

Taxane-based chemotherapy and risk of breast cancer-related lymphedema

Protocol for a systematic review and meta-analysis

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Abstract

Background: Many studies were performed to explore the correlation between taxane-based chemotherapy and the risk of breast cancer-related lymphedema (BCRL), however, with inconsistent results. Hence, the purpose of this study is to evaluate whether taxane-based chemotherapy is a risk factor for BCRL.

Methods: A comprehensive systematic search of clinical trials published in the PubMed, Embase and the Cochrane Library databases will be conducted to identify eligible studies up to the date of December 31, 2018. We will employ risk ratios with 95% confidence intervals (95% CIs) to estimate the correlations between taxane-based chemotherapy and BCRL. Meta-analysis will be performed using Stata SE version 12.0 software.

Results: The results of this systematic review and meta-analysis will provide a high-quality synthesis of existing evidence of the correlations between taxane-based chemotherapy and the risk of BCRL.

Conclusion: The protocol will provide updated evidence for the use of taxane-based chemotherapy in postoperative breast cancer patients.

Ethics and dissemination: It is not necessary for ethical approval because it is based on published studies. The protocol will be disseminated in a peer-reviewed journal or presented at a topic-related conference.

Trial registration: This systematic review protocol has been registered with a number of CRD42019123989.

Abbreviations: BCRL = breast cancer-related lymphedema, HR = hazard ratios, MOOSE = Meta-Analysis of Observational Studies in Epidemiology, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratios, PRISMA-P = preferred reporting items for systematic reviews and meta-analyses protocols.

Keywords: breast cancer-related lymphedema, protocol, systematic review, Taxane-based chemotherapy

1. Introduction

The Global Cancer Statistics showed that breast cancer is the highest cancer incidence and the leading cause of cancer death among women worldwide in 2012, and the breast cancer alone accounts for a quarter of all cancer cases and 15% of cancer deaths among females.^[1] In recent decades, with targeted

therapy, radiotherapy, chemotherapy, and endocrine therapy developing, the survival of breast cancer patients has been significantly improved. And the clinical focus has been shifted to the alleviation of disease burden and the treatment of chronic complications.^[2] One of the most common complications of breast cancer treatment is breast cancer-related lymphedema (BCRL), which is caused by accumulation of lymphatic fluid owing to remodeling of the tissue structure and fibrosis, leading to chronic swelling of the arms, breasts, or torso.^[3] And these symptoms may compromise the patient's wellgoing physical condition and decrease the quality of life.^[4,5] The well-established risk factors for developing lymphedema are ALND,^[2,6–14] regional lymph node radiation,^[6,8,13,15] and higher body mass index.^[7,8,14] The association between chemotherapy agents and lymphedema has been discussed in many studies,^[5] but the results are inconsistent. Taxane-based chemotherapy is the conventional treatment for breast cancer and can significantly improve progression-free survival and overall survival of patients.^[16,17] Taxane-based chemotherapy, especially docetaxel, results in fluid retention in extremities because of the increase of the extracellular fluid.^[18,19] Although many published studies have discussed the correlation between taxane-based chemotherapy and the risk of BCRL, owing to differences in research methods, sample size, and study population, the results of a single study are difficult to generalize to the entire population, resulting in inconsistent conclusions. Swaroop

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et al^[20] believed that taxane-based chemotherapy did not increase the risk of lymphedema in patients, whereas Cariati et al^[21] concluded that paclitaxel adjuvant chemotherapy played a key role in the generation of BCRL in postoperative patients. The purpose of this study is to evaluate whether taxane-based chemotherapy is a risk factor for BCRL through a comprehensive and systematic meta-analysis.

2. Methods

2.1. Study registration

The protocol for this systematic review and meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) platform with the registration number of CRD42019123989. And this protocol was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines and the Systematic Reviews and Meta-Analyses will be reported based on the PRISMA guidelines. Ethical approval is unnecessary because this is a literature-based study.

2.2. Data sources and search strategy

The search strategy for this study is based on Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and PRISMA statement. The 2 authors (SC and JJ) will independently conduct a comprehensive systematic search of clinical trials published on electronic databases such as the PubMed, Embase, the Cochrane Library databases and the ClinicalTrials.gov up to the date of December 31, 2018. The following terms will be used: “breast neoplasms OR breast cancer OR breastcancer OR breast tumor OR breast tumour OR mammary neoplasm OR mammary carcinoma OR breast malignan OR breast metastas OR mammary malignan OR mammary metastas OR breast neoplasm OR breast carcinoma” and “lymphoedema OR lymphedema OR lymphedema OR lymphatic edema OR oedema OR edema OR edema OR swelling OR elephantias” and “diterpenes OR paclitaxel OR docetaxel OR cabazitaxel OR taxoids.” The detailed retrieval strategy for Pubmed is illustrated in Table 1. This search strategy contains all the search terms, and the other strategies of Embase and the ClinicalTrials.gov will be conducted based on these results. As there is currently no RCT for this type of study, only observational studies were included. In addition, we will examine reference lists of all articles that meet our requirements to prevent omissions.

2.3. Inclusion and exclusion criteria

2.3.1. Types of studies. Published observational cohort and case-control studies will be included without limiting the sample

size and type of breast cancer. To avoid duplication, identical or overlapping studies will be included as one study with the sample size as the inclusion criteria. Case reports, case series, letters to the editor, conference abstracts, reviews, meta-analyses, and animal experiments will be excluded.

2.3.2. Types of participants. Women eligible for inclusion were clinically diagnosed with unilateral breast cancer based on histopathology and had undergone therapeutic breast surgery. But there are no restrictions between pathological stages, ages, countries, ethnic, economy, education backgrounds.

2.3.3. Types of interventions. Taxane-based chemotherapy includes paclitaxel (Taxol), albumin paclitaxel (Abraxane), and docetaxel (Taxotere). These 3 reagents are suitable for use alone or in combination with other chemotherapy drugs.

2.3.4. Types of Comparison. Patients in the control group are those who have not received taxane-based chemotherapy after unilateral breast cancer surgery with or without chemotherapy with other reagents.

2.3.5. Types of outcomes. The primary outcome was the incidence of BCRL. Owing to the lack of clear diagnosis and evaluation criteria for lymphedema, this study accepted objective measurement of arm circumference and subjective feelings (such as questionnaire) as the diagnostic criteria. The follow-up time should not be <6 months, and the number and interval of follow-up time should not be limited. The secondary outcomes will be the incidence of BCRL in different taxane-based chemotherapy interventions, study designs. Results of lymphedema will use a binary classification (presence or absence).

2.4. Selection of studies

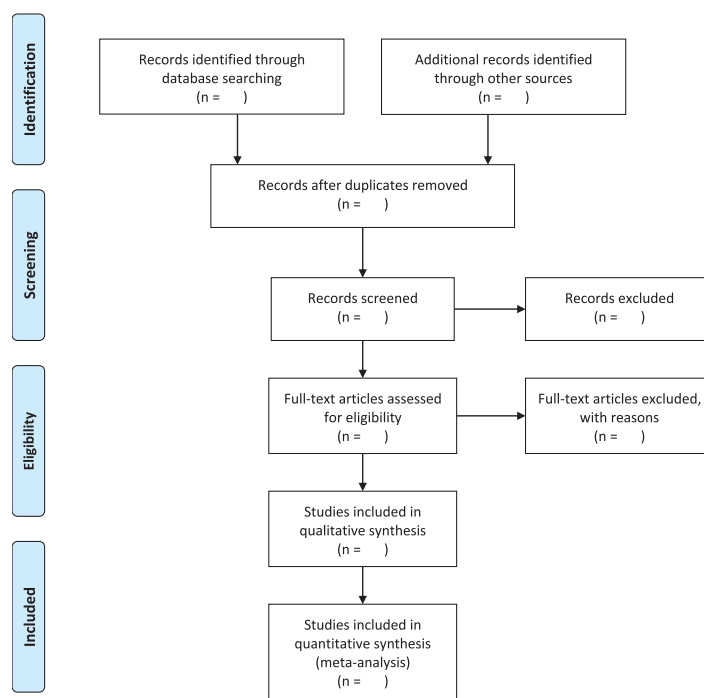
All review authors will receive training to understand the purpose and requirements of this review before selecting studies. Two review authors (RQ and XZ) will independently complete the retrieval of the titles, abstract, and keywords of all possible eligible articles. The eligible full text of the study was then downloaded and further evaluated independently by the 2 reviewers based on inclusion and exclusion criteria. Disagreements between the 2 review authors will be resolved by discussion, or a third author (ZZ) will be sought. The PRISMA flow chart (<http://www.prisma-statement.org>) will be used to show the literature retrieval process of this study, as shown in Figure 1.

2.5. Data extraction and management

The 2 review authors (RQ and XZ) will complete the standard data extraction form independently to complete data extraction

Table 1
Search strategy used in PubMed.

No.	Search items
No. 1	(((((breast cancer[Title/Abstract] OR breastcancer[Title/Abstract]) OR breast tumor[Title/Abstract] OR breast tumour[Title/Abstract] OR mammary neoplasm[Title/Abstract] OR mammary carcinoma[Title/Abstract] OR breast malignan[Title/Abstract] OR breast metastas[Title/Abstract] OR mammary malignan[Title/Abstract] OR mammary metastas[Title/Abstract] OR breast neoplasm[Title/Abstract] OR breast carcinoma[Title/Abstract]))))
No. 2	(((((lymphedema[MeSH Terms] OR lymphoedema[Title/Abstract] OR lymphatic edema[Title/Abstract] OR edema[MeSH Terms] OR edema[Title/Abstract] OR oedema[Title/Abstract] OR swelling[Title/Abstract] OR elephantias)))
No. 3	(((((taxane[Title/Abstract] OR Taxol[Title/Abstract] OR paclitaxel[Title/Abstract] OR albumin paclitaxel[Title/Abstract] OR Abraxane[Title/Abstract] OR docetaxel[Title/Abstract] OR Taxotere[Title/Abstract]))))
No. 4	#1 and #2 and #3



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 1. Flow of information through the different phases of a systematic review. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

of the included studies. The information extracted included: author, year of publication, type of study, sample size, definition of lymphedema, chemotherapy drugs, and follow-up time. We will contact the corresponding author, if the content to be extracted cannot be obtained through the full text. Any disagreements will be settled through discussion or an arbiter (ZZ).

2.6. Assessment of quality in included studies

The quality assessment of the included study will be performed independently by 2 review authors (XZ and ML) using the Newcastle–Ottawa Quality Assessment Scale (NOS), which contains 3 dimensions including selection, comparability, and—depending on the study type—outcome (cohort studies) or exposure (case–control studies).^[22] The total score of NOS in the study is ≥ 5 points, which is considered as a medium-high quality study; otherwise, it is a low-quality study. Any dispute will be settled through discussion or a third arbiter (ZZ).

2.7. Data synthesis

Analysis will be performed using Stata SE version 12.0. The pooled risk ratio with the corresponding 95% confidence intervals for all studies will be computed. If there is heterogeneity between studies, the random-effect model will be used for calculation. Otherwise, the fixed-effect model will be adopted. If

heterogeneity exists, we will conduct sensitivity and subgroup analysis to explore the reasons for its existence.^[23] If these data cannot be combined into a meta-analysis, we will summarize the description of this study.

2.8. Assessment of heterogeneity

Cochran Q test and Higgins I^2 method will be used to evaluate the heterogeneity. If P value is $< .1$ or I^2 value is $> 50\%$, we believe there is heterogeneity between studies.

2.9. Assessment of publication biases

Begg funnel plot and Egger test will be employed to assess the publication bias. Begg funnel plot is drawn using the logarithm of odds ratio (OR) (log OR) as the abscissa and the inverse of the standard error of OR ($1/SE[\log OR]$) as the ordinate. The Egger test is a test for linear regression to measure the symmetry of the funnel chart according to log OR. An asymmetric funnel plot or a P value $< .1$ indicates the publication bias.

2.10. Subgroup analysis

Subgroup meta-analysis will be used to explore possible factors that may cause high heterogeneity. In cases of high heterogeneity, we will conduct subgroup analysis according to the following aspects: the differences between the study design and interventions (paclitaxel, albumin paclitaxel, and docetaxel).

2.11. Sensitivity analysis

We will conduct sensitivity analysis with sequentially excluding each study and combining the remaining studies to find the impact of each study on the overall results.

3. Discussion

Taxane-based chemotherapy is a routine treatment for breast cancer patients after surgery. BCRL is also a common complication that affects the quality of life of patients. A meta-analysis^[7] shows that the postoperative incidence is 20%. In this study, a systematic and comprehensive analysis will be conducted to determine whether taxane-based chemotherapy is a risk factor for postoperative lymphedema in breast cancer patients and provide evidence for clinical chemotherapy. However, there are some limitations that need to be pointed out. First, the inconsistency of BCRL measurements may increase the heterogeneity of the study. Second, only studies published in English will be included, which may increase publication bias.

Author contributions

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Supervision: Honggang Zheng, Baojin Hua.

Writing – original draft: Zhenhua Zhang, Xiwen Zhang.

Writing – review & editing: Zhenhua Zhang.

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