INPLASY PROTOCOL

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None declared.

Meta-analysis of breast cancer risk associated with established germline pathogenic variants in breast cancer-predisposition genes in population-based studies

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Review question / Objective: **In breast cancer patients who received genetic testing for the established germline pathogenic variants in breast cancer predisposition genes, what is the frequency of these pathogenic variants in an unselected population, and what is the estimation of the breast cancer risk associated with these pathogenic variants in population-based studies.**
Condition being studied: **Breast cancer.**
Information sources: **Electronic databases, including: PubMed (MEDLINE), Embase, Cochrane Library, Web of Science, and trial registers: ClinicalTrials.gov.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 February 2021 and was last updated on 04 February 2021 (registration number INPLASY202120017).

INTRODUCTION

Review question / Objective: **In breast cancer patients who received genetic testing for the established germline pathogenic variants in breast cancer predisposition genes, what is the frequency of these pathogenic variants in an unselected population, and what is the estimation of the breast cancer risk associated with these pathogenic variants in population-based studies.**

Rationale: Large-scale population-based estimates of the risk of breast cancer associated with germline pathogenic variants in cancer-predisposition genes are critically needed for risk assessment and management in women with inherited pathogenic variants. However, equivocal results were reported in previous studies, which might be caused by inadequate sample size. A larger sample size could be achieved by meta-analysis.

Condition being studied: Breast cancer.

METHODS

Search strategy: Related English-language scientific literature were searched on PubMed (MEDLINE), Embase, Cochrane Library, Web of Science, ClinicalTrials.gov with no restriction on time or countries, using following search terms: ("Breast Neoplasms"[Mesh] OR "Hereditary Breast and Ovarian Cancer Syndrome"[Mesh] OR "breast carcinoma*" OR "Breast Neoplasm*" OR "Breast Tumors" OR "Mammary Carcinoma*" OR "Mammary Neoplasm*" OR "breast cancer*" OR "Cancer of the Breast" OR "Cancer of Breast" OR "mammary cancer*" OR "mammary gland cancer*" OR "mamma carcinoma" OR "Hereditary Breast and Ovarian Cancer Syndrome" OR "HBOC Syndrome" OR "HBOC Syndromes") AND ("multi-gene panel*" OR "multigene panel*" OR "gene panel*" OR "panel testing" OR "multiple-gene sequencing panel" OR "predisposition gene panel" OR "cancer predisposition testing panel" OR "panels of genetic testing" OR "next-generation sequencing" OR "next generation sequencing" OR "NGS" OR "predisposition gene*" OR "novel germline mutations" OR "Cancer Susceptibility Genes") AND ("ATM" OR "BARD1" OR "BRCA1" OR "BRCA2" OR "CDH1" OR "CHEK2" OR "NF1" OR "PALB2" OR "PTEN" OR "RAD51C" OR "RAD51D" OR "TP53").

Participant or population: Patients with breast cancer who received next-generation sequencing or multi-gene panel testing of germline pathogenic variants in breast cancer-predisposition genes. The tested genes should include at least one gene in the following: ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, and TP53. Those who only tested for BRCA1/2 were not included. Those oversampled from high-risk women who had a family history, diagnosed at young age, or had estrogen receptor negative cancers, or have a founder mutation were not included.

Intervention: Genetic testing using next-generation sequencing/multi-gene panel as a mutation detection method.

Comparator: Unaffected women (population-based, not oversampling from affected families) who received next-generation sequencing or multi-gene panel testing of germline pathogenic variants in breast cancer-predisposition genes. The tested genes should include at least one gene of the following: ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, and TP53.

Study designs to be included: Population-based case-control studies, not oversampling from a family with family history or early-onset diseases.

Eligibility criteria: The four key inclusion criteria were as follows: (i) Breast cancer patients; (ii) Genetic testing using next-generation sequencing/multi-gene panel as a mutation detection method; (iii) Tested genes should include at least one gene in the following list: ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, and TP53; (iv) study should be population-based. Exclusion criteria includes: (i) studies concerning only the BRCA1/2 genes. (2) studies oversampling from high-risk women who had a family history, diagnosed at young age, or had estrogen receptor negative cancers, or have a founder mutation. In cases of patients analyzed in more than one study (when it was clearly indicated), repeatable data were not used.

Information sources: Electronic databases, including: PubMed (MEDLINE), Embase,

Cochrane Library, Web of Science, and trial registers: ClinicalTrials.gov.

Main outcome(s): Frequency of germline pathogenic variants in the established breast cancer predisposition genes Breast cancer risk associated with germline pathogenic variants in the established breast cancer-predisposition genes. (measured in odds ratio).

Data management: The data extraction will be done by two independent reviewers. A standardized, pre-designed, MS Excel based data collection form will be used for data extraction. Data will be abstracted, wherever available, on author, publication year, study design, sample size of the case group and control group, number of mutation detected in the case group and control group, estrogen receptor status, race, and age group will be extracted.

Quality assessment / Risk of bias analysis: Risk of bias will be evaluated using ROBINS-I tool.

Strategy of data synthesis: Associations between germline pathogenic variants in selected predisposition genes and breast cancer risk were assessed using odds ratios (ORs) and 95% confidence intervals (95% CIs) based on a chi-squared test. Heterogeneity among studies will be evaluated using the Cochrane risk of bias assessment and the I^2 statistic.

Subgroup analysis: Subgroup analysis will be performed for patients using ER status, family history, race, and age if applicable.

Sensitivity analysis: Leave-one-out validation will be applied for sensitivity analysis.

Country(ies) involved: China.

Keywords: Breast cancer; risk; germline pathogenic variants; predisposition genes; population-based.

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