Association between the MDR1 rs1045642 polymorphism and breast cancer risk: An updated meta-analysis

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Abstract. Multidrug resistance 1 (MDR1) is a transmembrane transporter on the cell membrane. As an ATP-dependent efflux pump, MDR1 is mainly responsible for the adsorption, distribution, metabolism, excretion and transportation of anticancer drugs to cancer cells. Mutations of the MDR1 gene may be associated with the incidence of cancer. In the past decade, associations found between the MDR1 rs1045642 polymorphism and breast cancer have been inconsistent and inconclusive. Therefore, the present study performed a meta-analysis including studies published up until August 16, 2023 to systematically evaluate the association between the MDR1 rs1045642 polymorphism and breast cancer risk. A total of 21 published case studies involving 6,815 patients with breast cancer and 9,227 healthy participants were included in the meta-analysis. Overall, the MDR1 rs1045642 polymorphism was not significantly associated with breast cancer-associated risk. However, in the subgroup analysis, the MDR1 rs1045642 polymorphism was found to be notably associated with a higher risk of breast cancer among Asian populations in recessive models [TT vs. CT + CC; odds ratio (OR)=1.393; 95% confidence interval (CI), 1.143-1.698; P=0.001; I^2<25%]. The MDR1 C3435T polymorphism was also associated with a notable decrease in the incidence of breast cancer in mixed ethnicity populations (TT and CT + CC; OR=0.578; 95% CI, 0.390-0.856; P=0.006; I^2<25%). In Caucasian populations, the MDR1 rs1045642 polymorphism was not associated with breast cancer risk. In conclusion, the present meta-analysis demonstrated that the MDR1 rs1045642 polymorphism may increase the risk of breast cancer in Asian populations, is associated with a reduced risk of breast cancer in mixed populations but has no notable effect in Caucasian populations.

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Introduction

Breast cancer is recognized as the most common malignant tumour in women worldwide (1). One of the most common problems when treating breast cancer is drug resistance. This curable disease can be fatal if resistance to chemotherapy drugs develops, which leads to metastasis (2). The multidrug resistance 1 (MDR1) gene, a member of the ATP-binding cassette family, encodes a membrane-bound phosphoglycoprotein (P-gp) that acts as an ATP-dependent efflux pump, providing protection to normal cells against numerous substances, such as antibiotics, polysaccharides, organic cations and amino acids, and protection to the body against environmental toxins (3).

The human MDR1 gene mutation at exon 26, position 3435 (also known as C3435T) leads to decreased mRNA expression levels and P-gp activity (4). Although the C3435T mutation in exon 26 of the MDR1 gene is a silent mutation, this polymorphism affects the expression and function of P-gp in many ways (5), impacting susceptibility to cancer. When this gene mutation is overexpressed in breast cancer, it can cause cancer cells to become resistant to the drugs used for treatment (2), which leads to treatment failure.

In the past decade, the association between the MDR1 rs1045642 polymorphism and breast cancer in different populations has been studied; the association between the MDR1 rs1045642 polymorphism and breast cancer risk varies in different human populations (6). There are some previous studies on the association between MDR1 rs1045642 polymorphism and breast cancer risk. Such as, Cizmarikova *et al* (7), Gutierrez-Rubio *et al* (8), Abuhaliema *et al* (9) and Jaramillo-Rangel *et al* (10) performed studies on Slovak, Mexican, Jordanian and northern Mexican populations, respectively.Tatari *et al* (11), Henríquez-Hernández *et al* (12), Macias-Gomez *et al* (3), Ghafouri *et al* (13), Tazzite *et al* (14), Li *et al* (15) and Al-Eitan *et al* (16) studied Iranian, Spanish Canary Islands, Mexican, Kurdish, Moroccan, Chinese and Jordanian populations, respectively.Rubiś *et al* (17) reported that the association between MDR1 rs1045642 polymorphism and breast cancer risk in the Polish population. The results of several studies are inconsistent and inconclusive due to the limitations of individual studies. The inconsistent findings

may also be due to limited sample size, single population, sample heterogeneity and differences in study methods.

To obtain a more precise estimation of the association between MDR1 rs1045642 polymorphism and breast cancer susceptibility, all published case-control studies with a cut-off date of August 2023 were collected for a meta-analysis and rational research methods and models were used to detail the role of the MDR1 rs1045642 polymorphism in ethnically diverse patients with breast cancer. The strengths of the present meta-analysis are that it is an update involving the large number of relatively comprehensive ethnicities with little sample heterogeneity.

Materials and methods

Publication search and data extraction. The keywords used in the present meta-analysis included 'MDR1 C3435T', 'ABCB1 C3435T' or 'rs1045642' and 'polymorphism' or 'single nucleotide polymorphism', 'SNP', 'polymorphism' and 'Cancer'. A comprehensive literature search was performed using the PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com), Web of Science (https://www.webofscience.com), China National Knowledge Infrastructure (https://www.cnki.net) and Wanfang (https://med.wanfangdata.com.cn) databases. There were no restrictions on the earliest publication date or language of publication in the search criteria, the latest publication date was August 16, 2023). All eligible studies were retrieved and their reference citations searched to identify other relevant publications. Any relevant review articles retrieved were then searched to identify additional eligible studies. Only published full-text studies were included. The following eligibility criteria were used: i) Case-control studies assessing the association between the MDR1 rs1045642 polymorphism and cancer risk; ii) studies with available genotypes; and iii) studies collecting the number of different genotypes for estimation of the odds ratio (OR) and 95% confidence interval (CI). Animal model studies and non-case-control studies were excluded. Data retrieved from the studies included first author name, year of publication, ethnicity of the study population (classified as Asian, Caucasian or mixed) and, number of cases and controls for the MDR1 rs1045642 SNP genotype.

Statistical analysis. The χ^2 test was used to assess the Hardy-Weinberg equilibrium (HWE) for all calculated allele frequencies in the case and control groups in the eligible studies and an OR with 95% CI was calculated to assess the association between the rs1045642 polymorphism and breast cancer. The heterogeneity between studies was assessed using the Q statistical test of the χ^2 statistic. When $P<0.05$ or $I^2>50\%$, the heterogeneity of the studies was considered to be statistically significant. According to the recommendations provided by the Cochrane Handbook for Systematic Reviews of Interventions (18), the random-effects models was used for hierarchical analysis of subgroups. The following genetic models were used to test the association between the MDR1 C3435T polymorphism and breast cancer risk: Homozygous model (TT vs. CC), heterozygous model (TC vs. CC), dominant model (TT/TC vs. CC), recessive model (TT vs. TC/CC) and additive model (T vs. C). Publication bias was assessed using Begg's funnel plot. All statistical analyses were performed using Stata 11.0 software (StataCorp LP).

Results

Characteristics of eligible studies. A total of 21 relevant studies were included in the meta-analysis, including 6,815 patients and 9,227 controls (1,3-39). The main characteristics of the articles that met the research conditions are listed in Table I. A total of 925 articles were identified using the search terms and the study flow chart in Fig. 1 explains the selection process for the 21 eligible articles. All studies were case-control studies with breast cancer as the main research area, and all cases were diagnosed using histopathology.In the present meta-analysis, ethnicity was divided into three major groups: Asian, Caucasian and mixed. Among them, the classification of Asian and Caucasian was clear and uncontroversial. Three of the studies involved mixed ethnic populations: Macias-Gomez *et al* (3), Jaramillo-Rangel *et al* (10) and Gutierrez-Rubio *et al* (8). The population studied by Macias-Gomez *et al* (3) was that of Central Mexico, which is a mixed population of Spaniards, American-Indians and Africans; Jaramillo-Rangel *et al* (10) included those from the Mexican states of Coahuila, Nuevo Leon, San Luis Potosi, Tamaulipas and Zacatecas, which have ethnically diverse populations, with a mix of indigenous and people of European, African and Asian ancestry. The study population of Gutierrez-Rubio *et al* (8) were those from the State of Jalisco in Mexico, which is in the central and western part of Mexico and included those with Indo-European mixed, Indian and North American ethnicities. In the present meta-analysis, a total of 15 studies had Caucasian populations, 3 had Asian populations and 3 had populations of mixed ethnicities. Table I presents the HWE test results for all the studies included in the meta-analysis, with 19 of the 21 studies meeting HWE.

Meta-analysis. The present meta-analysis demonstrated no significant association between the MDR1 rs1045642 polymorphism and breast cancer risk overall. Subgroup analyses based on ethnicity were then performed, which indicated that the MDR1 rs1045642 polymorphism, especially in the recessive model, was associated with an increased risk of breast cancer in Asian populations (TT vs. CT + CC; OR=1.393; 95% CI, 1.143-1.698; P=0.001; $I^2<25\%$). The MDR1 rs1045642 polymorphism was also notably associated with an increased risk of breast cancer in Asians in both homozygous (TT vs. CC; OR=1.528; 95% CI, 0.933-2.503; P=0.092; $I^2<50\%$) and additive models (T vs. C; OR=1.201; 95% CI, 0.926-1.557; P=0.168; $I^2<75\%$). In mixed ethnicity populations, the MDR1 rs1045642 polymorphism was notably associated with a reduced risk of breast cancer in the recessive model (TT vs. CT/CC; OR=0.578; 95% CI, 0.390-0.856; P=0.006; $I^2<25\%$). The MDR1 rs1045642 polymorphism was also notably associated with a reduced breast cancer risk in mixed ethnicity populations in the homozygous (TT vs. CC; OR=0.543; 95% CI, 0.280-1.053; P=0.071; $I^2<75\%$) and additive models (T vs. C; OR=0.791; 95% CI, 0.579-1.081; P=0.141; $I^2<75\%$). However, in the Caucasian population, there was no significant association between the MDR1 rs1045642 polymorphism and breast cancer in all models. The results are presented in Fig. 2.

Table I. Main characteristics of all eligible studies in the meta-analysis.

First author/s, year	Ethnicity	Case group, n			Control group, n			P-value (HWE)	(Refs.)
		CC	CT	TT	CC	CT	TT		
Macias-Gómez *et al*, 2014	Mixed	15	41	8	37	103	43	0.086	(3)
Cizmarikova *et al*, 2010	Caucasian	46	108	67	35	54	24	0.709	(7)
Gutierrez-Rubio *et al*, 2015	Mixed	82	133	33	56	72	24	0.915	(8)
Abuhaliema *et al*, 2016	Caucasian	68	62	20	40	65	45	0.105	(9)
Jaramillo-Rangel *et al*, 2018	Mixed	78	129	31	25	64	29	0.350	(10)
Tatari *et al*, 2009	Caucasian	16	57	33	12	45	20	0.111	(11)
Henríquez-Hernández *et al*, 2009	Caucasian	35	70	30	85	162	54	0.127	(12)
Ghafouri *et al*, 2016	Caucasian	75	16	9	141	50	9	0.107	(13)
Tazzite *et al*, 2016	Caucasian	30	20	10	28	33	7	0.548	(14)
Li *et al*, 2017	Asian	40	42	18	35	50	15	0.677	(15)
Al-Eitan *et al*, 2019	Caucasian	102	84	34	79	90	48	0.024	(16)
Rubiś *et al*, 2012	Caucasian	48	96	65	52	103	50	0.943	(17)
Taheri *et al*, 2010	Caucasian	10	30	14	10	27	13	0.553	(23)
Nordgard *et al*, 2007	Caucasian	9	51	33	17	52	40	0.988	(25)
George *et al*, 2009	Asian	8	39	39	15	32	21	0.671	(26)
Ozdemir *et al*, 2013	Caucasian	26	20	14	41	12	5	0.013	(28)
Wu *et al*, 2012	Asian	388	565	220	440	624	180	0.084	(29)
Turgut *et al*, 2007	Caucasian	7	33	17	18	23	9	0.728	(30)
Fawzy *et al*, 2014	Caucasian	60	92	38	76	94	20	0.249	(31)
Abbas *et al*, 2010	Caucasian	703	1543	902	1228	2736	1522	0.981	(32)
Zeliha *et al*, 2020	Caucasian	25	37	41	16	40	32	0.575	(33)

HWE, Hardy-Weinberg equilibrium.

Publication bias. Begg's funnel plot was used to assess publication bias. No significant asymmetry was found in all four genetic models, indicating that there was no significant publication bias to the papers included in the present study. Plots are presented in Fig. 3.

Discussion

With the development of molecular biology, gene polymorphism analysis has been favoured by researchers (19) and gene polymorphisms are increasingly recognized as key risk factors for breast cancer (1). The present study performed a comprehensive meta-analysis of the association between MDR1 rs1045642 polymorphism and breast cancer to synthesize the basis of current relevant studies.

A genetic polymorphism of the MDR1 gene was first reported by Kioka *et al* (20) through in vitro studies of cancer cells. Subsequently, screening results for the entire MDR1 coding region have been reported (21). Similar meta-analyses have been performed to assess the association between the MDR1 rs1045642 polymorphism and breast cancer risk, but the results have varied. For example, Cizmarikova *et al* (7), Wang *et al* (6), Wang *et al* (22), Sharif *et al* (1), Abuhaliema *et al* (9) and Jaramillo-Rangel *et al* (10) reported an association between the MDR1 rs1045642 polymorphism and breast cancer. However, Taheri *et al* (23), Macias-Gomez *et al* (3), Tazzite *et al* (16), Li *et al* (15) and Totoń *et al* (24) reported that the MDR1 rs1045642 polymorphism was not associated with breast cancer. In the meta-analyses by Nordgard *et al* (25), George *et al* (26) and Sheng *et al* (4), there were biases in the digital entry of individual genotypes, which made their results less accurate. These data were cross-checked during the collection and analysis of the present meta-analysis. Sheng *et al* (4) reported that the MDR1 rs1045642 polymorphism may be associated with the risk of breast cancer in Caucasian but not in Asian populations; in contrast to the results of the present study, the authors reported that the genotype distribution of the Asian controls in their analysis was inconsistent with HWE. The present study performed a meta-analysis of 21 studies. The genotypic distribution of the remaining 19 controls was consistent with HWE, and the genotype distribution of the Asian control group was consistent with HWE. The data were reliable and the conclusion was more convincing.

When conducting subgroup analysis at the level of ethnicity, The study by Lu *et al* (27) showed that in Caucasians,the MDR1 rs1045642 polymorphism in the T allele contrast model and the TT genotype were associated with increased risk: (T vs. C, pooled OR=1.26; 95% CI:

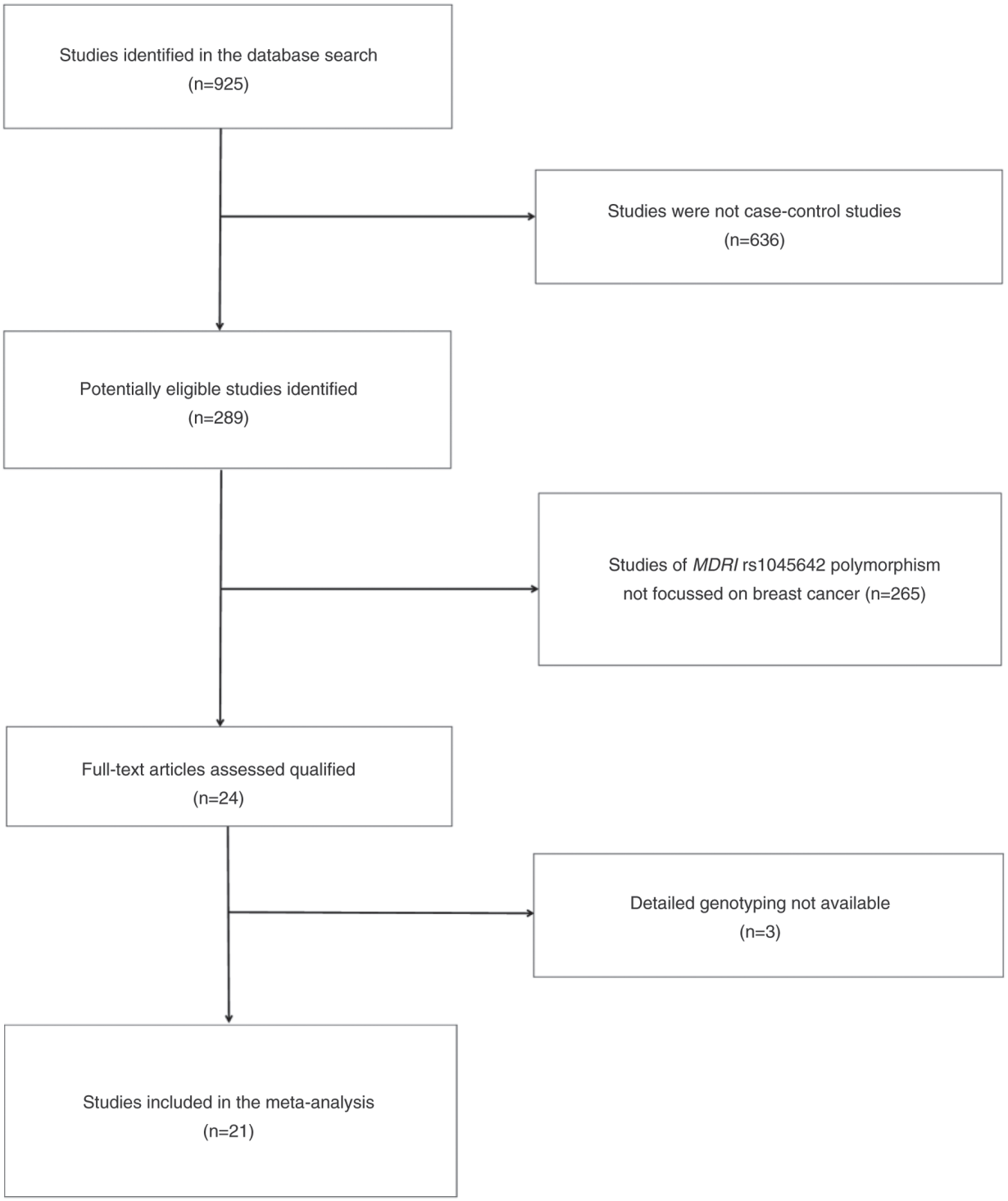

Figure 1. Selection process for the 21 eligible articles in the meta-analysis.

1.04-1.52) and (TT vs. CC, OR=1.48; 95%CI: 1.04-2.11). The dominant model yielded statistically significant results (pooled OR=0.71; 95%CI: 0.52-0.96). The analysis of these models concluded that the MDR1 rs1045642 polymorphism increase breast cancer risk in additive and homozygous models, while decrease breast cancer risk in dominant models. Wang *et al* (21) reported that the MDR1 rs1045642 polymorphism increased the risk of breast cancer in the Caucasian population and was not associated with breast cancer in the Asian population. In the studies by Wang *et al* (22) and Sharif *et al* (1), the MDR1 rs1045642 polymorphism was associated with an increased risk of breast cancer in both the Asian and Caucasian populations. In the present meta-analysis that involved extraction and analysis of a large amount of validated data, 15 studies included were performed with Caucasian populations, 3 with Asian populations and 3 with mixed ethnicity populations. The HWE test results were consistent with HWE in 19 of 21 studies, with inconsistent HWE test results for two studies: The P-values for heterogeneity were reported to be P=0.013 and P=0.024

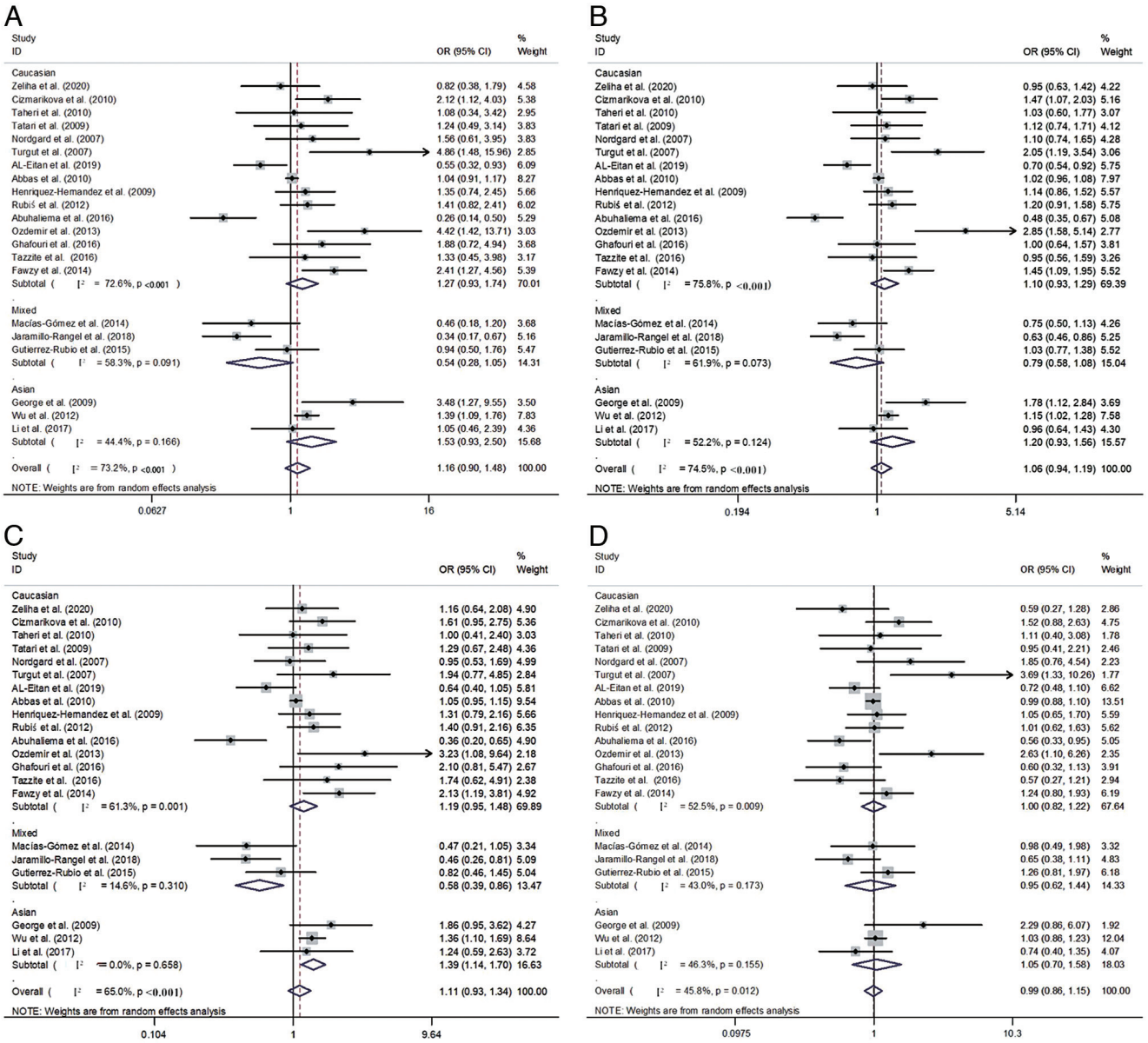

Figure 2. Forest plots of MDR1 rs1045642 polymorphism and breast cancer in all eligible studies. (A) Homozygous model (TT vs. CC). (B) Additive model (T vs. C). (C) Recessive model (TT vs. TC + CC). (D) Heterozygous model (CT vs. CC). OR, odds ratio.

for Ozdemir *et al* (28) and Al-Eitan *et al* (16), respectively. A test result of P<0.05 indicated that the heterogeneity of the study was considered significant. In subgroup analyses, the MDR1 rs1045642 polymorphism was found to be notably associated with a higher risk of breast cancer in Asian populations in the recessive model (TT vs. CT + CC; OR=1.393; 95% CI, 1.143-1.698; P=0.001; I^2<25%). The MDR1 C3435T polymorphism notably decreased the incidence of breast cancer in mixed populations (TT and CT + CC; OR=0.578; 95% CI, 0.390-0.856; P=0.006; I^2<25%). In the analysis of the Caucasian population, among the four models, the homozygous model (TT vs. CC;OR=1.270; 95%CI: 0.929-1.737; P=0.134; I^2>50%). In the additive model (T vs. C; OR=1.096; 95%CI: 0.933-1.287; P<0.265; I^2>75%). In the recessive model (TT vs. TC + CC; OR=1.189; 95%CI: 0.953-1.484; P=0.125; I^2>50%). In the heterozygous model (CT vs. CC; OR=0.997; 95%CI: 0.816-1.217; P=0.973; I^2<75%). Our analysis shows that in the Caucasian population, the MDR1 rs1045642 polymorphism was not associated with breast cancer.

In conclusion, the present meta-analysis demonstrated that the MDR1 rs1045642 polymorphism was associated with breast cancer risk at the subgroup level; however, the results of the present meta-analysis were inconsistent with other studies. The MDR1 rs1045642 polymorphism in the recessive model was notably associated with an increased risk of breast cancer in Asian populations. In mixed populations, the MDR1 rs1045642 polymorphism was notably associated with a reduced risk of breast cancer. The MDR1 rs1045642 polymorphism was also notably associated with an increased tendency of breast cancer in Asian populations in both the homozygous and additive models. In mixed populations, the homozygous and additive models also showed that the MDR1 rs1045642 polymorphism was notably associated with a reduced breast

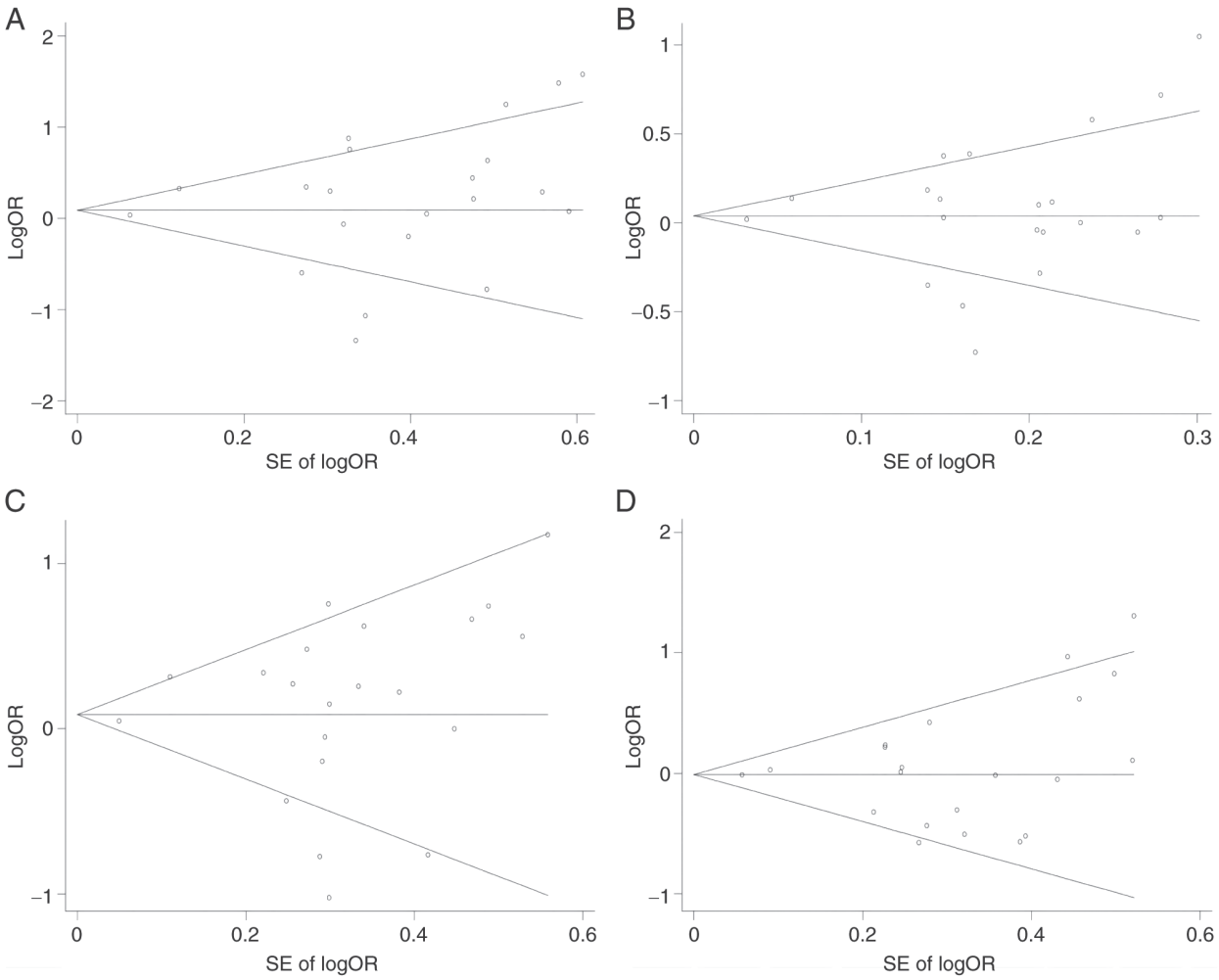

Figure 3. Begg's funnel plot of all publications with pseudo 95% confidence limits. (A) Homozygous model (TT vs. CC). (B) Additive model (T vs. C). (C) Recessive model (TT vs. TC + CC). (D) Heterozygous model (CT vs. CC). OR, odds ratio.

cancer risk. In Caucasian populations, there was no notable association between the MDR1 rs1045642 polymorphism and breast cancer in all models.

In the present study, a screening of ethnicity and a subgroup analysis were performed. However, the limitations of the present study cannot be ignored. Firstly, the current meta-analysis requires a more comprehensive racial analysis. There were also multiple factors associated with the wide variation in the results of MDR1 rs1045642 polymorphism, including tissue used for the original analysis, sampling time and method, oestrogen receptor status, and sample size (3), that may have affected the accuracy of the association of MDR1 rs1045642 with breast cancer. To obtain precise results, studies of gene-environment and gene-gene interactions are essential (1), and interactions between different polymorphic sites of the same gene may regulate cancer risk (22). To obtain more complete and accurate results, studies with larger sample sizes, well-established ethnic groupings and more relevant functional studies are needed.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

LG conceived and designed the study, analyzed data and wrote and edited the manuscript. GH designed the study and wrote the manuscript. NW, YC and LX analyzed data. All authors have read and approved the final manuscript. LG and GH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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