Meta-Analysis

Association between BRCA1 polymorphisms rs799917 and rs1799966 and breast cancer risk: a meta-analysis

Meiming Yang¹, Xiaoli Du², Feng Zhang² and Shifang Yuan¹

Abstract

**Background:** Several studies have reported correlations between BRCA1 polymorphisms rs799917 and rs1799966 with the risk of breast cancer (BC). However, this relationship remains controversial.

**Methods:** We conducted a meta-analysis of seven studies to assess the associations between BRCA1 rs799917 and rs179966 and BC risk, with the aim of more accurately determining the potential correlation. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to evaluate the correlation of rs799917 and rs179966 with BC risk.

**Results:** There was no overall correlation between BRCA1 rs799917 and BC risk (TT vs CC: OR = 0.87, 95% CI = 0.66–1.16; CT vs CC: OR = 1.02, 95% CI = 0.89–1.15; dominant model: OR = 0.99, 95% CI = 0.88–1.11; recessive model: OR = 0.87, 95% CI = 0.65–1.16). Subgroup analysis by ethnicity also revealed no significant correlation between rs799917 and BC risk in either Asians or Caucasians. There was also no significant association between BRCA1 rs179966 and BC risk (GG vs AA: OR = 0.70, 95% CI = 0.33–1.47; AG vs AA: OR = 0.68, 95% CI = 0.35–1.30; dominant model: OR = 0.76, 95% CI = 0.49–1.06; recessive model: OR = 0.82, 95% CI = 0.49–1.36).

**Conclusion:** BRCA1 polymorphisms rs799917 and rs179966 were not significantly associated with BC risk in this meta-analysis.

**Keywords**
BRCA1, breast cancer, meta-analysis, correlation, polymorphisms, ethnicity

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¹Department of Thyroid, Breast and Vascular Surgery, Xijing Hospital, Fourth Military Medical University, Xi’an, China
²Department of Nursing, Fourth Military Medical University, Xi’an, China

Corresponding author:
Shifang Yuan, Department of Thyroid, Breast and Vascular Surgery, Xijing Hospital, Fourth Military Medical University, Xi’an 710032, China.
Email: yuanshifang01@sohu.com

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Introduction
Breast cancer (BC) is among the most prevalent malignancies in women, accounting for about 23% of all female malignant tumors. More than 400,000 individuals worldwide die from BC each year.\(^1\) In spite of an incomplete understanding of the precise mechanisms of BC tumorigenesis, the etiology of BC is known to be associated with age, ethnicity, early or delayed menarche, use of oral contraceptives, and age at menopause.\(^2\) Additionally, individual variation, including single nucleotide polymorphisms, may alter the susceptibility for developing BC. Among these potential risk factors, polymorphisms in the breast cancer 1 gene (\(BRCA1\)) have been widely studied.

\(BRCA1\) plays a role in apoptosis regulation, cell cycle checkpoint control, DNA damage repair, and transcriptional modulation.\(^3\) Thus, \(BRCA1\) deficiencies can result in defects in spindle checkpoints and S and G2/M phases leading to genetic instability and subsequent DNA damage responses, thereby enhancing the risk of carcinogenesis.\(^4\) \(BRCA1\), a tumor suppressor gene located on chromosome 17q21, was successfully cloned in 1994 and is the first well-defined human familial breast and ovarian cancer vulnerability gene.\(^5\) Mutations in \(BRCA1\) have been shown to account for almost 16% of hereditary BC cases.\(^6\)

The relationship between \(BRCA1\) polymorphisms rs799917 and rs1799966 with BC risk has been investigated in various studies;\(^7\) however, it remains controversial. Specifically, ethnic differences and inadequate sample sizes in a single study contribute to the inconsistencies. Meta-analysis is a powerful tool to summarize diverse research results. Not only can it overcome the drawbacks of small samples or low statistical power, but it can also supply more convincing outcomes than single case–control research studies.\(^8\) Herein, a systematic meta-analysis was conducted to examine the correlation between \(BRCA1\) polymorphisms rs799917 and rs1799966 with BC risk.

Materials and methods

Publication search
We identified relevant studies by searching PubMed, Embase, Web of Science, and Google Scholar databases using the following terms: “\(BRCA1\)”, “breast cancer”, “polymorphism”, “single nucleotide polymorphism”, and “genetic polymorphism”. All searches were retrieved and checked for other possible articles. The last update was March 2018. The search process was independently performed by two reviewers. This study did not require approval by an ethics review committee because it is a meta-analysis.

Inclusion and exclusion criteria
The two investigators independently examined abstracts in duplicate to decide whether they should be included or eliminated; any discrepancies were discussed and solved by the investigators. The inclusion criteria were as follows: (1) case–control studies of BC cases and healthy controls; (2) studies concerning the correlation between \(BRCA1\) polymorphisms and BC vulnerability; and (3) studies with adequate genotype information. Articles were eliminated if they were: (1) not a case–control study; (2) a duplicate of previous research; (3) lacking adequate information; and (4) reviews, case reports, meta-analyses, letters, or editorials.

Data extraction
The following data were selected from eligible studies: the first author’s name, year of publication, number of patients and controls, region, distributions of genotypes and
alleles, and evidence of Hardy–Weinberg equilibrium (HWE), as listed in Table 1.

### Statistical analysis

The $\chi^2$ test was used to determine whether genotype frequencies of controls were in HWE. The odds ratio (OR) and corresponding 95% confidence interval (CI) were employed to evaluate the correlation intensity between the $BRCA1$ polymorphisms with BC under a homozygote comparison (aa vs AA), a heterozygote comparison (Aa vs AA), a dominant model (aa+Aa vs AA), and a recessive model (aa vs AA+Aa) between groups. In this study, “A” and “a” indicated major and minor alleles, respectively. The Q-test and $I^2$ statistics were used to assess heterogeneity among studies, where a fixed-effect model was used in the case of significant homogeneity ($P_{\text{heterogeneity}} \geq 0.1$ or $I^2 < 50\%$); otherwise, a random-effect model was employed. Sensitivity analysis by the sequential omission of one study was conducted to validate the major source of heterogeneity. Egger’s linear regression test was used to determine the possible publication bias through visually inspecting funnel plots. $P < 0.05$ was considered statistically significant. Stata software (version 12.0; StataCorp LP, College Station, TX, USA) was used for statistical analysis.

### Results

#### Study selection and features

A total of 615 individual records were identified according to the search criteria, with 14 full-text publications preliminarily selected for further assessment. Seven publications were eliminated based on the exclusion criteria, including one duplicated study, one meta-analysis, two studies without control groups, and three without sufficient data for extraction. Finally, as shown in Figure 1, seven studies were included in this meta-analysis. The flow chart of study selection is summarized in Figure 1. All seven were case–control studies that investigated the correlation of $BRCA1$ polymorphisms with BC susceptibility. The publication years ranged from 2000 to 2018. The main characteristics of the eligible studies are summarized in Table 1.

### Table 1. Study selection and subject characteristics of included studies in meta-analysis.

| Author | Year of publication | Country | Ethnicity | Number of cases | Number of controls | Genotypes for cases | Genotypes for controls | $P$ for HWE |
|--------|---------------------|---------|-----------|----------------|--------------------|---------------------|------------------------|------------|
| Dunning | 1997                | England | Caucasian | 801           | 572                | TT                  | CT                     | CC                     |
| Wang   | 2009                | China   | Asian     | 1004          | 1008               | 89 370              | 342 56 250            | 266 0.81               |
| Huo    | 2009                | China   | Asian     | 568           | 624                | 70 283              | 215                    | 84 285 255           |
| Dombernowsky | 2009      | Denmark | Caucasian | 1201          | 4119               | 155 496             | 550                    | 467 1896 1756 0.19 |
| Abbas  | 2010                | Germany | Caucasian | 3139          | 5481               | 13 417              | 2709                   | 38 680 4763 0.01     |
| Hasan  | 2013                | Saudi Arabia | Asian | 100           | 100                | 32 37 31            | 34 36 30              | 0.00                   |
| Dombernowsky | 2009      | Denmark | Caucasian | 75            | 301                | 133 508             | 557                    | 435 1834 1850 0.54   |
| Abbas  | 2012                | China   | Asian     | 3140          | 5487               | 352 1366            | 3521 648 2392         | 2447 0.09             |
| Wu     | 2013                | USA     | Caucasian | 335           | 408                | 63 164              | 108                    | 77 211 120 0.35      |

HWE, Hardy–Weinberg equilibrium.
Table 2. Summary ORs and 95% CIs of BRCA1 polymorphisms and BC risk.

| Subgroup          | Genetic model | Effects model | Test of heterogeneity | Test of association |
|-------------------|---------------|---------------|-----------------------|---------------------|
|                   |               |               | $I^2$ | $P$   | OR  | 95% CI     |
| **rs799917**      |               |               |       |       |     |            |
| Overall           | TT vs CC      | Random        | 72.0% | 0.00  | 0.87 | 0.66–1.16 |
|                   | CT vs CC      | Random        | 55.1% | 0.05  | 1.02 | 0.89–1.15 |
|                   | Dominant model| Random        | 52.3% | 0.06  | 0.99 | 0.88–1.11 |
|                   | Recessive model| Random       | 77.4% | 0.00  | 0.87 | 0.65–1.16 |
| Caucasians        | TT vs CC      | Fixed         | 46.6% | 0.15  | 1.05 | 0.88–1.24 |
|                   | CT vs CC      | Random        | 78.2% | 0.01  | 1.00 | 0.82–1.22 |
|                   | Dominant model| Random        | 68.4% | 0.04  | 1.01 | 0.86–1.18 |
|                   | Recessive model| Fixed    | 49.6% | 0.14  | 1.10 | 0.93–1.30 |
| Asians            | TT vs CC      | Random        | 68.8% | 0.04  | 0.77 | 0.50–1.18 |
|                   | CT vs CC      | Fixed         | 0.00% | 0.49  | 1.05 | 0.90–1.23 |
|                   | Dominant model| Fixed         | 49.2% | 0.14  | 0.95 | 0.82–1.10 |
|                   | Recessive model| Random | 63.3% | 0.07  | 0.75 | 0.52–1.06 |
| Consistent with HWE| TT vs CC | Fixed         | 0.00% | 0.68  | 1.08 | 0.92–1.26 |
|                   | CT vs CC      | Fixed         | 77.9% | 0.01  | 1.03 | 0.80–1.31 |
|                   | Dominant model| Fixed         | 70.2% | 0.04  | 1.03 | 0.85–1.26 |
|                   | Recessive model| Fixed    | 0.00% | 0.44  | 1.10 | 0.94–1.28 |
| **rs1799966**     | GG vs AA      | Random        | 96.9% | 0.00  | 0.70 | 0.33–1.47 |
|                   | AG vs AA      | Random        | 98.3% | 0.00  | 0.68 | 0.35–1.30 |
|                   | Dominant model| Random         | 96.5% | 0.00  | 0.76 | 0.49–1.06 |
|                   | Recessive model| Random  | 94.0% | 0.00  | 0.82 | 0.49–1.36 |

OR, odds ratio; CI, confidence interval.
rs799917
The findings of the association between BRCA1 rs799917 and BC risk are shown in Table 2. No significant correlation was detected in any of the genetic models (see Figure 2: TT vs CC: OR = 0.87, 95% CI = 0.66–1.16; CT vs CC: OR = 1.02, 95% CI = 0.89–1.15; dominant model: OR = 0.99, 95% CI = 0.88–1.11; recessive model: OR = 0.87, 95% CI = 0.65–1.16). In the stratification analysis by ethnicity, there was also no significant correlation in Caucasians or Asians. Sensitivity analysis conducted by omitting non-HWE studies did not change the final outcomes, suggesting their statistical significance (Table 2).

rs1799966
The results of the meta-analysis of BRCA1 rs1799966 and BC risk are summarized in Table 2. Pooled analysis of all studies revealed that the polymorphism was not significantly associated with BC susceptibility (see Figure 3: GG vs AA: OR = 0.70, 95% CI = 0.33–1.47; AG vs AA: OR = 0.68, 95% CI = 0.42–1.09).
CI = 0.35–1.30; dominant model: OR = 0.76, 95% CI = 0.49–1.06; recessive model: OR = 0.82, 95% CI = 0.49–1.36).

**Publication bias**

Egger’s test was performed to evaluate the publication bias of enrolled articles. According to the funnel plot shapes in all genetic models, there was no obvious asymmetry in the allele model, indicating the low publication bias in our meta-analysis.

**Discussion**

The etiology of BC is thought to be a complex interplay between environmental and polygenic factors, but its pathogenesis is not yet fully understood. Previous research involving transcriptional inhibition of cell cycle checkpoints and DNA damage repair studies implicated BRCA1 as a tumor suppressor. Notably, BRCA1 was the first identified BC susceptibility gene, with a high penetrance but low frequency whose mutations account for around 16% of all BC cases. Several studies have shown a correlation between BRCA1 polymorphisms with BC risk. Recently, two of the most common BRCA1 polymorphisms (rs799917 and rs1799966) were comprehensively investigated and shown to be related to the risk of BC. Our meta-analysis was conducted to obtain a more thorough understanding of their relationship with BC.

We found that neither rs799917 nor rs1799966 in BRCA1 were related to BC risk.

![Figure 3. Meta-analysis of the relationship between rs1799966 and BC risk.](image)
susceptibility. To account for any environmental differences, we performed an ethnicity-specific subgroup analysis but this also revealed no correlation between rs799917 and BC in either Asians or Caucasians. Because deviations of allele distribution from HWE could contribute to between-study heterogeneity, we carried out subgroup analysis by eliminating studies that were inconsistent with HWE; this revealed that our data were robust. Additionally, heterogeneity between studies may be related to limited sample sizes, case definition, and method selection. The expression of traits is influenced not only by genotypes, but also by lifestyle, geographical environment, economic level, and small sample size or lower power value in some comparisons, all of which potentially affect the results. Because only a small number of relevant articles were assessed in this meta-analysis, we cannot carry out further analysis in the present study.

There are certain limitations in our study. First, the power of subgroup analysis might be relatively low because of the limited number of studies. Second, original individual data could not be extracted from each study. Hence, the present findings are based on unadjusted estimates, so the introduction of heterogeneity is inevitable and may affect our results. Third, the possibilities of gene–gene as well as gene–environment interactions have not been considered in this study.

In summary, the present meta-analysis indicated that BRCA1 polymorphisms might not be related to BC risk. Large-scale, well-designed studies are required to confirm these results in the future.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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**ORCID iD**

Shifang Yuan http://orcid.org/0000-0003-3710-6362

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