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Systematic Review Protocol

Subtypes of Benign Breast Disease as a Risk Factor for Breast Cancer: A Systematic Review and Meta-Analysis Protocol

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Abstract

Breast cancer is a multifactorial disease. Benign breast disease (BBD) is one of the most important risk factors for breast cancer. The etiology of BBD is unknown. It is divided into nonproliferative and proliferative diseases. The selection of studies will be based on titles, abstract screening, inclusion and exclusion criteria, and quality assessment. Previous studies have shown that all types of BBD increase the risk of breast cancer, but the risk degree is different for each one. Accurate risk estimation of breast cancer in each category can be very important for proper clinical management. This systematic review and meta-analysis will be conducted on observational studies (traditional case control, nested case control, case cohort, and cohort) published in the Web of Science (ISI), PubMed (MEDLINE), Scopus, Google Scholar, and the key journals of this field such as Breast Cancer Research and Treatment and Cancer Research from January 2000 to June 2015. Reference lists and gray literature will be reviewed too. All the initial retrievals will be performed by 2 researchers independently. The data extraction form will consist of general information concerning the studies, study eligibility, method, risk of bias assessment, and results—including odds ratios, risk ratios, rate ratios, and hazard ratios. The PRISMA and MOOSE guidelines will be used to report our findings.

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Keywords ● Fibrocystic breast disease ● Mammary dysplasia ● Breast neoplasms ● Risk factors ● Systematic review

What's Known

- Past studies have shown that 3 categories of benign breast disease) BBD) constitute important risk factors for breast cancer.
- There are only a few meta-analyses on the degree of risk. Latest meta-analysis was published in 2015 on data from 1930–2007.

What's New

- Our study will encompass studies from 2000–2015 and provide fresh evidence on the degree of risk in BBD categories.
- In light of our results, we can recommend the use of different screening programs based on the histological classification of BBD, which could improve patients' health.

Introduction

According to the report of the World Health Organization (WHO), breast cancer is the most common cancer in women worldwide,[1-3] such that it accounts for 16% of all cancers in women.[1] In the recent decades, the incidence of breast cancer has increased in both developed and developing countries, primarily because of advances in diagnostic methods.[4]

Breast cancer is a multifactorial disease.[4,5] Benign breast disease (BBD) is one of the most important risk factors for breast cancer.[6-11] Breast cancer is more frequent in women with BBD than in the general population.[9] Previous studies have indicated that 90% of breast lesions are benign.[12] The etiology of BBD is unknown.[1,9]

Genetic predisposition and environmental elements such as diet, alcohol, and physical activity may convert these lesions into cancer via unknown mechanisms. Studies have suggested that some clinical factors such as menopausal status, family history of breast cancer, and age at the diagnosis of BBD also may change the risk of developing BBD to that of breast cancer.[12]

Pathologically, BBD is divided into nonproliferative disease, proliferative disease without atypia, and proliferative disease with atypia.[7,11-13]

According to the findings of previous studies, all 3 subtypes of BBD increase the risk of breast cancer, but the risk degree is different in each of them.[6,14,15] The risk is higher in proliferative disease, especially atypical proliferative lesions.[6,16] Although only a few studies have been previously conducted on the relationship between nonproliferative lesions and subsequent breast cancer,[6,8,17] the existing evidence shows that the cancer risk for nonproliferative lesions is lower than that of the other subtypes of BBD.[6]

Over the recent years, mammography screening programs have been widely used to detect malignant and benign breast diseases, but there are no specific guidelines or protocols to follow-up the subtypes of BBD separately—except for proliferative lesions with atypia.[14] The researchers of the present study think that the reason may be insufficient evidence to support a particular follow-up based on the pathological categories of BBD. Thus, it is necessary to carry out more research, systematic reviews, and meta-analyses. Decision-makers in this field need a regular combination of available scientific information. Today, it is easy for a person to be up to date in scientific knowledge because of the burst of information in such a vast array of literature. Review articles and meta-analyses, which summarize the knowledge in a scientific field, eliminate this need.[18] We hope that the findings of the current research will provide more relevant evidence and that we will be able to recommend the use of different screening programs for the subtypes of BBD based on our results with a view to improving patients' health. Early diagnosis and proper management of disease can prevent the complications of cancer and lessen the economic burden on patients and their families.

We found 2 meta-analyses related to our review.[9,19] The results of the newest meta-analysis, published in 2015, confirmed that BBD elevates later risk of breast cancer; that study was performed on articles which included data from 1930 to 2007.[9] We found no other relevant study in this field apart from the aforementioned one. Most of the studies before 2000 did not have enough information about the degree of breast cancer risk associated with the subtypes of BBD.[20] On the other hand, the diagnosis of BBD in different studies has been based on different histological criteria; accordingly, the current study will be conducted on all studies from 2000 to 2015. We need information on the subtypes of BBD because an accurate risk estimation of breast cancer for each category is crucial for the improvement of BBD clinical management.[1]

In the present systematic review and meta-analysis, we will seek to answer the questions whether the subtypes of BBD are associated with an elevated risk of later breast cancer and how much is the risk degree of each subgroup of BBD.

Objectives

1. To estimate breast cancer risk associated with proliferative disease with/without atypia versus nonproliferative disease
2. To estimate the age-adjusted risk of breast cancer associated with proliferative disease with/without atypia versus nonproliferative disease
3. To estimate the menopause-adjusted risk of breast cancer associated with proliferative disease with/without atypia versus nonproliferative disease
4. To estimate the family history-adjusted risk of breast cancer associated with proliferative disease with/without atypia versus nonproliferative disease.

Methods

Type of Studies

We will enter all studies in our systematic review and meta-analysis which have clearly defined breast cancer risk in women with proliferative disease with/without atypia versus nonproliferative disease. These studies encompass both retrospective and prospective investigations with each of the following designs: Traditional case-control, nested case-control, and cohort.

Type of Participants

The participants of the selected studies will be women with a biopsy confirmation of the subtypes of BBD (nonproliferative, proliferative without atypia, and proliferative with atypia). The women will be of any age, and there will be no restriction in terms of menopause status, family history of breast cancer in the person or a first-degree relative, race or ethnicity, and parity.

Inclusion and Exclusion Criteria

Inclusion

Studies included in the present review will be those that have reported breast cancer risk associated with all pathologic categories of BBD, including nonproliferative and proliferative diseases with/without atypia. We will select the eligible studies from January 2000 to June 2015. All studies in the English language will be included in our review. The main effect size measures reported in the studies will include odds ratios, risk ratios, rate ratios, and hazard ratios.

Exclusion

All studies which have no clear pathologic category, are nonstratified, and have reported only the breast cancer risk associated with BBD will be excluded. As regards studies whose abstracts are available only, if it is possible, we will purchase the articles; otherwise, we will exclude them from our review.

Type of Outcome Measures

Primary outcomes

We will estimate the relative risk of breast cancer in individuals with proliferative disease with/without atypia versus nonproliferative breast disease.

Secondary outcomes

The relative risk of breast cancer in patients with a confirmed pathologic diagnosis of BBD will be estimated based on subgroups of age, menopause status, and family history of breast cancer in a first-degree relative.

Search Strategy and Information Sources

Strategy

In order to achieve the aims of the present study, we will conduct electronic search in the following databases: Web of Science (ISI), PubMed (MEDLINE), Scopus, Google Scholar, and the key journals of this field such as Breast Cancer Research and Treatment and Cancer Research. Our search will be restricted to published studies in the English language from January 2000 to June 2015. All the initial retrievals will be performed by 2 researchers independently. Gray literature will also be reviewed.

We will find unpublished studies by searching Google Scholar. If those studies are eligible, we will include them in our review. In PubMed, first we will find equivalent words for BBD based on MeSH terms. Then, we will create our appropriate syntaxes. The main syntax will be "Breast Cancer"[tiab] AND ("Benign Breast Disease"[tiab] OR "Nonproliferative Breast Disease" OR "Proliferative Breast Disease" OR "Mammary Dysplasia"[tiab] OR "Mastopathy"[tiab] OR "Breast Fibrocystic Changes"[tiab] OR "Microglandular Adenosis*"[tiab] OR "Chronic Cystic Mastitis"[tiab]). Proportionate syntax for the Web of Science (ISI) will be "Breast Cancer" AND "Benign Breast Disease" OR "Nonproliferative Breast Disease" OR "Proliferative Breast Disease" OR "Mammary Dysplasia" OR "Mastopathy". Our syntax in Scopus will be "Breast Cancer" AND "Benign Breast Disease" OR " Nonproliferative Breast Disease" OR "Proliferative Breast Disease" OR "Mammary Dysplasia" OR "Mastopathy" OR "Breast Fibrocystic Changes" OR "Microglandular Adenosis*" OR "Chronic Cystic". Proportionate syntax for Google Scholar will be "Breast Cancer" + "Benign Breast Disease" + "Proliferative Breast Disease" + "Mastopathy". Our syntax in specialized journals ("Breast Cancer Research and Treatment" and "Cancer Research") will be "Breast Cancer" AND "Benign Breast disease" OR "Nonproliferative Breast Disease" OR "Proliferative Breast Disease".

In the final step of the search, we will check the list references of the included articles as the last source of our search. Finally, after finding all relevant studies, we will select the main studies according to the following steps.

Study Selection

The selection of the main studies for inclusion in our review will be done in 2 stages. In the first stage, assessment will be conducted based on title/abstract screening and duplicates. Studies will be excluded from our study if there is no access to the full text of the study, if there are no primary data according to the aims of our study, and if there is no report of the effect size measures. After removing the irrelevant articles by providing reasons, in the second stage, we will perform full text assessment according to the inclusion and exclusion criteria. Articles will be excluded if they are nonstratified as regards BBD, if they contain no clear pathologic categories of BBD, if they contain unknown histology, and if they do not report the effect size measures. Both stages will be performed by 2 reviewers independently, and any disagreement between the reviewers will be resolved by discussion; otherwise, the opinion of a 3rd reviewer will be sought. If there is some unclear information, we will contact the corresponding author(s) of the studies. Figure 1 summarizes the process of literature selection in the present systematic review and meta-analysis.

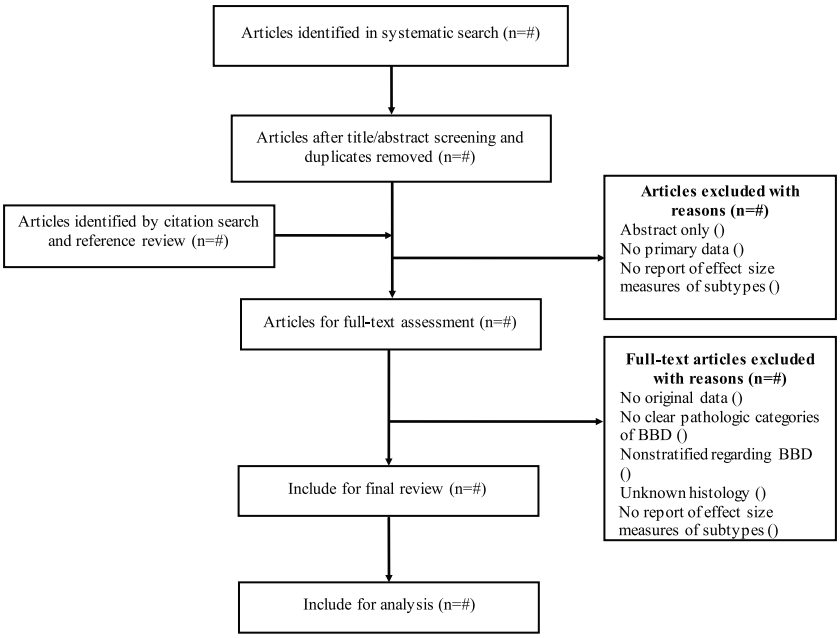

Figure 1: Flow diagram of the systematic search and selection process of articles.

Data Extraction

After removing the irrelevant articles and determining the main studies, we will conduct the last review to complete data extraction for each of the final articles. The data extraction form (Appendix I) consists of general information on the studies, study eligibility, method, risk of bias, quality assessment, and results.

- General information: Code of the article, title of the article, reference number, reviewers' initials, publication details, first author, journal's title, year of publication, volume, and first page
- Study eligibility: Name of the country, total study period, participants, study setting, inclusion criteria (in the study), exclusion criteria (in the study), total population at the start of the study, age of the study population, and type of the outcome measures
- Method: Aims of the study, study design (traditional case-control, nested case-control, and cohort), and ethical approval obtained for the study
- Risk of bias assessment: Quality assessment through a modified form of quality assessment (STROBE: Special checklist for observational studies) (table 1)

Results of studies: Odds ratios, risk ratios, rate ratios, and hazard ratios

Risk of Bias Assessment

The checklist of the modified form of STROBE will be filled for each study by the 2 reviewers independently. To determine the eligibility of the articles, we will use the sum score of quality items. All studies with any score will be included in the review, and finally subgroup analysis will be performed on low-quality and high-quality studies, if it is applicable, and the cutoff score will be 15.

Missing Data

If there is any unclear information, we will contact the corresponding author(s) of the studies. We will report all the missing data if we cannot find them.

Heterogeneity Assessment

The heterogeneity of the studies will be assayed using the χ^2 test of homogeneity (significant at $P<0.1$), and I^2 statistic will be performed on the quantitative data. In cases where heterogeneity between studies is extensive in a way that pooling analysis is not possible, we will report only a narrative presentation. When there is heterogeneity between the studies (I^2 >50%), a Mantel–Haenszel random-effects model will be used to pool the data in a meta-analysis. To determine the factors that are associated with breast cancer, we will use meta-regression. We will include age at biopsy, family history of breast cancer, and menopause status in the meta-regression models.

Report of Biases Assessment

Publication bias will be assessed using the Begg plot and test and the Egger plot and test in addition to the Funnel plots.

Data Synthesis

We will estimate the risk of breast cancer according to the subtypes of benign breast disease (proliferative disease with/without atypia

Table 1: Quality assessment form (modified form of STROBE)

Items		Yes=1	No=0	Unclear=0
Abstract	1. Clearly define the study design and the main results of the study			
Objectives	2. State specific objectives, including any prespecified hypotheses			
Study design	3. Present the key elements of the study design early in the paper			
Setting	4. Describe the setting			
	5. Introduce the locations			
	6. Include the periods of recruitment			
	7. Present case definition/exposure			
Participants	8. Give the eligibility criteria			
	9. List the sources and methods of the selection of the participants			
	10. Describe the methods of follow-up/Give the rationale for the choice of cases and controls			
	11. For matched studies, give the matching criteria and the number of exposed and unexposed/controls per case			
Variables	12. Clearly define all the outcomes			
	13. Clearly define the potential confounders and effect modifiers			
Data sources/measurement	14. Give the sources of data and details of the methods of assessment			
Bias	15. Address the potential sources of bias			
Study size	16. Explain how the study size was arrived at			
Statistical methods	17. Describe all the statistical methods			
	18. Include methods used to control for confounding			
	19. If applicable, explain how loss to follow-up/matching of cases and controls was addressed			
	20. Describe any sensitivity analyses			
Total				

vs. nonproliferative disease). The following subgroups will be analyzed, if possible.

Subgroup Analysis

We will do subgroup analysis based on age at biopsy, family history of breast cancer, and menopause status, if applicable.

Reporting of the Review

The PRISMA and MOOSE guidelines will be used to report our systematic review and meta-analysis protocol. A Flow diagram will be drawn to depict the systematic search and the selection process of the articles. The list of the excluded studies and the reason for that will be reported too. The qualitative data of the studies will be described in the text.

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Conflict of Interest: None declared.

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Appendix

Appendix I: Data extraction form	
Review title	
1. General information	
Code of the article	
Reference number	
Reviewers' initials	
Publication details:	
First author	
Journal's title and year	
Volume and first page	
2. Study eligibility	
Name of the country	
Total study period	
Participants:	
Study setting (e.g., urban, rural, hospital- based, or population-based)	
Inclusion criteria (in the study)	
Exclusion criteria (in the study)	
Total population at the start of the study	
Age of the study population	
Type of the outcome measures	Odds Ratio/Risk Ratio/Rate Ratio/Hazard Ratio
Should this study be included in the review?	Yes No Maybe Reasons for No or Maybe:
3. Method	
Aims of the study	
Study design	Traditional case control Nested case control Case cohort Cohort
Ethical approval obtained for the study	
4. Risk of bias assessment	
Quality scale	Yes=1/No=0/Unclear=0
Items	
Abstract	1. Clearly define the study design and the main results of the study
Objectives	2. State specific objectives, including any prespecified hypotheses
Study design	3. Present the key elements of the study design early in the paper
Setting	4. Describe the setting
	5. Introduce the locations
	6. Include the periods of recruitment
	7. Present case definition/exposure
Participants	8. Give the eligibility criteria
	9. List the sources and methods of the selection of the participants
	10. Describe the methods of follow-up/Give the rationale for the choice of cases and controls
	11. For matched studies, give the matching criteria and the number of exposed and unexposed/controls per case
Variables	12. Clearly define all the outcomes
	13. Clearly define the potential confounders and effect modifiers
Data sources/measurement	14. Give the sources of data and details of the methods of assessment
Bias	15. Address the potential sources of bias
Study size	16. Explain how the study size was arrived at
Statistical methods	17. Describe all the statistical methods
	18. Include methods used to control for confounding

(Contd...)

Appendix I: *(Continued)*	
Review title	
	19. If applicable, explain how loss to follow-up/matching of cases and controls was addressed
	20. Describe any sensitivity analyses
Total	
5. Results:	
Outcome	
Number of cases	
Number of controls	
Number of exposed cases	
Number of unexposed cases	
Crude results (95% CI)	
Adjusted results (95% CI)	
Adjusted for which confounders?	