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Depression and survival of breast cancer patients
A protocol for systematic review and meta-analysis

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Abstract

Background: Breast cancer is the most common malignancy in women worldwide. Compared with other malignant tumors, breast cancer patients have a higher incidence of depression and other psychiatric symptoms. The purpose of this meta-analysis was to determine the association between long-term survival and depression in patients with breast cancer.

Methods: This review will include cohort studies only. Multiple databases will be searched by 2 independent reviewers, including PubMed, EMBASE, the Cochrane Library, and PsycINFO. The language of studies should be English and Chinese, published from inception to the September 2020. Two independent reviewers will carry out literature screening, research selection and data extraction. Revman5.3 software will be used to generate funnel map, assess heterogeneity, make the subgroup analysis and complete sensitivity analysis.

Results: This review will summarize the available evidence to determine the association between depression and survival in breast cancer patients.

Conclusion: The results of this study will provide reference for the development of comprehensive treatment for breast cancer, and will promote further research.

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Abbreviations: 95% CI = 95% confidence interval, HR = hazard ratio, MST = median survival time.

Keywords: breast cancer, depression, protocol, survival, systematic review

1. Introduction

Breast cancer is the most common malignant tumor in women all over the world. According to the 2018 global cancer epidemic statistics, there are about 2.089 million new cases of female breast cancer every year, and about 627,000 deaths from breast cancer in the same period.[1] Even with advances in early screening and treatment, the death rate from breast cancer remains high.[2–4] In order to prolong the survival time and reduce the mortality of breast cancer patients, it is important to identify the risk factors affecting the survival of breast cancer patients. A study from Singapore showed that depression significantly shortened the survival time of cancer patients and could predict the prognosis. Depression was associated with an increased mortality rate among breast cancer survivors in women (Hazard Ratio [HR]: 11.6, 95% confidence interval [95% CI]: 0.69–194.1, $P = .089$). The risk of depression-related death was very high among cancer patients who lived over 5 years after cancer diagnosis (adjusted HR: 4.69, 95% CI: 1.76–12.5, $P = .002$).[5] After breast cancer diagnosed, the patients are worried about shortened survival time, recurrence and metastasis. Because most of them are female patients, they need to face impaired body image and decreased quality of sexual life caused by surgery and other treatments. Therefore, compared with other malignant tumors, the incidence of depression and other psychiatric symptoms in breast cancer patients are higher,[6–8] which is also closely related to the lack of female secondary characteristics and physical symptoms such as nausea, vomiting, fatigue, hair loss, and insomnia caused by chemotherapy.[9–13] Although the correlation between psychological factors and the survival of breast cancer patients has been extensively studied, the findings were not consistent. Some studies

No.	Search terms
#1	((((((((((((((("Breast Neoplasms"[Mesh]) OR ("Breast Neoplasm*"[Title/Abstract])) OR ("Breast Tumor*"[Title/Abstract])) OR ("Breast Cancer"[Title/Abstract])) OR ("Cancer, Breast"[Title/Abstract])) OR ("Mammary Cancer*"[Title/Abstract])) OR ("Malignant Neoplasm of Breast"[Title/Abstract])) OR ("Breast Malignant Neoplasm*"[Title/Abstract])) OR ("Malignant Tumor of Breast"[Title/Abstract])) OR ("Breast Malignant Tumor*"[Title/Abstract])) OR ("Cancer of Breast"[Title/Abstract])) OR ("Cancer of the Breast"[Title/Abstract])) OR ("Mammary Carcinoma, Human"[Title/Abstract])) OR ("Human Mammary Carcinoma*"[Title/Abstract])) OR ("Human Mammary Neoplasm*"[Title/Abstract])) OR ("Breast Carcinoma*"[Title/Abstract]))
#2	(((("Depression"[Mesh]) OR ("Depression*"[Title/Abstract])) OR ("Depressive"[Title/Abstract]))
#3	((((((("Survival"[Mesh]) OR ("Mortality"[Mesh])) OR ("Survival*"[Title/Abstract])) OR ("Mortality*"[Title/Abstract])) OR ("Death*"[Title/Abstract])) OR ("Case Fatality Rate*"[Title/Abstract]))
#4	#1 AND #2 AND #3

* Represent one or more characters of all characters.
MeSH = medical subject headings.

believed that depression was related to the shortened survival and increased mortality of breast cancer patients,[14,15] while some studies believed that there was no correlation between the 2.[16,17] A meta-analysis incorporating literature data found that depression was associated with a 30% increased risk of all-cause death in breast cancer patients, a 29% increased risk of specific death, and a 24% increased risk of breast cancer recurrence.[18] However, the association between depression and breast cancer survival was not integrated.

Based on the above background, we designed this meta-analysis to collect and was to integrate data on survival, mortality, and risk of death in breast cancer patients with depression, in order to determine the correlation between long-term survival in patients with breast cancer and depression.

2. Method

This meta-analysis has been registered on PROSPERO (www.crd.york.ac.uk /prospero/) with number CRD42020202200, and referred to the guidance on conducting systematic reviews and meta-analyses of observational studies of a etiology.[19] It will follow the reporting guidelines and criteria set in the Preferred Reporting Items for Systematic Reviews and Meta-analyses[20] statement checklist and Meta-analysis Of Observational Studies in Epidemiology [21] checklist. Methods followed guidelines by the Cochrane Collaboration for the conduction of systematic reviews.[22] Ethical approval is unnecessary for this study.

2.1. Inclusion criteria for study selection
2.1.1. Study types. This review will include cohort studies only, including the vertical and horizontal designed with both prospective and retrospective studies.

2.1.2. Participant types. The review will include patients with breast cancer who have been clearly diagnosed by imaging or pathology. Among them, patients diagnosed with depression should have the clear diagnosis time and methods. There will be no restrictions on age, gender, race, clinical stage, pathological type, and so on.

2.1.3. Outcomes.

(1) The median survival time (MST) of depressed and non-depressed breast cancer patients.
(2) The mortality rate of depressed and non-depressed breast cancer patients.
(3) The HR of death between depressed breast cancer patients and nondepressed ones.

2.1.4. Exclusion criteria. Repetitive reports, conference summaries, case reports, review papers, or animal studies, and so on.

2.1.5. Search strategy. Multiple databases will be searched by 2 independent reviewers, including PubMed, EMBASE, the Cochrane Library, and PsycINFO. The search terms include Breast Neoplasm, Breast Cancer, Breast Tumor, Mammary Cancer, Depression, Depressive, Mortality, Death, Survival, Case Fatality Rate, and so on. The language of studies should be English, published from inception to the September 2020. At the same time, reference lists of previous studies and reviews will be used as supplementary sources. PubMed database is taken as an example, and the retrieval strategy is shown in Table 1.

2.2. Data collection and analysis
2.2.1. Research selections. Two independent reviewers will carry out literature screening, research selection and data extraction. The obtained documents will be imported into EndnoteX8, and the duplicate files will be searched and deleted first. Then, the title and abstract are screened, and studies that do not meet the inclusion criteria are deleted. After reading the full text of the remaining studies, the final included studies were determined. If the full text is not found, the corresponding author will be contacted. If there is a disagreement between the 2, the third reviewer will decide. The research selection process is shown in the Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart (Fig. 1).

2.2.2. Extraction of data and information. The main data extracted by the 2 independent reviewers will include:

(1) The basic information included in the study, including the first author, publication time, area, published magazine, and impact factor.
(2) The baseline characteristics of the research object, including the sample size of each group, tumor stage, and diagnosis time and tools, follow-up time, and so on.
(3) Number of people diagnosed with depression, survivors, deaths, MST, the adjusted HR of death and 95% CI.

If the above data are not given directly in a study, the information in the study can be used to calculate. If the original data are not available or computable, this study will be excluded. A third senior author will help to reconcile any divergences between 2 authors.

2.2.3. Heterogeneity assessment. Before the meta-analysis, the heterogeneity test was first performed using the I^2 test. If the
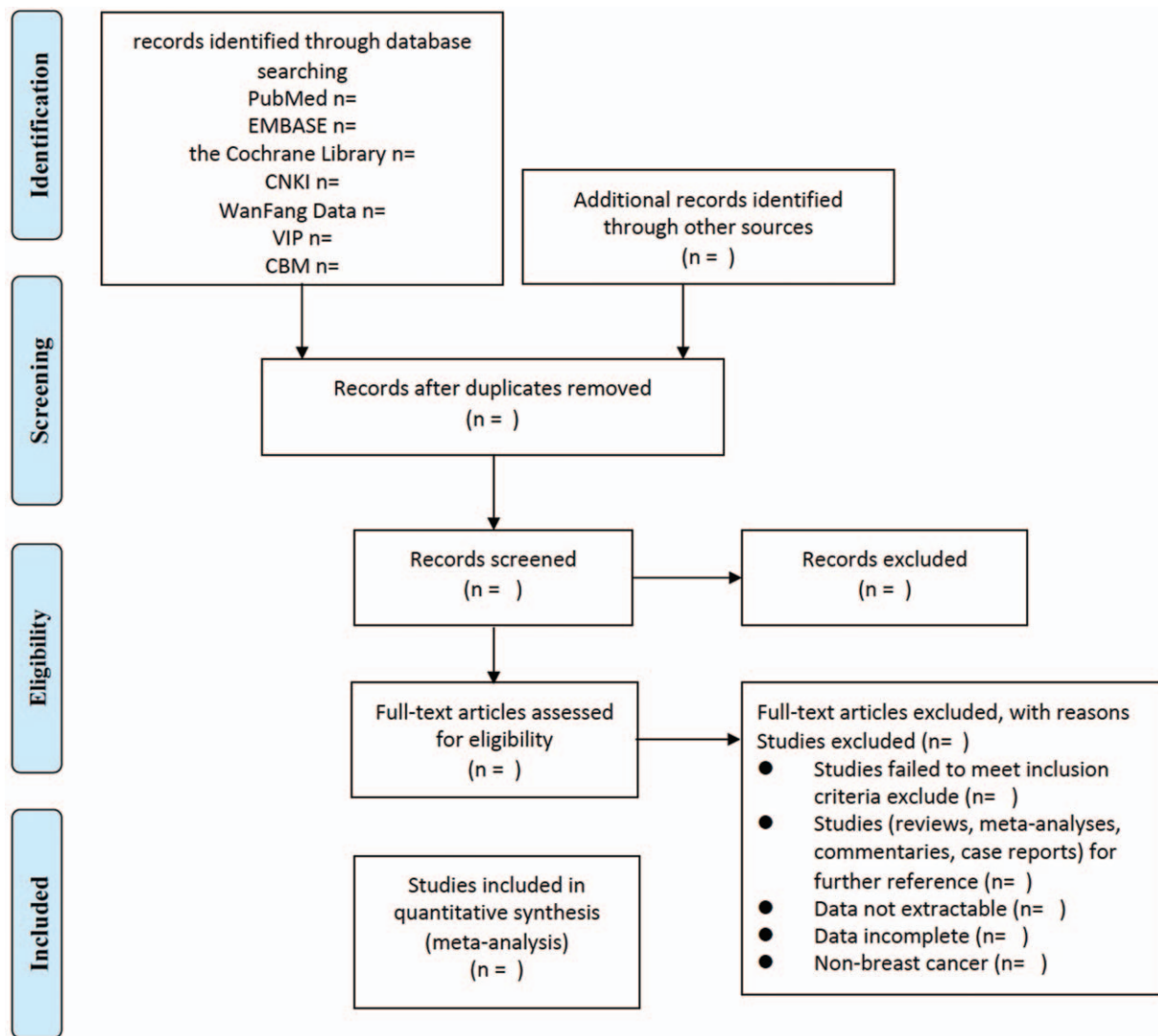
Figure 1. Flowchart of study selection.

heterogeneity was small ($P > .05$ and $I^2 < 50\%$), the fixed effect model was used for analysis. The random effect model would be used, when the heterogeneity was large ($P \leq .05$ or $I^2 \geq 50\%$).[23]

2.2.4. Evaluation of studying quality. Two researchers independently adopted the Newcastle–Ottawa scale[24] to conduct a bias risk assessment on the included studies. Newcastle–Ottawa scale, with a total score of 9 stars, has a total of 8 items. If there was a disagreement, the 2 decided after a discussion; if it could not be resolved, a third researcher would assist.

2.2.5. Assessment of reporting deviations. If necessary, we will examine the reporting bias using funnel plot and Egger regression test, when >10 trials are included.[25,26]

2.2.6. Data synthesis. Pooled effect sizes were calculated for the outcome. To extract the MST in the included studies, we used the software STATA 15.1 software to calculate the natural logarithm of HR and the standard error. In each study, the number of depression and nondepressive breast cancer patients, the number of deaths and adjusted HR of death of depression breast cancer

patients were extracted. Based on the above information, the natural logarithm of the correction effect value (Relative Risk [RR]/ HR) and standard error were calculated. RevMan 5.3 software was used for the meta-analysis, calculating the comprehensive effect value (RR/ HR) and 95% CI, to draw forest maps.

2.2.7. Subgroup analysis. The subgroup analysis of the meta-analysis results for each outcome was required. The subgroup only includes items related to the study design, for example, stage, location, and follow-up time. The evaluation subgroup analysis will be conducted in accordance with the guidelines for credibility assessment.[27]

2.2.8. Sensitivity analysis. The method of deleting studies one by one needed to be used to complete the sensitivity analysis of the results to ensure stability.

2.2.9. Quality of evidence. The system grading of recommendations assessment, development, and evaluation was used in evaluating the evidence level of outcomes.[28,29]

3. Discussion

People is with the mental disorders, which predict unhealthy lifestyles such as smoking, alcohol consumption, insomnia, and so on, which may lead to cardiovascular disease and increase the risk of death.[30] In addition, the treatment adherence of breast cancer patients diagnosed with depression is also one of the issues concerned by clinicians, such as difficulty in completing the full course of chemotherapy and endocrine therapy, leading to shortened survival time.[31] Suicide is also one of the factors leading to shortened survival of breast cancer patients.[32] Moreover, Kamiya A. et al found that chronic stress accelerated the growth and development of cancer by stimulating the sympathetic nerve in the tumor, affecting the survival of patients.[33] Through this meta-analysis, we hope to integrate current data related to depression and survival of breast cancer patients, so as to provide reference for the development of comprehensive treatment for breast cancer.

4. Amendments

If amendments are needed, we will update our protocol to include any changes in the whole process of research.

Author contributions

Conceptualization: Guanghui Zhu, Jie Li.
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Validation: Guanghui Zhu, Minghao Dai.
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References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[2] Plevritis SK, Munoz D, Kurian AW, et al. Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. JAMA 2018;319:154–64.

[3] Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. JAMA 2020;324:369–80.

[4] DeSantis CE, Bray F, Ferlay J, et al. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiol Biomarkers Prev 2015;24:1495–506.

[5] Jiang MJ, Jin AZ, Feng L, et al. Late life depression predicts mortality among long-term cancer survivors. Ann Acad Med Singapore 2014;43: S42–3.

[6] Nikbakhsh N, Moudi S, Abbasian S, et al. Prevalence of depression and anxiety among cancer patients. Caspian J Intern Med 2014;5:167–70.

[7] Maass SWMC, Boerman LM, Brandenbarg D, et al. Symptoms in long-term breast cancer survivors: a cross-sectional study in primary care. Breast 2020;54:133–8.

[8] Purkayastha D, Venkateswaran C, Nayar K, et al. Prevalence of depression in breast cancer patients and its association with their quality of life: a cross-sectional observational study. Indian J Palliat Care 2017;23:268–73.

[9] Perry S, Kowalski TL, Chang CH, et al. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. Cancer Nursing 2017;40:108–16.

[10] Hsu YH, Chen VC, Hsieh CC, et al. Subjective and objective cognitive functioning among patients with breast cancer: effects of chemotherapy and mood symptoms. Breast Cancer 2020;doi: 10.1007/s12282-020-01168-y. Epub ahead of print.

[11] So WK, Marsh G, Ling WM, et al. Anxiety, depression and quality of life among Chinese breast cancer patients during adjuvant therapy. Eur J Oncol Nurs 2010;14:17–22.

[12] Ratcliff CG, Zepeda SG, Hall MH, et al. Patient characteristics associated with sleep disturbance in breast cancer survivors. Support Care Cancer 2020;doi: 10.1007/s00520-020-05777-3. Epub ahead of print.

[13] Hack TF, Pickles T, Ruether JD, et al. Predictors of distress and quality of life in patients undergoing cancer therapy: impact of treatment type and decisional role. Psycho-oncology 2010;19:606–16.

[14] Vodermaier A, Linden W, Rnic K, et al. Prospective associations of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer. Breast Cancer Res Treat 2014; 143:373–84.

[15] Goodwin JS, Zhang DD, Ostir GV. Effect of depression on diagnosis, treatment, and survival of older women with breast cancer. J Am Geriatrics Soc 2004;52:106–11.

[16] Phillips KA, Osborne RH, Giles GG, et al. Psychosocial factors and survival of young women with breast cancer: a population-based prospective cohort study. J Clin Oncol 2008;26:4666–71.

[17] Onitilo AA, Nietert PJ, Egede LE. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. Gen Hosp Psychiatry 2006;28:396–402.

[18] Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. Mol Psychiatry 2020;doi: 10.1038/s41380-020-00865-6. Epub ahead of print.

[19] Dekkers OM, Vandenbroucke JP, Cevallos M, et al. COSMOS-E: guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. PLoS Med 2019;16:e1002742.

[20] Moher D, Liberati A, Tetzlaff J, et al. PRISMA GroupPreferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[21] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008–12.

[22] Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane. Available at: https://www.training.cochrane.org/handbook. https://training.cochrane.org/handbook/current [access October 21, 2019].

[23] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[24] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analysis. Eur J Epidemiol 2010;25:603–5.

[25] Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.

[26] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[27] Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:850–4.

[28] Atkins D, Best D, Briss PA, et al. GRADE Working GroupGrading quality of evidence and strength of recommendations. BMJ 2004; 328:1490.

[29] Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

[30] Strine TW, Mokdad AH, Dube SR, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. Gen Hosp Psychiatry 2008;30:127–37.

[31] Souza BFD, Moraes JAD, Inocenti A, et al. Women with breast cancer taking chemotherapy: depression symptoms and treatment adherence. Rev Lat Am Enfermagem 2014;22:866–73.

[32] Kim JM, Jang J-E, Stewart R, et al. Determinants of suicidal ideation in patients with breast cancer. Psycho-oncology 2013;22:2848–56.

[33] Kamiya A, Hayama Y, Kato S, et al. Genetic manipulation of autonomic nerve fiber innervation and activity and its effect on breast cancer progression. Nat Neurosci 2019;22:1289–305.