Effect of online interventions on reducing anxiety and depression for women with breast cancer: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction Breast cancer has becoming the most common malignancy in women globally. Various online interventions have been conducted to help women with breast cancer to manage their psychological symptoms. However, there has been not yet a network meta-analysis that has synthesised scientific evidence about online intervention on reducing anxiety and depression for women with breast cancer. To fill the literature gap, this protocol aims to generate a systematic review and network meta-analysis to assess the effectiveness of online interventions on reducing anxiety and depression for these women with breast cancer. The study results may inform the recommendations for clinical guidelines and facilitate the decision-making process to improve psychological health of women with breast cancer.

Methods and analysis The protocol is in compliance with the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols and for Systematic Reviews and Network Meta-Analysis. The electronic databases of Pubmed, EMBASE, CINAHL, PsycINFO, Web of Science, Cochrane Central Registry of Controlled Trials and OpenGrey will be used for searching of related randomised controlled trials from their inception. No restrictions on publication date and language will be applied. The primary outcomes are the symptoms of anxiety and depression, and the secondary outcome is the satisfaction with the received healthcare. Two reviewers independently evaluate the risk of bias using the Cochrane Collaboration’s Risk of Bias tool. The assessment of heterogeneity, inconsistency, subgroup analysis, sensitivity analysis and publication bias will be conducted. The netmeta package of R software will be used to perform the network meta-analysis.

Ethics and dissemination This study will be based on previous research findings, so that ethics approval is not required. Data searching commences in July 2023 and expects to complete in January, 2024. The findings will be disseminated through peer-reviewed journals and academic conferences.

INTRODUCTION

WHO reported that approximate 2.26 million women suffered from breast cancer, with 685,000 deaths in 2020.1 Nowadays, breast cancer has been becoming one of the most common malignant tumours diagnosed with women and the main cause of cancer-related deaths worldwide.5–4 Despite the increased incidence of breast cancer, patients’ cure rate and survival time have been significantly increased because of the current standardised screening and diagnosis and the comprehensive treatments such as operation, chemotherapy, radiotherapy, hormonal and biological therapy.5 6 Accompanied by prolonged follow-up period, women with breast cancer inevitably experienced an increasing range of health issues associated with disease and treatment that could be always persistent throughout their lives.5 7 For instance, sound evidence indicated that women with breast cancer were more likely to encounter negative psychological status.8 Of which, anxiety and depression were the most reported difficulties of breast cancer survivors owing to multiple reasons (i.e., fear of recurrence, discomfort, fatigue, pain and hormonal changes with treatment).9–11 The other study identified 96,862 women with...
breast cancer and found that these women were at an elevated likelihood of developing anxiety and depression disorders. A systematic review based on 17 studies reported that the prevalence rates of anxiety and depression in breast cancer survivors were ranged from 17.9% to 33.3% and from 9.4% to 66.1%, respectively. These mental health problems have become great challenges in the management of women with breast cancer, not only influencing the quality of life but also affecting disease recurrence and death, which calls for the effective and accurate targeted interventions.

It is well known that psychosocial interventions can improve the psychological well-being of patients with breast cancer, mainly with the traditional face-to-face delivery. However, some factors pose challenges on the feasibility of the traditional face-to-face interventions especially during the COVID-19 pandemic. First, the increasing numbers of patients with breast cancer and the shortage of breast cancer health professionals negatively affect the generalisability of the traditional face-to-face intervention. Furthermore, time constraints and distance problems hinder women to seek face-to-face professional help. Moreover, the social isolation and health service disruptions caused by the pandemic are the barriers for the feasibility of face-to-face intervention.

Fortunately, e-health technology is the innovative method using internet technology in health field. In comparison with the traditional face-to-face intervention, online interventions can contain more tailor information, reach larger groups of patients, provide more anonymity and have less financial and time spend. To date, a number of online interventions have been conducted to help women with breast cancer to manage their psychological symptoms. For example, Zhu et al conducted a randomised controlled trial (RCT) to determine the effectiveness of an app-based breast cancer e-support programme to address Chinese women’s symptoms of anxiety and depression. Another RCT by Fergus et al evaluated a professionally facilitated, web-based programme to help Canadian young couples facing breast cancer to alleviate their depression and anxiety. The other RCT was conducted to explore the psychological outcomes of a mindfulness-based internet-streamed yoga video in American breast cancer survivors and found that the online intervention could reduce women’s anxiety. By contrast, Satoko et al conducted an RCT in Japan to examine whether a breast cancer patient support system by an app is effective for supporting patients undergoing chemotherapy; but no significant improvement was seen in anxiety or depression at the end of treatment between eHealth patients and control patients.

It needs to note that an individual RCT rarely includes all competing interventions of interest and cannot make appropriate decisions in evidence-based practice as it may have certain biases. By contrast, data derived from meta-analysis of multiple RCTs are regarded as the highest level of evidence for clinical practice. There was one new meta-analytic review reporting the effectiveness of mobile health-based interventions in patients with breast cancer; however, the majority of their participants were from Asia, which could limit the cross-cultural generalisability of findings. The other new systematic review was conducted to understand whether internet-based support interventions positively improve patients with breast cancer’s health outcomes, but no data synthesis was conducted for meta-analysis, and only narrative analysis was conducted. Moreover, the network meta-analysis well fits for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. To the best of our knowledge, there has been not yet a network meta-analysis that has synthesised scientific evidence about the effectiveness of online interventions on reducing anxiety and depression for women with breast cancer. Therefore, the aim of the current systematic review and network meta-analysis is to evaluate the effectiveness of different online interventions in the improvement of psychological health of women with breast cancer.

Our research question is ‘What is the comparative effectiveness of online interventions to alleviate anxiety and depression in women with breast cancer aged 18 years or above compared with the routine healthcare?’ The research findings may inform the recommendations for clinical guidelines and facilitate the decision-making process to improve psychological health of women with breast cancer.

**METHODS**

**Design and registration**

The present systematic review and network meta-analysis will be conducted to assess the comparative effectiveness of online interventions on reducing anxiety and depression for women with breast cancer. The protocol is in compliance with the guideline of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis and has registered on the international prospective register of systematic review.

**Eligibility criteria**

**Types of studies**

We will include all the RCTs about online intervention on reducing anxiety and depression for women with breast cancer. The quasi-experience studies, qualitative studies, reviews, guidelines, surveys, commentaries, editorials, case reports, conference papers or animal studies will be excluded.

**Types of population**

A woman diagnosed with breast cancer within the age group of 18 years and above will be recruited. Participants’ race, educational level, marital status, income level, treatment method and pathological stage are not limited.
Types of interventions and comparison

The review will include the online interventions for women with breast cancer conducted by the internet or web or m-health or mobile phone or tablet or Facebook or Twitter or WeChat or online learning or mobile application. The control group will include the routine healthcare, such as usual care or treatment.

Types of outcomes

The main outcomes associated with psychological health of women with breast cancer will be compared. The primary outcomes include the symptoms of anxiety and depression. The secondary outcome is the satisfaction with the received healthcare. There is no limit to the types of outcome measurements and measuring time points.

Search strategy

The search strategy is developed by our research team. The comprehensive systematic searches to identify all relevant studies will be performed within the following electronic databases: PubMed (including MEDLINE), EMBASE, CINAHL, PsycINFO, Web of Science, Cochrane Central Registry of Controlled Trials and OpenGrey. These databases are searched from their inception. No restrictions on publication date and language will be applied. The search terms in the current study are formulated owing to the participants, intervention, outcomes and research types. The Medical Subject Headings (MeSH) terms and free-entry terms as appropriate will be included in the search strategy. Boolean operators of ‘AND’, ‘OR’ are used to combine with the search terms; and the search techniques, that is, truncation, phrase marks or wildcard are used for slight modifications in the databases. Using PubMed database as an example, the specific search strategy is described in table 1. The search strategies for the other databases are described in online supplemental file. We will invite an expert to review our search strategies and revise where needs.

To decrease publication bias, unpublished literature will be searched via OpenGrey and conference proceedings; and the international trial register platforms such as Clinical Trial Registration and WHO–International Clinical Trials Registry Platform will also be searched to identify the ongoing trials (see online supplemental file). The reference lists and bibliographies of all identified articles will be searched for additional studies. Hand searching likewise will be used for retrieving other studies meeting inclusion criteria through journals and conference abstracts. If necessary, we will contact experts in the field to identify other trials.

Study selection

All retrieved articles will be imported into Endnote V.X7 (Thomson Reuters LLC, Philadelphia). The systematic review software Rayyan Qatar Computing Research Institute (QCRI) will be used to delete the duplicated articles. After eliminating the duplicates, the titles and abstracts of all identified studies will be initially examined for eligibility based on the inclusion criteria independently by two reviewers (QC and WL), and the irrelevant studies will be excluded. Then, the full texts of retained studies will be obtained and reviewed, and the eligibility criteria will be evaluated for final inclusion. All the study selection processes will be carried out independently by two reviewers (QC and WL). Once a consensus reaches, it
will proceed to the next stage. Otherwise, any discrepancy between them will be solved through discussion and consultation. If necessary, a third independent senior reviewer (JX) will double check the data to make a decision. The selection of studies in the systematic review will be illustrated in the flowchart of figure 1, according to the PRISMA 2020 statement for reporting new systematic reviews.31

Data extraction

Data extraction will be conducted independently by two reviewers (QC and WL) for all included studies. Any disagreements will be arbitrated with a third senior reviewer (JX). A purpose-built, standard data extraction form is developed based on the Cochrane handbook.32 The following data will be extracted from studies including information about: study general data (eg, authors, journal, year of publication, country of study, study design, methods of randomisation and blinding); participant characteristics (eg, sample size, age, cancer type, treatment methods); intervention and control (eg, type of intervention, duration, frequency, intensity, follow-up, control group); outcome (eg, numbers and types of outcomes, measures of effect) and access time. If there is any missing data, we will try to contact the corresponding author by email or telephone to obtain the complete data.

Risk of bias assessment

The methodological quality of the included studies will be examined independently by two reviewers, resolving discrepancy by a third reviewer. We will assess the risk of bias potentially using version 2 of the Cochrane tool for assessing risk of bias in randomised trials (RoB 2),33 including the fixed domain information of ‘bias arising from the randomisation, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result’. Each domain of bias is classified into three levels ‘low risk of bias’, ‘some concerns’ and ‘high risk of bias’.

**Data synthesis and analysis**

**Pairwise and network meta-analysis**

In the network geometry, we are planning to group interventions to examine comparative effectiveness among different online intervention type, such as routine healthcare (A), intervention by APP (application) (B), by internet or web-based (C), by social software (Facebook, Twitter, Wetchat) (D), or combination (E). Evidence will be synthesised for each group of outcomes such as anxiety and depression of women with breast cancer. If feasible, the conventional pairwise meta-analysis will be conducted for direct comparisons. Mantel-Haenszel for ORs will be used to calculate the pooled effect size of categorical variable data. By contrast, standardised mean difference (SMD) will be conducted to calculate the pooled effect size of continuous outcomes.34 The related 95% CIs of SMD and OR will also be computed; and a p value (two tailed) less than 0.05 will be considered statistically significant. If necessary, the additional summary measures will be used, such as the surface under the cumulative ranking curve and the P-score to quantify intervention ranking. It could help clinicians to appraise intervention for women with breast cancer. If meta-analysis is not available, a narrative synthesis of findings will be conducted and reported according to the Synthesis Without Meta-analysis guidelines.35

In order to compare the effects of different online interventions on psychological outcomes in women with breast cancer, the Bayesian Network Meta-analysis method using Markov-chain Monte Carlo simulation will be required to improve statistical efficacy for indirect comparisons.36 The ‘netmeta’ package of R software (R Foundation for Statistical Computing, Vienna, Austria) will be used to perform the network meta-analysis.36 Both of the direct and indirect comparison results will be presented as a network diagram.

**Heterogeneity assessment**

We will perform a meta-analysis if the included studies are sufficiently homogeneous in terms of participants, interventions and outcomes. Thereby, before the combination of effect size, heterogeneity will be assessed using the $\chi^2$ test ($X^2$ or Cochrane $Q$) and inconsistency index ($I^2$) to check whether the results of individual studies could be combined.37 When $I^2 < 25\%$ is regarded as no heterogeneity, 25%–49% as lower heterogeneity, 50%–74% as moderate heterogeneity and $\geq 75\%$ as high heterogeneity.
A common method to allow for heterogeneity is via a random effects model. In the present study, an I² value greater than 50% will be considered evidence of substantial heterogeneity, in which the random effects model can be used for meta-analysis; otherwise, the fixed effect model will be used to combine the effect size.

Assumption of transitivity
It is of significance to evaluate the characteristics about patient and study that compare pairs of intervention when conducting a network meta-analysis, and these characteristics are regarded as effect modifiers. In the present study, patient age, symptom duration, disease severity, treatment method, intervention modality, duration and intensity will be considered as effect modifiers. The assumption of transitivity can be violated when there are major differences between the included studies regarding the significant characteristics about patient and study. Thus, we assume that the main effect modifies are as similar as possible among the included studies. By contrast, if transitivity is not suspected, the presence of effect modifies affecting intervention should be checked first.

Inconsistency assessment in the network
Consistency is a significant principle for network meta-analysis. Thus, we will investigate for consistency between direct and indirect comparative results. Inconsistency for both anxiety and depression outcomes will be assessed by Node-splitting owing to its straightforward interpretation. In every closed loop, it involves separating out the evidence for a particular intervention comparison into the direct and indirect evidence and assessing the discrepancy between them. Local inconsistency will be deemed statistically significant if loop-specific 95% CIs do not include zero.

Subgroup analysis, sensitivity analysis and publication bias
We will also perform subgroup analyses, if possible, according to different types of interventions and different characteristics of participants. Furthermore, sensitivity analysis will be conducted based on the bias assessment to evaluate robustness of results. One study with unclear or high risk of bias will be excluded to check whether the results would change. Moreover, the publication bias will be evaluated by visual inspection of the asymmetry of the funnel plot and egger’s test.

Evidence quality assessment
The quality of the body of evidence will be assessed by the Grading of Recommendation Assessment, Development and Evaluation system. It will be judged as very low, low, moderate and high according to the assessments of the risk of bias, indirectness of evidence, inconsistency, imprecision and publication bias. The assessment of evidence quality will be conducted independently by two reviewers (QC and WL).

Patient and public involvement
Patients and the public will not be directly involved in this systematic review.

ETHICS AND DISSEMINATION
This study will be based on previous research findings, so that ethics approval is not required. The research findings will be disseminated through the form of original article published in an international peer-reviewed journal and through the form of oral or postcommunication in academic conferences of breast cancer. We will update the review process annually and regenerate the findings when new pertinent RCT is available. Reproduction will be sought when there is a change in conclusions.

Implication
In recent years, breast cancer has becoming the most common malignancy in women globally. Previous studies found that women with breast cancer suffered from negative psychological health. Thus, various online interventions have been conducted to help women with breast cancer to manage their psychological symptoms of anxiety and depression. It is well known that data derived from meta-analysis of multiple RCTs are regarded as the highest level of evidence in the evidence hierarchy for clinical practice. However, there has been not yet a network meta-analysis that has synthesised scientific evidence about online intervention and its effectiveness on reducing anxiety and depression of women with breast cancer. The results of the systematic review and network meta-analysis will generate the best and most current research evidence from vast number of RCT findings, which could help health professionals to inform the recommendations for clinical guidelines and facilitate the decision-making process to improve psychological health of women with breast cancer.

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Contributors
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REFERENCES

The search strategies for databases and trial registers

Using PubMed database as an example, the specific search strategy is described in Table 1 of the manuscript. The search strategies for the other databases and trial registers are described in the supplementary file.

EMBASE

1. breast neoplasms [exp]
3. #1 OR #2
4. internet-based intervention [exp]
6. #4 OR #5
8. #3 AND #6
9. #7 AND #8
CINAHL (via EBSCOhost)

1. breast neoplasms [Mesh]
3. #1 OR #2
5. #3 AND #4
6. Clinical trial [Mesh]
7. randomized controlled trial [Title/Abstract] OR controlled clinical trial [Title/Abstract] OR randomized [Title/Abstract] OR randomised [Title/Abstract] OR randomly [Title/Abstract] OR trial [Title/Abstract] OR random [Title/Abstract]
8. #6 OR #7
9. #5 AND #8
PsycINFO


4. #1 AND #2

5. #3 AND #4
Web of Science
1. TS= (breast neoplasm OR breast malignan* OR breast tumor OR breast tumors OR breast tumour OR breast tumours OR breast carcinoma OR breast carcinomas OR breast cancer OR breast cancers OR human mammary neoplasm OR human mammary carcinoma)
2. TS=(internet-based intervention OR e-health based intervention OR ehealth based intervention OR internet* based intervention OR web-based intervention OR online intervention OR mhealth OR mobile phone OR face book OR twitter OR mobile application)
3. TS=(randomized controlled trial OR controlled clinical trial OR randomized OR randomised OR randomly OR trial OR random)
4. #1 AND #2
5. #3 AND #4
Cochrane Central Registry of Controlled Trials (CENTRAL)

1. MeSH descriptor: [breast neoplasms] explode all trees


3. MeSH descriptor: [internet-based intervention] explode all trees


5. MeSH descriptor: [Controlled Clinical Trial] explode all trees

6. randomized controlled trial [Title/Abstract] OR controlled clinical trial [Title/Abstract] OR randomized [Title/Abstract] OR randomised [Title/Abstract] OR randomly [Title/Abstract] OR trial [Title/Abstract] OR random [Title/Abstract]

7. #1 OR #2

8. #3 OR #4

9. #5 OR #6

10. #7 AND #8

11. #9 AND #10
**OpenGrey**

1. breast neoplasm OR breast tumor OR breast tumors OR breast tumour OR breast tumours OR breast carcinoma OR breast cancer
2. internet-based intervention OR e-health based intervention [Title/Abstract] OR web-based intervention OR online intervention
3. randomized controlled trial OR randomized OR randomised
4. #1 AND #2
5. #3 AND #4

**Clinical Trial Registration**


1. breast cancer [Condition or disease] OR breast carcinoma [Condition or disease] OR breast tumor [Condition or disease] OR breast tumors [Condition or disease]
2. Interventional studies (Clinical trials) [study type]
3. #1 AND #2

**World Health Organization–International Clinical Trials Registry Platform**

https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal

1. breast cancer [Title] OR breast carcinoma [Title] OR breast tumor [Title] OR breast tumors [Title]
2. Intervention study [study type]
3. #1 AND #2