13.95]	< 0.0001	32%
Physical function	7	(Random) 10.46 [4.41, 16.52]	0.0007	85%	Removing Xu, 2017 and Zhu, 2017	5	(Fixed) 14.70 [11.06, 18.33]	< 0.00001	0%
Cognitive function	7	(Random) 7.96 [3.08, 12.85]	0.001	60%	Removing Zhu, 2017	6	(Fixed) 9.86 [6.08, 13.65]	< 0.00001	42%
Insomnia	8	(Random) -0.31 [-0.72, 0.10]	0.14	77%	Removing Xu, 2013, Xu Mengna, 2018 and Cao, 2017	5	(Fixed) -0.17 [-0.43, 0.08]	0.17	46%
Loss of appetite	9	(Random) -0.80 [-1.54, -0.07]	0.03	92%	Removing Xu, 2013, Xu Mengna, 2018, Xie, 2017 and Zhang Min, 2014	5	(Fixed) -0.58 [-0.84, -0.33]	< 0.00001	0%
Pain	5	(Random) -0.70 [-1.37, -0.03]	0.04	84%	Removing Xu, 2013, Xu, 2017, Enkh, 2010	2	(Fixed) -0.84 [-1.25, -0.44]	< 0.0001	0%
A global QOL scale	9	(Random) 0.88 [0.54, 1.22]	< 0.00001	67%	Removing Zhang Mengxue, 2016	8	(Fixed) 0.74 [0.53, 0.94]	< 0.00001	0%

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Declaration of Competing Interest

The author(s) declare that they have no conflict of interests.

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Hai-Li Ma contributed to the conception and design. Hai-Li Ma, Li-Fang Lou, Zhi-Hong Sun, Bao-Liang Lv and Bing Yang contributed to the completion of the articles, data extraction, data calculations and designing of figures and tables. All authors proof-read the article. All authors approved the final manuscript.

Appendix 1 Searching strategies

#1 Neoplasm [MeSH Terms]

#2 (Neoplasm*[Title/Abstract] OR Cancer [Title/Abstract] OR Carcinoma*[Title/Abstract] OR Tumor*[Title/Abstract] OR Tumor* [Title/Abstract] OR Oncolog*[Title/Abstract] OR Malignant [Title/Abstract])

#3 #1 or #2

#4 fatigue [MeSH Terms]

#5 (Lassitude [Title/Abstract] OR Fatigue [Title/Abstract])

#6 #4 or #5

#7 Moxibustion [MeSH Terms]

#8(“Needl* Warm*” [Title/Abstract] OR? Moxibustion [Title/Abstract] OR moxa [Title/Abstract] OR “warm* acupuncture” [Title/Abstract])

#9 #7 or #8

#10 #3 AND #6 AND

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