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Prevalence and risk factors of anxiety and depression among breast cancer patients: a protocol for systematic review and meta-analysis

Jie Li[1], Feng Zhang[1], Wenchun Wang[2], Rizhao Pang[2], Jiancheng Liu[2], Qiuhong Man[4], , Anren Zhang[3]

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LJ and ZF contributed equally.

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ABSTRACT

Background: Patients with breast cancer often experience severe psychological distress, especially anxiety and depression, leading to poorer quality of life, shortened survival time and increased mortality. We aim to summarize data on the prevalence and risk factors of anxiety and depression in patients with breast cancer.

Methods and analysis: We will search Web of Science, PubMed, EMBASE, Wan Fang Data Knowledge Service Platform, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), China National Knowledge Infrastructure(CNKI) and for studies on the prevalence and risk factors of depression in patients with breast cancer, which should be published from inception to Feb 2020 in English and Chinese. The selection of studies, data extraction, and risk of bias assessment will be done independently by two reviewers. Data synthesis will be carried out using Rev Man $_{V.}$5.3 software. The heterogeneity will be determined by the I^2 test. Publication bias will be evaluated by generating a funnel plot and performing the Begg and Egger test. The quality of the systematic review will be assessed using the GRADE criteria.

Ethics and dissemination No ethical approval is required. This protocol will not involve individual patient information and endangering participant rights. The results will be reported in a peer- reviewed

journal or disseminated in relevant conferences.

OSF registration number: DOI 10.17605/OSF.IO/D6A4P

Strengths and limitation of this study

The study aim to summarize data on the prevalence and risk factors of anxiety and depression in patients with breast cancer.

The selection of studies, data extraction, and risk of bias assessment will be done independently by two reviewers.

The quality of the systematic review will be assessed using the GRADE criteria.

In this review, only studies published in English or Chinese will be considered, which may cause a potential risk of publication bias.

Different measurements and tools might lead to inconsistent levels of outcomes.

INTRODUCTION

According to the data of Cancer Statistics,[1] for women, the 3 most common cancers are breast, lung, and colorectal, accounting for 50% of all new diagnoses; breast cancer alone accounts for 30% of female cancers and has been listed as the most frequent cancer diagnosis of female malignancy. According to global cancer statistics,[2] 2088849 new cases were reported in 2018.

Published epidemiological reports around the world[3] show that there is a significant increase in the death rate from breast cancer over the past two decades. Approximately 0.5 million people worldwide die from metastatic breast cancer every year even after receiving many therapies. Breast cancer patients suffer from psychological and physical cancer-related stressors which may affect patients for many years after treatment.[4] Women with breast cancer may suffer from those treatment-related effects such as treatment-induced symptoms, surgical trauma, scarring, mastectomy, and lymphedema. According to the medical data,[5 6] these effects will easily lead to body image distortion, sexual dysfunction/intimacy problems as well as low self-esteem. Compared with the general population, when these patients are diagnosed with breast cancer, these effects will cause nearly 50% breast cancer patients to experience more considerable psychological distress, such as depression and anxiety, the prevalence of depression and anxiety in the year after diagnosis is around twice as high as in the general female population.[7 8] Besides, lack of intimate confiding support will also lead to chronic depression and anxiety. The quality of life of patients with psychological symptoms is poor and the risk should not be ignored,[9 10 11] the

depressive symptoms in patients with breast cancer can lead to physical deterioration and increased mortality.[12 13] Early screening for depression is essential because of its severity.

However, complete screening for depression is difficult due to its complex etiology and pathogenesis. These groups are becoming more prevalent, which may improve diagnostic capacity. Therefore, it is imperative to identify high-risk groups is of tremendous assistance. Some previous studies have linked the prevalence of depression to their factors, such as physical symptom burden, marital status, age, level of education, financial status and the number of therapies.[14 15] However, some of the results are inconsistent. Some researchers have shown that the chemotherapy can reduce the risk of depression, the studies reveal the values are lower than before,[14] while others have found that the risk of depression is not affected by clinical factors such as prognosis, type of surgery, or adjuvant radiotherapy, they consider that adjuvant chemotherapy may increase the risk of depression, anxiety, or both during.[16 17 18 19 20] Only after screening out unified risk factors, and looking for high-risk patients can we effectively provide more targeted treatment strategies and improving quality of life in breast cancer patients and survivors. To provide strong evidence on the risk factors related to depression, we will conduct a systematic review of evidence-based medicine and a meta-analysis. The validated findings will give recommendations for physicians to identify breast cancer patients with depression and the management of emotional problems for patients, and we can also give some suggestions on improving the quality of life of these patients.

Methods

Inclusion criteria for study selection

Types of studies.

Observational studies with available data on the prevalence and risk factors associated with anxiety and depression among patients with breast cancer will be considered. Cross-sectional, cohort and case-control studies will be excluded. Case reports, case series, opinion papers, qualitative research, letters to the editor, comments, conference proceedings, policy documents, reviews and meta-analyses, study protocols without baseline data, and animal studies will be also excluded.

Types of patients.

Study population inclusion criteria will be all patients diagnosed with breast cancer, regardless of demographic age, race, and education status.

Types of outcome measures

(1) Prevalence of anxiety and depression among patients with breast cancer. (2) Risk factors associated with anxiety and depression in patients with breast cancer. (3) The strength of the correlation between each risk factor and anxiety and depression.

Search methods for the identification of studies

Data sources

Retrieval databases include Web of Science, PubMed, EMBASE, Wan Fang Data Knowledge Service Platform, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), China National Knowledge Infrastructure (CNKI). We will also conduct unpublished academic research data. Databases will be searched from inception to Feb 2020. The reference lists of review articles will be conducted and the following search terms will be used: breast cancer, breast carcinoma, breast tumor, mammary cancer, mammary adenocarcinoma, anxiety, depression, depressive disorder, et al. And we will use the search strategy provided in **Table 1** for searching the database. The authors will also search relevant trials from Clinical Trials.gov, Google Scholar and WHO International Clinical Trials Registry Platform.

Table 1 Search strategy in PubMed database

No.	Search items
1	randomized controlled trial. Mesh.
2	controlled clinical trial.ti.ab.
3	randomized. ti.ab.
4	randomly.ti.ab.
5	trial. ti.ab.
6	1 or 2-5
7	**breast cancer**.Mesh.
8	**breast carcinoma**.ti.ab.
9	**breast tumor**.ti.ab.
10	**mammary cancer**.ti.ab.
11	**mammary adenocarinoma**.ti.ab.
12	7 or 8-11
13	**anxiety**.Mesh.
14	**anxious**.ti.ab.
15	hypervigilance.ti.ab.
16	nervousness.ti.ab.
17	social anxiety.ti.ab.

18 anxieties, social.ti.ab.
19 anxiety, social.ti.ab.
20 social anxieties.ti.ab.
21 13 or 14-20

22 depression.Mesh.

23 depressions.ti.ab.
24 depressive symptoms.ti.ab.
25 depressive symptom.ti.ab.
26 symptom, depressive.ti.ab.
27 symptoms, depressive.ti.ab.
28 emotional depression.ti.ab.
29 depression, emotional.ti.ab.
30 depressions, emotional.ti.ab.
31 emotional depressions.ti.ab.
32 23 or 24-31

33 6 and 12 and 21 and 32

Study selection

Studies imported into Endnote X8 software after deleting duplicates will be independently reviewed by two authors based on the exclusion and inclusion criteria. The researchers will read the full text of relevant articles to confirm the final inclusion of studies. For unclear dates, the researchers will contact the author for details to determine whether this literature would be included. Any disagreement between reviewers will be resolved by discussion or a third rater. The study screening process is shown in **Figure 1.**

Risk of bias assessment

The risk of bias/method quality of the included studies will be assessed independently by two authors at the study and outcome levels. Any disagreements will be settled by discussion or with the arbitrament of the third author. In this study, we will use the Newcastle-Ottawa Scale to evaluate the quality of studies. This scale is a quality assessment tool for non-randomized controlled trials, with scores ranging from 0 to 9; scores of 0–4 and 5–9 mean low quality and high quality, respectively.

Statistical collection and analysis

Data extraction and management.

Extracted information include the first author's name, date of publication, journal, type of study (cross-sectional/cohort/case-control), country and region, sample size (N and male/ female), duration of the

study, baseline age, diagnostic criteria for breast cancer and anxiety and depression, incidence of anxiety and depression/mean and SD for anxiety and depression score, variables, OR values, 95% CI, and other relevant data for quality evaluation and risk of bias assessment. And the reasons for the exclusion of studies while extracting will also be recorded. Possible risk factors include but are not limited to gender, age, occupation, marital status, education level, social support, alcohol status, smoking status, pathological type, cancer clinical-stage, disease course, and therapy method. The extracted variables will be adjusted during the process, as it is likely that more and more variables that need to be included will turn up. Data collection will be done by two reviewers independently. And if they are inconsistent in the process, they will discuss the results. A third reviewer will be consulted to resolve the doubts. For unclear details, the researchers will contact the corresponding authors.

Measurements of prevalence and risk factors

Rev Man $_{V}$.5.3 will be used to calculate the OR values and 95% CIs of the reported risk factors for anxiety and depression in breast cancer. When the CI of the OR value is not equal to 1 and $p<0.05$, it is considered statistically significant. The prevalence estimates reported by the individual studies will be extracted or converted into prevalence percentages, and their respective SEs will be calculated. For the anxiety and depression scores, Standardized Mean Difference (SMD) will be used for analysis. We will use the Freeman-Tukey double arcsine transformation to stabilize the variance of study-specific prevalence. The prevalence of each study will be recalculated to confirm numerators and denominators, and adjustments as necessary.

Assessment of heterogeneity

The I^2 test will be used to determine the extent of heterogeneity. When the I^2 value is less than 50%, the fixed-effects model will be used. If the I^2 value is higher than 50%, the random-effects model will be used, because we think the results of each study vary markedly.

In this study, factors of high heterogeneity will be removed one by one to identify the source of any observed heterogeneity. The causes of heterogeneity may include differences in study design, statistical methods, and participants.

Data synthesis

We will use RevMan $_{V}$.5.3 software for analysis. Meta-analysis will be performed when the heterogeneity is low or the source could be found, although heterogeneity is high. A systematic narrative synthesis will be conducted if it is impossible to complete any meta-analysis. If there is significant heterogeneity, we will use the subgroup analysis.

Subgroup analysis

Subgroup analysis will be done when data are available. The groups may be designed based on country or region, diagnostic criteria for anxiety and depression, bias score, time since diagnosis (long-term vs

short-term survivors), severity/staging of breast cancer and study design.

Assessment of reporting biases

We will evaluate publication bias by generating a funnel plot and performing the Begg and Egger test ($p< 0.05$ indicates the existence of publication bias).

Quality control of the systematic review and meta-analysis

The methodological quality of the systematic review will be evaluated using the Measurement Tool to Assess Systematic Reviews (AMSTAR). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) will also be used to evaluate the strength of evidence produced by the systematic review.

Discussion

This study will review current researches to provide effective evidence on the risk factors related to depression, and the results of systematic review and meta-analysis will provide significant help in identifying high-risk groups. These unified risk factors of depression will be screen out to advise on the management of emotional issues for patients. There may be some limitations to this review. Firstly, in this review, only studies published in English or Chinese will be considered, which may cause a potential risk of publication bias. Secondly, there may be heterogeneity in the diagnostic criteria for different types of anxiety and depression, as well as in the staging of cancer and depression. Different measurements and tools might lead to inconsistent levels of outcomes.

Author Contribution

LJ and ZF will identify eligible studies after reading titles and abstracts. WWC a will read the full texts to perform further selection. Several studies from different opinions will be determined by the PRZ. Data will be extracted from the original reports by LZC. The assessment of the risk of bias will be carried out by MQH, ZAR, and LJ. Any discrepancies will be resolved by discussion with a third ZAR. LJ and ZF will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. LJ conceived the review protocol and drafted the manuscript. ZF will monitor each procedure of the review. All authors have read and approved the publication of the protocol.

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Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Patient and Public Involvement

No patient involved

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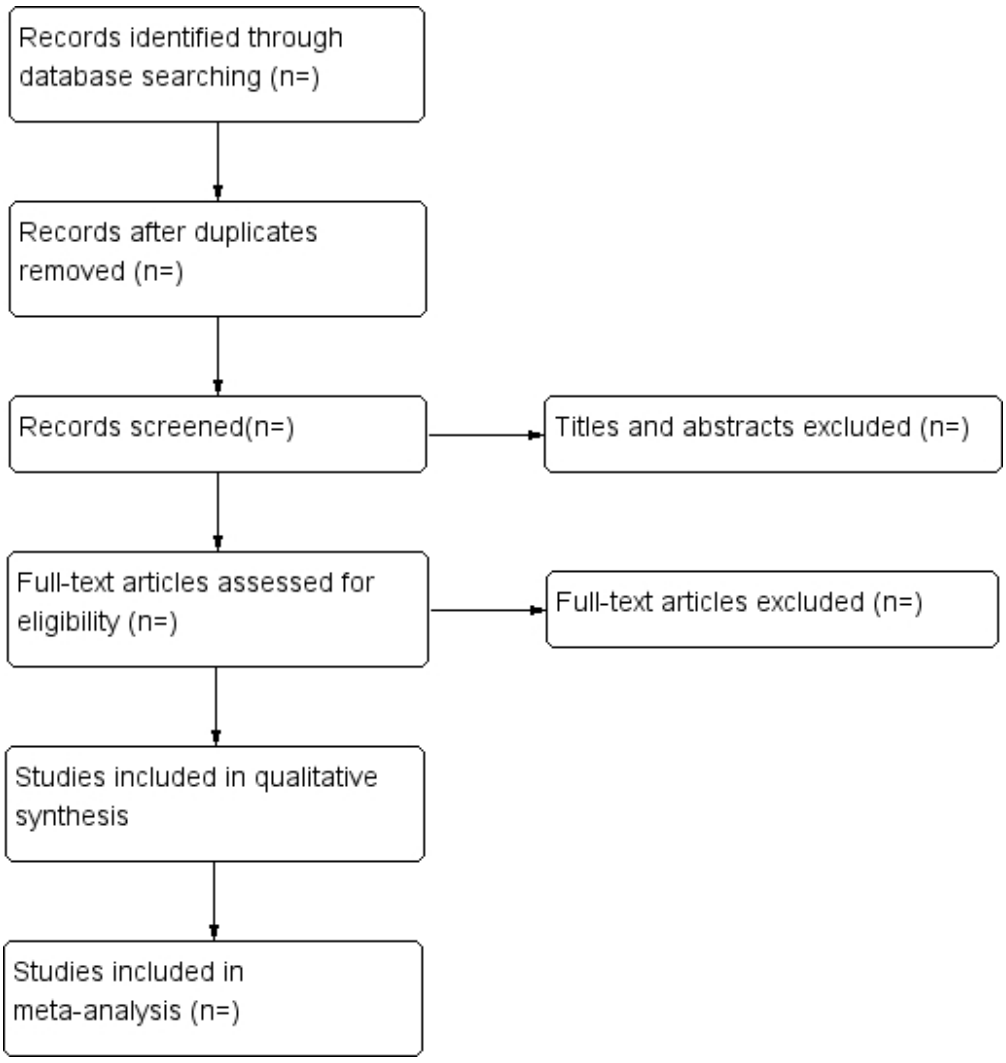

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Primary Subject Heading:	Oncology
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LJ and ZF contributed equally.

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ABSTRACT

Background: Patients with breast cancer often experience severe psychological distress, especially anxiety and depression, leading to poorer quality of life, shortened survival time and increased mortality. The objective of the review will be to summarize data on the prevalence and risk factors of anxiety and depression in patients with breast cancer.

Methods and analysis: Two reviewers will be applied in 7 databases, including Web of Science, PubMed, EMBASE, Wan Fang Data Knowledge Service Platform, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), China National Knowledge Infrastructure (CNKI) and for studies on the prevalence and risk factors of depression in patients with breast cancer, which should be published from inception to Feb 2020 in English, Chinese, French and Spanish. The selection of studies, data extraction, and risk of bias assessment will be done independently by two reviewers. Data synthesis will be carried out using Rev Man $_{v.5.3}$ software. The heterogeneity will be determined by the I^2 test. Publication bias will be evaluated by generating a funnel plot and performing the Begg and Egger test. The quality of the systematic review will be assessed using the Grading of Recommendations Assessment, Development and Evaluation Tool (GRADE) criteria.

Ethics and dissemination: No ethical approval is required. This protocol will not involve individual patient information and endangering participant rights. The results will be reported in a peer-reviewed journal or disseminated in relevant conferences.

OSF registration number: DOI 10.17605/OSF.IO/D6A4P

Strengths and limitation of this study

The study aims to summarize data on the prevalence and risk factors of anxiety and depression in patients with breast cancer.

The selection of studies, data extraction, and risk of bias assessment will be done independently by two reviewers.

The quality of the systematic review will be assessed using the GRADE criteria.

In this review, only studies published in English or Chinese will be considered, which may cause a potential risk of publication bias.

Different measurements and tools might lead to inconsistent levels of outcomes.

INTRODUCTION

Breast cancer in women is increasing worldwide. The Cancer Statistics [1] produced the 3 most common cancers, including breast cancer, lung cancer, and colorectal cancer, accounting for 50% of all new diagnoses. Prevalence of breast cancer alone accounts for 30% of female cancers and has been listed as the most frequent cancer diagnosis of female malignancy. It is known as global cancer statistics;[2] 2088849 new cases were reported in 2018.

Published epidemiological reports around the world[3] show that there is a significant increase in the death rate from breast cancer over the past two decades. Approximately 0.5 million people worldwide die from metastatic breast cancer every year even after receiving many therapies. Breast cancer patients suffer from psychological and physical cancer-related stressors which may affect patients for many years after treatment.[4] Women with breast cancer may suffer from treatment related side effects such as surgical trauma, scarring, mastectomy, and lymphedema. According to the medical data,[5 6] these effects will easily lead to body image distortion, sexual dysfunction/intimacy problems as well as low self-esteem. Compared with the general population, when these patients are diagnosed with breast cancer, these effects will cause nearly 50% breast cancer patients to experience more considerable psychological distress, such as depression and anxiety, the prevalence of depression and anxiety in the year after diagnosis is around twice as high as in the general female population.[7 8] Besides, lack of intimate confiding support will also lead to chronic depression and anxiety. The quality of life of patients with psychological symptoms is poor and the risk should not be ignored,[9 10 11] the depressive symptoms in patients with breast cancer can lead to physical deterioration and increased mortality.[12 13] Early screening for depression is essential because of its severity.

However, complete screening for depression is difficult due to its complex etiology and pathogenesis. Some previous studies have linked the prevalence of depression to the following factors , such as physical symptom burden, marital status, age, level of education, financial status and the number of therapies.[14 15] However, some of the results are inconsistent. Some researchers have shown that the chemotherapy can reduce the risk of depression,[14] while others have found that the risk of depression is not affected by clinical factors such as prognosis, type of surgery, or adjuvant radiotherapy, they consider that adjuvant chemotherapy may increase the risk of depression, anxiety, or both during.[16 17 18 19 20] Only after screening out unified risk factors, and looking for high-risk patients can we effectively provide more targeted treatment strategies and improve quality of life in breast cancer patients and survivors. To provide strong evidence on the risk factors related to depression, we will conduct a systematic review of evidence-based medicine and a meta-analysis. The validated findings will give recommendations for physicians to identify breast cancer patients with depression and the management of emotional problems for patients, and we can also give some suggestions on improving the quality of life of these patients.

Methods

This study consists the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The systematic review protocol has been registered with OSF with registration number DOI 10.17605/OSF.IO/D6A4P.

Inclusion criteria for study selection

Types of studies.

Observational studies with available data on the prevalence and risk factors associated with anxiety and depression among patients with breast cancer will be considered. For study selection, we will exclude cross-sectional, cohort studies, case-control studies, case reports, case series, opinion papers, qualitative research, letters to the editor, comments, conference proceedings, policy documents, reviews and meta-

analyses, study protocols without baseline data, and animal studies.

Types of patients.

Study population inclusion criteria will be all patients diagnosed with breast cancer, regardless of demographic age, race, and education status.

Types of outcome measures

(1) Prevalence of anxiety and depression among patients with breast cancer. (2) Risk factors associated with anxiety and depression in patients with breast cancer. (3) The strength of the correlation between each risk factor and anxiety and depression.

Search methods for the identification of studies

Data sources

The following databases will be used: Web of Science, PubMed, EMBASE, Wan Fang Data Knowledge Service Platform, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), China National Knowledge Infrastructure (CNKI). We will also conduct unpublished academic research data, contacting authors in the field for information. Two systematic reviews will be carried out from inception to Feb 2020. The reference lists of review articles will be conducted and the following search terms will be used: breast cancer, breast carcinoma, breast tumor, mammary cancer, mammary adenocarcinoma, anxiety, depression, depressive disorder, et al. And we will use the search strategy provided in Table 1 for searching the database. The authors will also search relevant trials from Clinical Trials.gov, Google Scholar and WHO International Clinical Trials Registry Platform.

Table 1 Search strategy in PubMed database

No.	Search items
1	observational study. Mesh.
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3	observe. ti.ab.
4	study. ti.ab.
5	1 or 2-4
6	breast cancer. Mesh.
7	breast carcinoma. ti.ab.
8	breast tumor. ti.ab.
9	mammary cancer. ti.ab.
10	mammary adenocarinoma. ti.ab.
11	6 or 7-10
12	anxiety. Mesh.
13	anxious. ti.ab.
14	hypervigilance. ti.ab.
15	nervousness. ti.ab.
16	social anxiety. ti.ab.
17	anxieties, social. ti.ab.
18	anxiety, social. ti.ab.
19	social anxieties. ti.ab.
20	12 or 13-19
21	depression. Mesh.
22	depressions. ti.ab.
23	depressive symptoms. ti.ab.

24 depressive symptom. ti.ab.
25 symptom, depressive. ti.ab.
26 symptoms, depressive. ti.ab.
27 emotional depression. ti.ab.
28 depression, emotional. ti.ab.
29 depressions, emotional. ti.ab.
30 emotional depressions. ti.ab.
31 21 or 22-30
32 5 and 11 and 20 and 31

Study selection

Studies imported into Endnote X9 software after deleting duplicates will be independently reviewed by two authors (LJ and ZF) based on the exclusion and inclusion criteria. The researcher (WWC) will read the full text of relevant articles to confirm the final inclusion of studies. For unclear study, the researcher (PRZ) will contact the author for details to determine whether this literature would be included. Any disagreement between reviewers will be resolved by discussion or a researcher (LZC). The study screening process is shown in Figure 1. The documents selection will be demonstrated on a PRISMA flow chart.

Risk of bias assessment

The risk of bias will be assessed applying the Cochrane's 'Risk of bias' tool. The quality of the included studies will be assessed independently by two authors (MQH and ZAR) at the study and outcome levels. Any disagreements will be settled by discussion or with the arbitrament of the third author (LJ). In this study, we will use the Newcastle-Ottawa Scale to evaluate the quality of studies. This scale is a quality assessment tool for non-randomized controlled trials, with scores ranging from 0 to 9; scores of 0–4 and 5–9 mean low quality and high quality, respectively.

Statistical collection and analysis

Data extraction and management.

Extracted information include the first author's name, date of publication, journal, country and region, sample size (N and male/ female), duration of the study, baseline age, diagnostic criteria for breast cancer and anxiety and depression, incidence of anxiety and depression/mean and SD for anxiety and depression score, variables, OR values, 95% CI, and other relevant data for quality evaluation and risk of bias assessment. And the reasons for the exclusion of studies while extracting will also be recorded. The extraction of possible risk factors will be included gender, age, occupation, marital status, education level, social support, alcohol status, smoking status, pathological type, cancer clinical-stage, disease course, and therapy method. The extracted variables will be adjusted during the process, as it is likely that more and more variables that need to be included will turn up. Data collection will be done by two reviewers (LJ and ZF) independently using Review Manager software. And if they are inconsistent in the process, they will discuss the results. A third reviewer will be consulted to resolve the doubts. For unclear details, the researchers will contact the corresponding authors by email for detailed information.

Measurements of prevalence and risk factors

Rev Man $_{V.5.3}$ will be used to calculate the OR values and 95% CIs of the reported risk factors for anxiety and depression in breast cancer. When the CI for the OR does not include 1, it is considered statistically significant. The prevalence estimates reported by the individual studies will be extracted or converted into prevalence percentages, and their respective SEs will be calculated. For the anxiety and depression

scores, Standardized Mean Difference (SMD) will be used for analysis. We will use the Freeman-Tukey double arcsine transformation to stabilize the variance of study-specific prevalence. The prevalence of each study will be recalculated to confirm numerators and denominators, and adjustments as necessary.

Assessment of heterogeneity

The I^2 test will be used to determine the extent of heterogeneity. When the I^2 value is less than 50%, the fixed-effects model will be used. If the I^2 value is higher than 50%, the random-effects model will be used. In this study, factors of high heterogeneity will be removed one by one to identify the source of any observed heterogeneity. The causes of heterogeneity may include differences in study design, statistical methods, and participants.

Data synthesis

We will use RevMan $_{V.5.3}$ software for analysis. Meta-analysis will be performed when the heterogeneity is low or the source could be found, although heterogeneity is high. A systematic narrative synthesis will be conducted if it is impossible to complete any meta-analysis. If there is significant heterogeneity, we will use the subgroup analysis.

Subgroup analysis

Subgroup analysis will be done when data are available. The groups may be designed based on country or region, diagnostic criteria for anxiety and depression, bias score, time since diagnosis (long-term vs short-term survivors), severity/staging of breast cancer and study design.

Meta-regression analysis

Meta-regression analysis will be used to evaluate important factors (gender, age, occupation, marital status, education level, social support, alcohol status, smoking status, pathological type, cancer clinical-stage, disease course, and therapy method) on our study, which may explain heterogeneity across studies in the pooled effect size.

Assessment of reporting biases

Funnel plots will be used to assess publication bias. We will evaluate publication bias by performing the Begg's and Egger's tests. The significant p value (< 0.05) indicates the existence of publication bias.

Quality control of the systematic review and meta-analysis

The methodological quality of the systematic review will be evaluated using the Measurement Tool to Assess Systematic Reviews (AMSTAR). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) will also be used to evaluate the strength of evidence produced by the systematic review (LJ and ZF).

Discussion

This study will review current researches to provide effective evidence on the risk factors related to depression and anxiety, and the results of systematic review and meta-analysis will provide significant help in identifying high-risk groups. These unified risk factors of depression will be screen out to advise on the management of emotional issues for patients. There may be some limitations to this review. Firstly, a limitation will be the high heterogeneity studies may not be appropriate to be used in meta-analysis. Secondly, there may be heterogeneity in the diagnostic criteria for different types of anxiety and depression, as well as in the staging of cancer and depression. Different measurements and tools might lead to inconsistent levels of outcomes.

Author Contribution

LJ and ZF will identify eligible studies after reading titles and abstracts. WWC a will read the full texts to perform further selection. Several studies from different opinions will be determined by the PRZ. Data will be extracted from the original reports by LZC. The assessment of the risk of bias will be carried out

by MQH, ZAR, and LJ. Any discrepancies will be resolved by discussion with a third ZAR. LJ and ZF will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. LJ conceived the review protocol and drafted the manuscript. ZF will monitor each procedure of the review. All authors have read and approved the publication of the protocol.

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Competing interests

None declared.

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Patient and Public Involvement

No patient involved

Figure 1 Flow diagram of the trial selection process.

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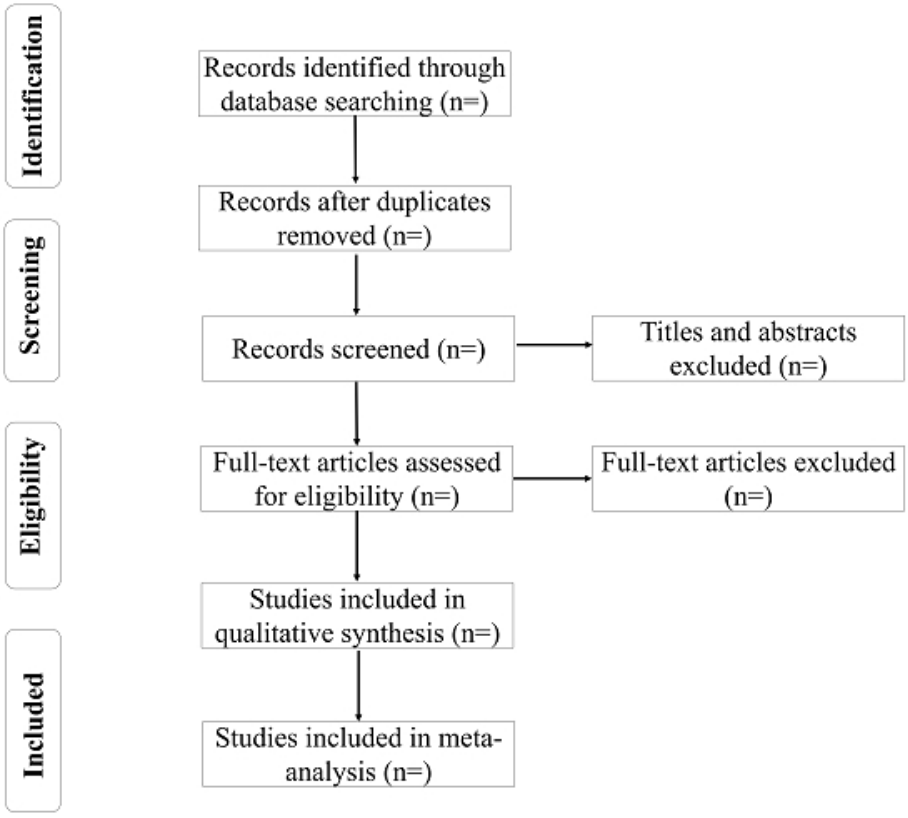

Figure 1 Flow diagram of the trial selection process.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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