The burden of BRCA1 and BRCA2 gene mutations among Vietnamese women and their associated factors: A protocol for a systematic review and meta-analysis [version 1; peer review: awaiting peer review]

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Abstract

Background: BReast CAncer gene (BRCA)1 and BRCA2 mutation carriers are frequently provided genetic counselling. A precise estimation of the prevalence of BRCA gene mutations is essential to provide an appropriate risk prediction. However, the data in Vietnam is ambiguous and include unreliable risk factors from individual studies. Hence, the objective of this protocol is to provide a method to synthesize evidence pertaining to the proportion of BRCA mutations among Vietnamese women and their risk factors for cancer.

Methods: PRISMA-P was followed in developing and reporting this protocol. From the databases' inception until June 2023, a comprehensive search will be undertaken in electronic PubMed and Scopus databases. In two stages, title/abstract screening and full-text screening, two independent authors will assess all retrieved articles for inclusion. This review includes papers providing the relevant results reflecting the prevalence of BRCA gene mutations in Vietnamese women who are at least 18 years old with or without cancer. Predefined selection criteria will be used to establish each publication's eligibility. Using the Newcastle-Ottawa Scale and Cochrane Risk of Bias tools, the quality of included studies will be assessed, and overall evidence quality will be appraised using the GRADE approach. All pertinent data from the included articles will be entered into an Excel spreadsheet for meta-analysis, which will be imported into Rstudio. Meta-analyses using random effects will be...
used to obtain the pooled percentages. The chi-squared test and I^2 parameter will be used to evaluate heterogeneity. Publication bias will be investigated visually using funnel plots for asymmetry and Egger's statistical tests.

**Conclusions:** Based on the prevalence of BRCA mutations and its associated comprehensive and specific risk factors, we hope our findings will provide a reference for future strategies to build an effective treatment plan and manage the risk of cancer development.

**Registration:** PROSPERO (CRD42022340152; 30 June 2022).

**Keywords**
Vietnam, Breast cancer, Ovarian cancer, BRCA1, BRCA2

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**Author roles:** Trân PT: Conceptualization, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Trân DQ: Conceptualization, Data Curation, Formal Analysis, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Vu CTQ: Software, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; Phan QN: Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Nguyễn ATT: Software, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

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**How to cite this article:** Trân PT, Trân DQ, Vu CTQ et al. The burden of BRCA1 and BRCA2 gene mutations among Vietnamese women and their associated factors: A protocol for a systematic review and meta-analysis [version 1; peer review: awaiting peer review] F1000Research 2022, 11:852 https://doi.org/10.12688/f1000research.123884.1

**First published:** 28 Jul 2022, 11:852 https://doi.org/10.12688/f1000research.123884.1
Introduction

A significant risk of getting breast cancer and ovarian cancer is posed to women with a pathogenic germline mutation in either the BReast CANcer gene (BRCA1) and BRCA2 gene, which was discovered in the 1990s.1 For women with a BRCA1 pathogenic variation, the cumulative lifetime risk of breast cancer varies from 40–87%, and the risk of ovarian cancer ranges from 16–68%. Women with a BRCA2 pathogenic variation have a comparable risk, with a lifetime breast cancer risk of 27–84% and ovarian cancer risk of 11–30%. In 2020, an estimated 2.3 million women will be diagnosed with breast cancer, leading to the death of 685,050 people worldwide. There were 7.8 million women who had been diagnosed with breast cancer in the last five years as of the end of 2020, making it the most common disease globally.3 Although it is far less frequent than breast cancer, ovarian cancer is the eighth most prevalent form of cancer in women and the 18th most prevalent form of cancer overall. There were around 300,000 new cases of ovarian cancer diagnosed in 2018, and almost 200,000 deaths were attributed to the illness.4 Among them, approximately 10% of breast cancers are inherited and may be traced back to germline mutations in breast cancer susceptibility genes, most notably in the BRCA1 and BRCA2 genes.5 In comparison, the figure is much higher among those diagnosed with ovarian cancer—approximately 15%.6

In population, it is well established that the BRCA frequency varies significantly. For instance, compared to the general population, which has an inherited mutation rate of 0.2–0.3%, Ashkenazi Jews make up roughly 2.0% of those with a deleterious variation in either BRCA1 or BRCA2. While in the United States, the prevalence of BRCA1 has been reported as high as 11.1%, the prevalence in Japan was just 2.6%.7 Because there is a wide range of estimates, it may be difficult for physicians to choose which one to use.

In Vietnam, the cancer burden has been steadily increasing over the last 30 years, with approximately 165,000 new cancer cases and 115,000 cancer-related deaths occurring annually. The age-adjusted cancer death rate in Vietnam is 104 per 100,000 people, which ranks 57 internationally.8 The epidemiology of BRCA mutations in Vietnamese communities is plagued by a lack of high-quality data and studies devoted to it, even though the incidence of breast cancer is on the rise, with an estimated 21,555 new cases and 9,345 deaths every year. At the same time, ovarian cancer had 1,404 cases and 923 fatalities per year (ranked 21st) in 2020.9

Analysis of the BRCA1 and BRCA2 genes is becoming more popular as a method for detecting pathogenic variations in the context of both preventative and therapeutic concerns. Access to BRCA tumour testing in a timely manner is becoming more significant in the therapeutic field to identify cancer patients who may benefit from therapy with poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi).10 Although the test is highly recommended by professional groups such as the Society of Gynecologic Oncology (SGO) and the National Comprehensive Cancer Network (NCCN)11; however, in Vietnam, the availability of such genetic testing is severely restricted because of the exorbitant cost, as well as a shortage of properly equipped labs and well-trained healthcare professionals.12

Furthermore, no comprehensive statistics about the prevalence of BRCA1 and BRCA 2 gene mutations in Vietnam women are available. Consequently, our study aims to fill this knowledge gap by systematic review and meta-analysis of all the available evidence on the prevalence of BRCA1 and BRCA2 gene mutations among Vietnamese women, including in hospitals and the community.

Research questions

1. What is the pooled prevalence of the BRCA1 and BRCA2 gene mutations in the Vietnamese female population, including in-hospital and community?

2. Which risk factors of Vietnamese women should prompt a physician to perform a BRCA gene test for the client/patient?

Objectives

Our overall objective is to assist physicians and researchers in better understanding the prevalence of BRCA1 and BRCA2 gene mutations and their related risk factors in Vietnamese women. Future research efforts may better guide therapeutically relevant goals.

Methods

The study protocol and reporting

This procedure is carried out in accordance with the standards provided by Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) for systematic review protocols13 and the completed checklist can be found under Reporting Guidelines.20 This protocol for a systematic review has been submitted to the PROSPERO
Observational Studies in Epidemiology (MOOSE) guidelines\textsuperscript{15} will be used to construct a systematic review and meta-analyses to formulate our search strategy. An exhaustive computerized search of PubMed (RRID:SCR_004846) and Scopus (RRID:SCR_022559) databases from the beginning of the database systems to June 2023 will provide relevant research on the incidence of mutations in BRCA1 and BRCA2. In these database searches, we will use the specified keywords and index terms for this purpose. The scope of the searches will be restricted to English language and human studies only. We do not aim to look for previously unreleased content or manuscripts. Our searches were based on a combination of key phrases and index terms (MeSH and Emtree). The following terms will be used for the search strategy (in all fields): “Vietnam”, “Vietnamese”, “women”, “female”, “breast cancer”, “breast carcinoma”, “mammary cancer”, “breast tumor”, “ovarian cancer”, “ovarian tumors”, “ovarian carcinomas”, “brca1”, “brca2”, “brca” with the cognitive logical operators “AND” and “NOT” are utilized for the purpose of efficiently finding publications. Table 1 provides comprehensive search algorithms for all databases.

Using the Mendeley Data (RRID:SCR_002750) online bibliography management application, we will collect, arrange, and export citations from the aforementioned databases. Duplicates will be detected and eliminated. The remaining citations will be considered for research selection.

Inclusion and exclusion criteria

Types of studies

Only peer-reviewed publications and all research designs to determine the frequency of BRCA1 and/or BRCA2 gene mutations in Vietnamese women will be included; while, case studies, literature reviews, systematic reviews, editorials, letters, and dissertations will not be included in this review.

Types of participants

Studies that include Vietnamese women who are at least eighteen years old will be eligible for inclusion.

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<th>Database</th>
<th>Search strategy</th>
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<td>PubMed</td>
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<td>Scopus</td>
<td>ALL (((vietnam OR vietnamese) OR (breast OR brca1 OR brca2 OR brca OR brca1 OR brca2 OR brca1 OR brca2 OR brca2) OR brca2 OR brca)))</td>
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Types of comparison/exposure

Studies investigating individual characteristics, cancer diagnoses (if any), and pathogenic mutations in BRCA1 and BRCA2 genes are considered eligible. The primary risk of this review will be on patient characteristics that have the potential to serve as risk factors or predictive variables for a future aggravation or malignancy, or cancer development.

Types of outcome measures

We will incorporate the original papers that include the proportion of Vietnamese women who have BRCA1/BRCA2 gene mutations in order to diagnose/to robustly diagnose cancer disease (e.g., breast cancer, ovarian cancer and other relevant cancers) or to estimate the risk of developing these cancers.

Selection of studies for inclusion in the review

The first step will be to create an online sheet in Microsoft Excel (RRID:SCR_016137) for data extraction that can be shared among the team members. After that, we will run a pilot test with five articles chosen randomly and use the results to fine-tune the data extraction form appropriately. Two independent reviewers will evaluate the abstracts of all identified studies. Possible studies include articles that will be collected in full text for further evaluation. We will reach out to the authors to inquire about ambiguous points and request clarification. Disputes over inclusion will be resolved by consensus; if this is not feasible, we intend to bring in a third author who would then make a decision.

Data extraction

These could consist of, but are not limited to, the following:

- Study characteristics (e.g., names of the authors, the publishing year, the journal, and the research design, hospital or community);
- Demographic characteristics (e.g., age, education, profession, socioeconomic status, beginning menstrual cycles early, entering menopause later);
- Prevalence of BRCA gene mutations (e.g., BRCA1, BRCA2 and both mutations);
- Oncogenic mutations in BRCA1 and BRCA2 genes (e.g., type of genetic analysis method, BRCA variants, novel variant, distribution of pathogenic variants);
- Cancer-related characteristics of the patients (e.g., type of cancer, age at diagnosis of cancer, cancer stage, tumour size);
- Various health-related factors (e.g., smoking, co-morbidities, Body Mass Index, radiation treatment, exposure to diethylstilbestrol, genetic cancer predisposition syndromes);
- Included in this research are those looking at various cancer risk factors, and family history is one of them. The family includes all relatives (parents, siblings, or other biological family members). Registers, medical records, or self-reported information are potential sources for obtaining data on family history. Cancer in the family history should be considered for any cancer, including but not limited to cancer diagnosed at a younger age, particular forms of cancer, relatives who have been diagnosed with two or more cancers or multiple cases of cancer, and relatives that have previously been shown to be carriers of cancer-causing mutations.

Using a tool that has already been pre-piloted, the essential data will be retrieved to an online sheet in Microsoft Excel Online. The data will be gathered separately by the two authors.

Assessment of risk of bias

For observational studies, the included articles will be evaluated using the Newcastle Ottawa Scale (NOS),\(^\text{16}\) and for randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB) tool\(^\text{17}\) will be utilized. Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria\(^\text{18}\) will be used to grade the quality and strength of the evidence. Both evaluations will be conducted independently by two authors. The first five included studies will be evaluated, and inconsistencies in the assessment will be discussed before reviewing the remainder of the included
research to ensure the two authors make equivalent risk assessments. In circumstances when there is disagreement, reaching a consensus will be accomplished via discussion.

Data synthesis
Our narrative synthesis of the results from the included studies will be framed around the characteristics of the subjects, the distribution of probable predictors and outcomes. When applicable, ranges, means (standard deviations) or medians (interquartile ranges), and frequencies (%) will be included in summary statistics. The extracted data will be loaded into RStudio (RRID:SCR_000432) software (version 2022.02.1 Build 461) with “meta” (RRID:SCR_019055), “metafor” (RRID:SCR_003450), and “ggplot2” (RRID:SCR_014601) packages for analysis. Using a random-effects model, the pooled prevalence estimate of BRCA1 gene mutation/BRCA2 gene mutation/both mutations in Vietnamese women will be calculated. The existence of statistical heterogeneity will be evaluated by the Cochrane’s Q statistic (with P<0.10 indicating the presence of statistically significant heterogeneity). \(^{19}\) In addition, the I\(^2\) statistic will be used to gauge the degree of statistical heterogeneity among the research (low, medium, and high heterogeneity, respectively, are defined by values of 25, 50, and 75\%). If adequate data are available, we will conduct subgroup analyses based on the individual and family factors to identify plausible sources of heterogeneity and to study their effect on the prevalence of BRCA gene mutations. The examination of a funnel plot for signs of asymmetry and the use of Egger’s test will be used to determine the existence of publication bias in the analyses. If P<0.05, we will consider the possibility of publication bias to be present.

Ethics and dissemination
There is no need for ethical approval for this systematic review.

An earlier version of this article can be found on Research Square (https://doi.org/10.21203/rs.3.rs-1818425/v1).

Study status
This project is still in progress. Given the scarcity of relevant publications, searching for potential information sources such as grey databases are presently underway to carry out this systematic evaluation.

Discussion
Contextually, there is a paucity of national cancer screening programs and a shortage of infrastructure to deal with the rapidly expanding cancer treatment demands in Vietnam. Moreover, although legislative frameworks are in place for cancer control in Vietnam, there is still a lack of suitable financial and governance structures to support long-term cancer prevention and treatment plan. Therefore, the immediate requirement for enhanced cancer screening programs, enhanced risk stratification at clinical decision points, and the determination of the optimal timing for genetic testing concerning surgical decision-making in breast/ovarian cancer patients who carry the BRCA gene mutations are all issues that require urgent attention.

To the best of our knowledge, this systematic review and meta-analysis will be the first to synthesize the data from separate studies to derive reliable estimates of the prevalence of BRCA gene mutations and its related factors among Vietnamese women with and without a cancer diagnosis. Based on our findings, the general public and healthcare practitioners will also have a heightened awareness of the significance of genetic testing and risk management for individuals who possess germline mutations.

Data availability
Underlying data
No data are associated with this article.

Reporting guidelines

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).
References

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