Meta-Analysis

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

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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 rs1799966 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 rs1799966 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* rs1799966 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 rs1799966 were not significantly associated with BC risk in this meta-analysis.

Keywords

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

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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

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
rs799917						TT	CT	CC	TT	CT	CC	
Dunning	1997	England	Caucasian	801	572	89	370	342	56	250	266	0.81
Wang	2009	China	Asian	1004	1008	140	483	381	142	283	215	0.00
Huo	2009	China	Asian	568	624	70	283	215	84	285	255	0.76
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
rs1799966						GG	AG	AA	GG	AG	AA	
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.

alleles, and evidence of Hardy–Weinberg equilibrium (HWE), as listed in Table 1.

Statistical analysis

The χ^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 ($P_{heterogeneity} \geq 0.1$ 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.[9–15] 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.

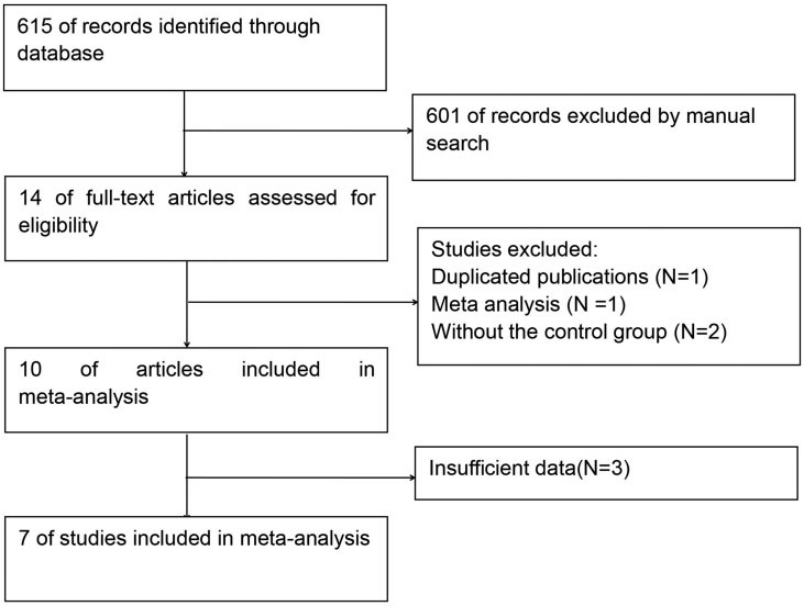

Figure 1. Study selection and inclusion process.

Table 2. Summary ORs and 95% CIs of *BRCA1* polymorphisms and BC risk.

			Test of heterogeneity		Test of association	
Subgroup	Genetic model	Effects model	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%

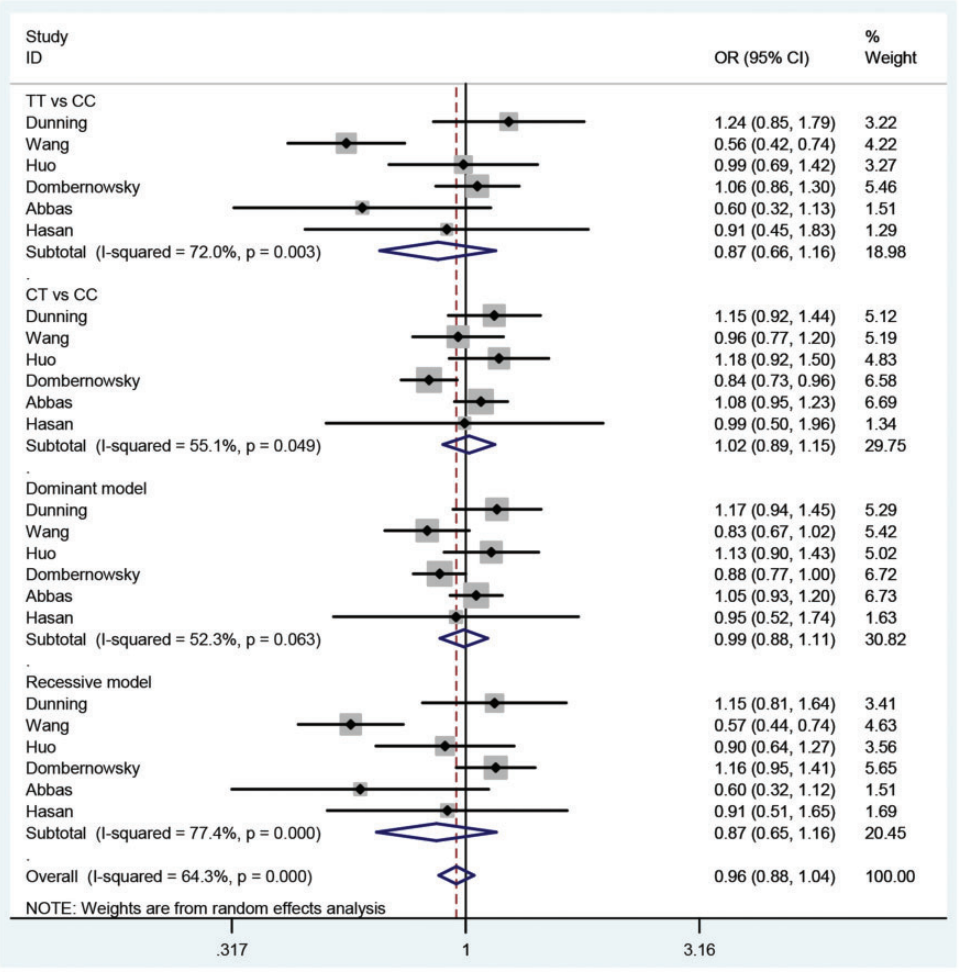

Figure 2. Meta-analysis of the relationship between rs799917 and BC risk.

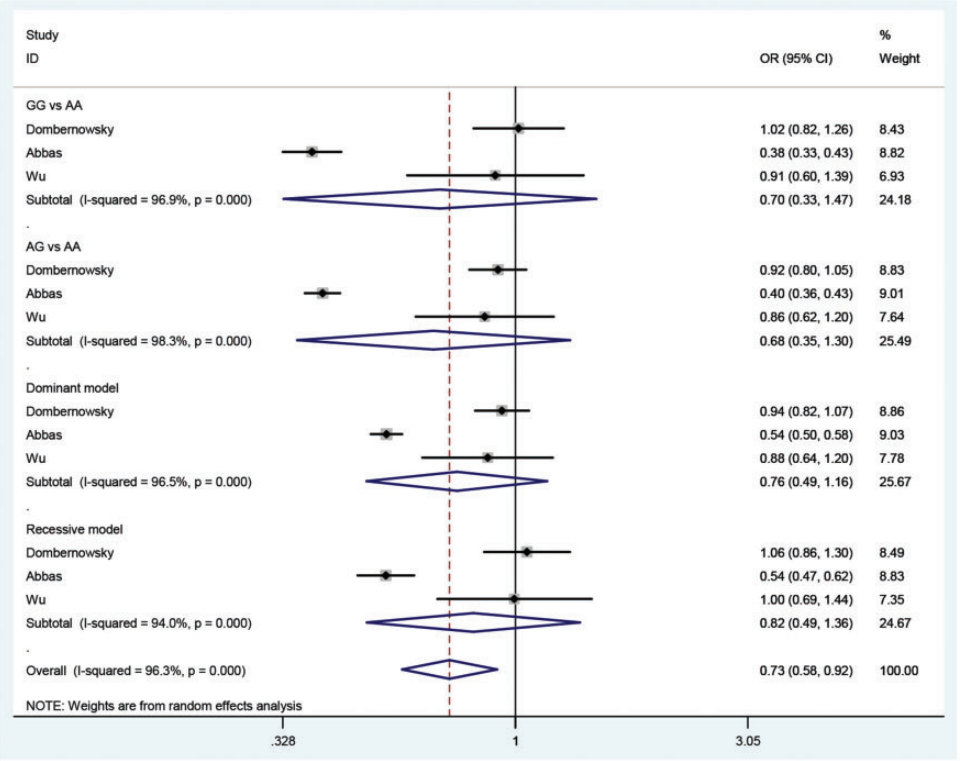

Figure 3. Meta-analysis of the relationship between rs1799966 and BC risk.

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 polygenetic factors,[16] 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.[17] 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.[18] 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.[19] 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

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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