

Comparative efficacy of non-pharmacological adjuvant therapies for quality of life in the patients with breast cancer receiving chemo- or radio-therapy

A protocol for systematic review and Bayesian network meta-analysis

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Abstract

Background: Breast cancer is the most frequently diagnosed cancer in women worldwide. When treated by chemotherapy and/or radiotherapy, there are various non-pharmacological adjuvant therapies (NPATs) recommended for helping the patients with breast cancer alleviate multiple side effects induced by chemotherapy and/or radiotherapy and improve quality of life (QoL). However, the existing evidence does not suggest the therapy with the best effectiveness among a variety of NPATs. This study is to compare the effectiveness of different NPATs on QoL in the patients with breast cancer using Bayesian network meta-analysis (NMA).

Methods and analysis: We will conduct a comprehensive search strategy in the relevant databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, World Health Organization (WHO), International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialsearch/Default.aspx>), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Wan Fang Data). The random or quasi-random controlled trials that compare different NPATs in patient with breast cancer who received the chemotherapy and/or radiotherapy will be included. We only focus on the outcome of QoL which can be assessed by a series of tools. The risk of bias for included studies will be appraised using the Cochrane Collaboration's tool for assessing risk of bias. The standard pairwise meta-analysis and a Bayesian NMA will be conducted.

Ethics and dissemination: Ethical approval and patient consent are not required since this is an NMA based on published studies. We will submit our NMA to a peer-reviewed journal for publication.

PROSPERO registration number: CRD42017078143.

Abbreviations: CI = confidence interval, CrIs = credible intervals, DIC = deviance information criteria, EORTC = European Organization for Research and Treatment of Cancer, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, FACT = functional assessment of cancer therapy, GRADE = Grading of Recommendation, Assessment, Development and Evaluation, ICTRP = International Clinical Trials Registry Platform, MBSR = mindfulness based stress reduction, MDs = mean differences, NCCN = National Comprehensive Cancer Network, NMA = network meta-analysis, NPATs = non-pharmacological adjuvant therapies, PRISMA-P = preferred reporting items for systematic review and meta-analysis protocol, QLACS = quality of life in adult cancer survivors, QoL = quality of life, RCTs = randomized clinical trials, SCNS = supportive care needs survey, SF-36 = 36-item short form health survey, SUCRA = cumulative ranking area, WHO = World Health Organization.

Keywords: breast cancer, chemotherapy, network meta-analysis, non-pharmacological, quality of life, radiotherapy

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Patient consents are not required since this is meta-analysis based on published studies.

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1. Background

Breast cancer is one of the top frequently diagnosed cancers, with estimated 1,676,600 new cases and 521,900 deaths worldwide every year.^[1] For the patients with breast cancer, chemotherapy and/or radiotherapy play an essential role in reducing recurrence rate and improving overall survival rate, which has been presented in a range of existing researches.^[2–6] Moreover, the clinical guideline for breast cancer from National Comprehensive Cancer Network (NCCN) recommends numerous chemotherapy and radiotherapy regimens as well.^[7] However, there are various adverse effects (such as fatigue, nausea, vomiting, insomnia, anxiety, pain, phlebitis, peripheral neuropathy, alopecia, and mucositis) caused by chemotherapy and/or radiotherapy in patients with breast cancer^[8–11] which may reduce quality of life (QoL) and adherence of treatment.

Therefore, some types of adjuvant therapies, particularly non-pharmacological adjuvant therapies (NPATs) (such as relaxation, mindfulness-based stress reduction (MBSR), music therapy, massage;^[12] yoga, acupuncture, meditation, qigong, reflexology, and stress management^[13]) are usually combined with chemotherapy and/or radiotherapy. In addition, evidence from the existing systematic reviews also finds that Tai chi and expressive writing have positive impact on QoL of patients with breast cancer.^[14,15] These NPATs do not cause any severe adverse side effects and are inexistent of drug interactions, which makes it more acceptable for patients compared with pharmacological adjuvant therapies.^[16] However, all of the existing meta-analyses only conducted pairwise meta-analysis to compare efficacy of different types of NPATs. In order to assess the effects of different types of NPATs on QoL of the patients with breast cancer, it is necessary to produce highly compelling and persuasive evidence to draw a firm conclusion.

Network meta-analysis (NMA)^[17] can be used for addressing this problem, which is able to evaluate the relative effectiveness among all the potential interventions and rank the order of interventions by estimated effect size as head-to-head comparisons are lacking. This study is a comprehensive systematic review and NMA on different types of NPATs for patients with breast cancer.

2. Objective

The objective of this study is to compare the effectiveness of different NPATs on QoL in the patients with breast cancer using Bayesian network meta-analysis of randomized clinical trials (RCTs).

3. Methods

3.1. Design

A systematic review and Bayesian NMA will be carried out in this study.

3.2. Registration

We registered the protocol of the present systematic review on the international prospective register of systematic reviews, PROSPERO (Register number: CRD42017078143). The protocol was conducted in accordant with the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P),^[18,19] and the PRISMA extension statement for reporting of systematic reviews incorporating NMAs of healthcare interventions.^[20]

3.3. Eligibility criteria

3.3.1. Types of studies. We plan to include truly random or quasi-random controlled trials. In addition, the relevant systematic reviews or meta-analyses will also be included to track their references.

3.3.2. Type of patients. Adult women (age of eighteen or over) diagnosed as breast cancer and receiving chemotherapy and/or radiotherapy are eligible for this review, whereas patients will be excluded if metastasis is found in other organs.

3.3.3. Type of interventions. The NPATs below will be included: yoga, acupuncture, meditation, qigong, reflexology, stress management, relaxation, music therapy, massage, acupuncture, expressing writing, and Tai chi.

3.3.4. Type of outcomes. We only focus on the outcome of QoL which can be assessed by a series of tools such as European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), Functional Assessment of Cancer Therapy (FACT), McGill QoL Questionnaire, City of Hope QoL Questionnaire, Supportive Care Needs Survey (SCNS), 36-Item Short Form Health Survey (SF-36), Quality of Life in Adult Cancer Survivors (QLACS), etc.

3.4. Information source

The search strategy will be developed by consulting the librarians of Lanzhou University. And the information sources include the databases below:

MEDLINE (via PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, PsycINFO, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialsearch/Default.aspx>), Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Wan Fang Data

The references of included articles and reviews will be tracked to identify other relevant studies.

3.5. Search strategy

No limitation about language and publication date will be restricted. The search terms contain the relevant text words regarding breast cancer, chemotherapy, radiotherapy and quality of life. The details of PubMed search strategy are as follows:

#1 “Breast Neoplasms”[Mesh] OR “Breast Cancer Lymphedema”[Mesh] OR “Breast Neoplasm*”[Title/Abstract] OR “Breast Tumor*”[Title/Abstract] OR “Breast Carcinoma*”[Title/Abstract] OR “Mammary Cancer*”[Title/Abstract] OR “Mammary Carcinoma*”[Title/Abstract] OR “Mammary Neoplasm*”[Title/Abstract] OR “Mammary Tumor*”[Title/Abstract]

#2 “Radiotherapy”[Mesh] OR “Drug Therapy”[Mesh] OR chemotherap*[Title/Abstract] OR chemo-therap*[Title/Abstract] OR “drug therapy”[Title/Abstract] OR irradiation[Title/Abstract] OR radiotherap*[Title/Abstract] OR radio-therap*[Title/Abstract] OR radiation[Title/Abstract] OR chemo-radio-therap*[Title/Abstract] OR chemoradi*[Title/Abstract] OR radiochemo*[Title/Abstract]

#3 “Quality of Life”[Mesh] OR “Quality of Life”[Title/Abstract] OR “Life Quality”[Title/Abstract]

#4 #1 AND #2 AND #3

All the details of search strategy of the databases can be seen in the supplement file.

3.6. Study selection and data extraction

The results of electronic search will be imported to EndNote X7 literature management software for study selection which is composed of 2 steps: title and abstract selection, full-text selection. In the stage of title and abstract screening, the potentially relevant researches will be identified. And then full-texts will be reviewed to confirm eligible studies in the next step. The trials excluded and the reasons for their exclusion in the second stage will be listed and examined by a third reviewer.

We will conduct a standard data extraction form using Microsoft Excel 2013 to carry out data extraction. The following data will be collected: study characteristics (such as title, first author, publication type, publication year, country, journal, and the sponsor), study design (inclusion and exclusion criteria, generation of allocation sequence, allocation concealment, and blinding, length of follow-up), participant data (sample size, race, age, tumor stage, diagnostic criteria, time of diagnose, comorbidities, and lost/withdrawal/abscission), details of chemotherapy or radiotherapy (dose, duration, and combination), details of interventions of interest (type, frequency, and duration), and outcomes (assessment tools, assessment time point, and assessment result).

A pilot test will be performed for literature selection and data extraction, and a “cheat sheet” with detailed definitions and examples will be developed to ensure high inter-rater reliability among the reviewers. Study selection and data extraction will be accomplished individually by 2 researchers. Any disagreements will be resolved by discussion, and conflicts will be solved by a third researcher.

3.7. Risk of bias assessment

The risk of bias of included RCTs will be appraised using the Cochrane Collaboration’s tool for assessing risk of bias^[21] by 2 independent researchers, and conflicts will be resolved by a third researcher. The tool contains 7 domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain is evaluated as low, high, and unclear risk of bias. We will record the explanation of the result of each domain.

3.8. Dealing with missing data

If the researchers didn’t report the important data (such as the standard deviation, standard errors of continue outcome), we will try to calculate it first using algebraic manipulation based on the reported information such as confidence interval (CI). If failed, we will contact the authors to obtain these data. If that would be still not possible, the methods suggested by Furukawa et al will be used to retrieve the missing data.^[22] The assumptions derived from these data will be tested through sensitivity analysis.

3.9. Standard pairwise meta-analysis

We will perform pairwise meta-analysis, using STATA V.12.0 software (Stata Corporation, College Station, Texas), and pool ORs with 95% CI for dichotomous outcomes and mean differences (MDs) with 95% CI for continue outcomes. We will

assess heterogeneity of treatment effects across trials by c^2 and I^2 statistics. If the P value $>.1$ and $I^2 <50\%$, it means that there is no statistical heterogeneity, and the Mantel–Haenszel fixed effects model will be used for meta-analysis. If the P value $<.1$ and $I^2 >50\%$, subgroup analysis and meta-regression will be used for exploring the sources of heterogeneity. If there is no clinical heterogeneity, the Mantel–Haenszel random effects model will be used to perform meta-analysis.^[21] We will examine reporting bias using the Begg’s and Egger’s funnel plot method.^[23,24] Additionally, we plan to use the contour-enhanced funnel plot as an aid to distinguish asymmetry, if some more other factors leading to publication bias.^[25]

3.10. Network meta-analysis

First, in order to ensure that an NMA is feasible, we will draw a network plot to describe and present the geometry of the treatment network of comparisons across trials. Trials will be excluded if the trials are not connected by treatments. In the network geometry, nodes represent different interventions, and edges represent the head-to-head comparisons between interventions. The size of nodes and thickness of edges are associated with sample sizes of intervention and numbers of included trials, respectively.

Next, the NMA will be conducted based on a Bayesian framework using the code invented by Dias et al^[26] through WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) to combine the direct evidence within trails and the indirect evidence across trails, as well as rank the efficacy of all feasible NPATs. The pooled estimation and the probability of which treatment is the best will be obtained using the Markov Chain Monte Carlo method. Three Markov Chains will be run simultaneously with different arbitrarily chosen initial values. We will first generate 50,000 simulations for each chain, and these simulations will then be discarded as the ‘burn-in’ period. Then posterior summaries will be based on 100,000 subsequent simulations. The model convergence will be assessed by trace plots and Brooks–Gelman–Rubin plots.^[27] The statistical heterogeneity in the entire network will be assessed on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from the NMA models using R-3.2.2 software (R Foundation for Statistical Computing, Vienna, Austria). The results of dichotomous outcomes will be reported as posterior medians of OR with 95% credible intervals (CrIs), and medians of MD with 95% CrI for continue outcomes. If a loop connecting 3 arms exists, inconsistency between direct and indirect comparisons will be evaluated using a node splitting method.^[28] The choices between fixed and random effect models, consistent and inconsistent models, will be made by comparing the deviance information criteria (DIC) for each model.^[26,29] The model with the lowest DIC will be preferred (differences >3 are considered significant).

Clinical decisions about the choices of treatments can be recommended based on the probability results of ranking when the differences in effect size of different treatments are small.^[30] The surface under the cumulative ranking area (SUCRA) will be calculated to summarize and report the probability values. SUCRA values are expressed as percentages—SUCRA value will be 100% for the best treatment, while SUCRA value will be 0% for the worst treatment.^[31]

In order to explore the sources of heterogeneity or inconsistency in the entire network, we will perform network meta-regression or subgroup analysis. Network meta-regression will be

conducted using random effects network meta-regression models to examine potential effect moderators such as follow-up and sample size.

If we include enough trials per comparison, a sensitivity analysis will be conducted. We will conduct a sensitivity analysis excluding trials that are missing relative data, and we will conduct another sensitivity analysis excluding trials with a total sample size of <50 randomized patients.

3.11. Grading of quality of evidence

The GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach will be used to assess the quality of evidence which presents the confidence we have about the effect estimation.^[32] The process will be performed on the platform of GRADEpro—GDT (<https://gradepr.org/>).

4. Ethics and dissemination

4.1. Ethical issues

Ethical approval and patient consent are not required since this is a meta-analysis based on published studies. We will submit our NMA to a peer-reviewed journal for publication.

4.2. Strengths and limitations of this study

- As far as we know, this is the first NMA which compares the efficacy of different NPATs for enhancing QoL of patients with breast cancer receiving chemo- and/or radio-therapy.
- The results of this NMA will assist clinicians and patients to make the best choice of NPATs for the patients with breast cancer.
- Our conclusion will rely on both the quality and quantity of the original studies available for review.

Author contributions

Contributors: Conception and design of this systematic review and Bayesian network meta-analysis (Zhiyun He, Ailin Song, and Zhongtao Zhang); tested the feasibility of the study (Zhiyun He, Ailin Song, Xi Lv, and Yumin Li); developed the search strategy (Youcheng Zhang, Xiaokang Liu, Lei Zhao, Guosheng Ren); drafted this protocol (Zhiyun He, Ailin Song). All authors provided critical revisions of the protocol and approved the final manuscript.

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References

- [1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.
- [2] Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
- [3] Darby S, McGale P, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16.
- [4] McGale P, Taylor C, et al. EBCTCG (Early Breast Cancer Trialists' Collaborative Group) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–35.
- [5] Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b trial. *N Engl J Med* 1997;337:949–55.
- [6] Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641–8.
- [7] National Comprehensive Cancer Network (NCCN). Breast Cancer (Version 2. 2017). [https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf].
- [8] Smithson J, Paterson C, Britten N, et al. Cancer patients' experiences of using complementary therapies: polarization and integration. *J Health Serv Res Policy* 2010;15(Suppl 2):54–61.
- [9] Sirois FM, Gick ML. An investigation of the health beliefs and motivations of complementary medicine clients. *Soc Sci Med* 2002;55:1025–37.
- [10] Partridge AH, Burstein HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. *J Natl Cancer Inst Monogr* 2001;30:135–42.
- [11] de Souza BF, de Moraes JA, Inocenti A, et al. Women with breast cancer taking chemotherapy: depression symptoms and treatment adherence. *Rev Lat Am Enfermagem* 2014;22:866–73.
- [12] Witt CM, Cardoso MJ. Complementary and integrative medicine for breast cancer patients—evidence based practical recommendations. *Breast* 2016;28:37–44.
- [13] Greenlee H, DuPont-Reyes MJ, Balneaves LG, et al. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. *CA Cancer J Clin* 2017;67:194–232.
- [14] Lee PL, Tam KW, Yeh ML, et al. Acupoint stimulation, massage therapy and expressive writing for breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med* 2016;27:87–101.
- [15] Tao WW, Jiang H, Tao XM, et al. Effects of acupuncture, tuina, Tai chi, qigong, and traditional Chinese medicine five-element music therapy on symptom management and quality of life for cancer patients: a meta-analysis. *J Pain Symptom Manage* 2016;51:728–47.
- [16] Boon HS, Olatunde F, Zick SM. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005. *BMC Womens Health* 2007;7:4.
- [17] Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ* 2013;346:f2914.
- [18] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- [19] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P): 2015, elaboration and explanation. *BMJ* 2015;350:g7647.
- [20] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
- [21] Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions version 5.1.0 [www.cochrane-handbook.org].
- [22] Furukawa TA, Barbui C, Cipriani A, et al. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.
- [23] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [24] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [25] Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* 2008;61:991–6.
- [26] Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;33:607–17.
- [27] Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist Sci* 1992;7:457–72.
- [28] Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105–24.

- [29] David JS, Nicola GB, Bradley PC, et al. Bayesian Measures of Model Complexity and Fit. *J R Statist Soc B* 2002;64:583–639.
- [30] Wu HY, Huang JW, Lin HJ, et al. Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and Bayesian network meta-analysis. *BMJ* 2013;347:f6008.
- [31] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
- [32] Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.