

# Association between the rs4784227-CASC16 polymorphism and the risk of breast cancer

## A meta-analysis

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### Abstract

**Objective:** Although several studies have identified an association between the rs4784227-cancer susceptibility candidate gene 16 (CASC16) polymorphism and breast cancer, the results remain inconclusive. Therefore, we conducted a meta-analysis to assess the relationship between the rs4784227-CASC16 polymorphism and breast cancer risk.

**Methods:** Studies were searched in the PubMed, Web of Science, Embase, Google Scholar, and Cochran Library databases until June 10, 2021, to identify all potential literature on rs4784227-CASC16 polymorphism and breast cancer risk association. Fixed-effect or random-effect models were used to calculate odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). Subgroup analyses, publication bias, and sensitivity analyses were also conducted.

**Results:** Seventeen eligible studies involving 34,719 subjects (18,445 cases and 16,274 healthy controls) from 7 articles were included in the current meta-analysis. The pooled ORs regarding the association between the rs4784227-CASC16 polymorphism and breast cancer risk were statistically significant [T vs C: OR = 1.244, 95% CI = 1.202–1.287; TT vs CT + CC: OR = 1.407, 95% CI = 1.296–1.528; CC vs CT + TT: OR = 0.777, 95% CI = 0.745–0.811; TT vs CC: OR = 1.544, 95% CI = 1.419–1.681; CT vs CC: OR = 1.244, 95% CI = 1.189–1.301]. On subgroup analysis, the rs4784227-CASC16 T/C gene has a certain correlation with breast cancer susceptibility in Asian and North American populations, but no significant risk in the Australian population.

**Conclusion:** Our pooled analysis showed a significant association between the rs4784227- (T) allele and breast cancer susceptibility in Asian and North American populations, and intervention with this mutation might be a new therapeutic strategy for breast cancer. However, large-scale and well-designed studies are needed in different populations to further evaluate the role of the rs4784227-CASC16 polymorphism in breast cancer.

**Abbreviations:** CI = confidence interval, FOXA1 = Forkhead box A1, GWAS = Genome-wide association studies, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, ORs = odds ratios, SNPs = single-nucleotide polymorphisms, TLE = Gro/transducin-like enhancer of split, TOX3 = TOX high-mobility box protein group family member 3.

## 1. Introduction

Breast cancer is the most malignant neoplasm among females and the leading cause of death among women worldwide.<sup>[1]</sup> An estimated 2.1 million new cases of breast cancer were diagnosed worldwide in 2018.<sup>[2]</sup> The mechanism of breast carcinogenesis is still not fully understood. Environmental variables and germline mutations are 2 well-known risk factors that contribute to the development of breast cancer.<sup>[3]</sup> Epidemiological studies have indicated that age, age of menarche, obesity, family history, and menstrual history are associated with an increased susceptibility to breast cancer.<sup>[4,5]</sup> Many single-nucleotide polymorphisms (SNPs) in critical genes, such as BRCA1, BRCA2, TP53, and PTEN, have been identified to contribute to increased susceptibility to breast cancer.<sup>[6–8]</sup> However, the involvement of genes in breast cancer has not yet been fully elucidated.

In the past few years, several genome-wide association studies (GWAS) have identified numerous novel genetic susceptibility variants and loci that are independently associated with an increased risk of breast cancer.<sup>[9–11]</sup> Forkhead box A1 (FOXA1) and TOX high-mobility box protein group family member 3 (TOX3) are believed to be other probable candidates that cause breast cancer susceptibility.<sup>[12]</sup> Breast cancer risk-associated SNPs are enriched in the cisomes of FOXA1 in a cancer and cell-type-specific manner.<sup>[13]</sup> TOX3 is a nuclear protein that can modify chromatin structure. Its clinical implications and its role in tumor development and invasion have been shown in the risk of breast cancer.<sup>[12]</sup> Rs4784227 is a site of cancer susceptibility candidate gene 16 (CASC16). CASC16 is a noncoding RNA, located at chromosome 16q12, that may affect the DNA-binding sequence change on FOXA1 and subsequently, trigger the FOXA1-binding affinity to the TOX3 gene promoter.<sup>[13]</sup>

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The datasets generated during and/or analyzed during the current study are publicly available.

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Growing evidence suggests that rs4784227 (a C-to-T transition) is strongly correlated with the risk of breast cancer.<sup>[14–21]</sup> Considering the relatively small sample size in most studies, it is possible to perform a quantitative synthesis of the evidence for potential correlations with rigorous methods. Meta-analysis has been proven to be an effective statistical method combining available studies to produce a precise conclusion. A meta-analysis article was published in 2021 July and included 8284 subjects (4055 breast cancer cases and 4229 controls).<sup>[22]</sup> However, many studies were still excluded from that meta-analysis. Additionally, the study population of the previous meta-analyze was limited to the Asian population. It is undetermined whether sample sizes are sufficient to reach a definite conclusion. Therefore, we performed a meta-analysis of 17 published studies that included 34,719 subjects (18,445 breast cancer cases and 16,274 healthy controls) to identify the precise association between the rs4784227-CASC16 C/T polymorphism and breast cancer risk. Moreover, the association between the rs4784227-CASC16 C/T polymorphism and breast cancer risk in Asian, North American, and Australian populations was explored by subgroup analyses.

## 2. Materials and Methods

### 2.1. Search strategy

Search term combinations were keywords relating to rs4784227 (e.g., “rs4784227”, “CASC16”, “chromosome 16q12”, “LOC643714”) and in combination with words related to breast cancer (e.g., “breast cancer”, “breast carcinoma”, “malignant breast neoplasm”) and polymorphism or variation. These keyword retrieval strategies were used in PubMed, Web of

Science, Embase, Google Scholar, and Cochran Library databases for entries until June 2021.

### 2.2. Inclusion and exclusion criteria

All studies included in the meta-analysis met the following inclusion criteria:

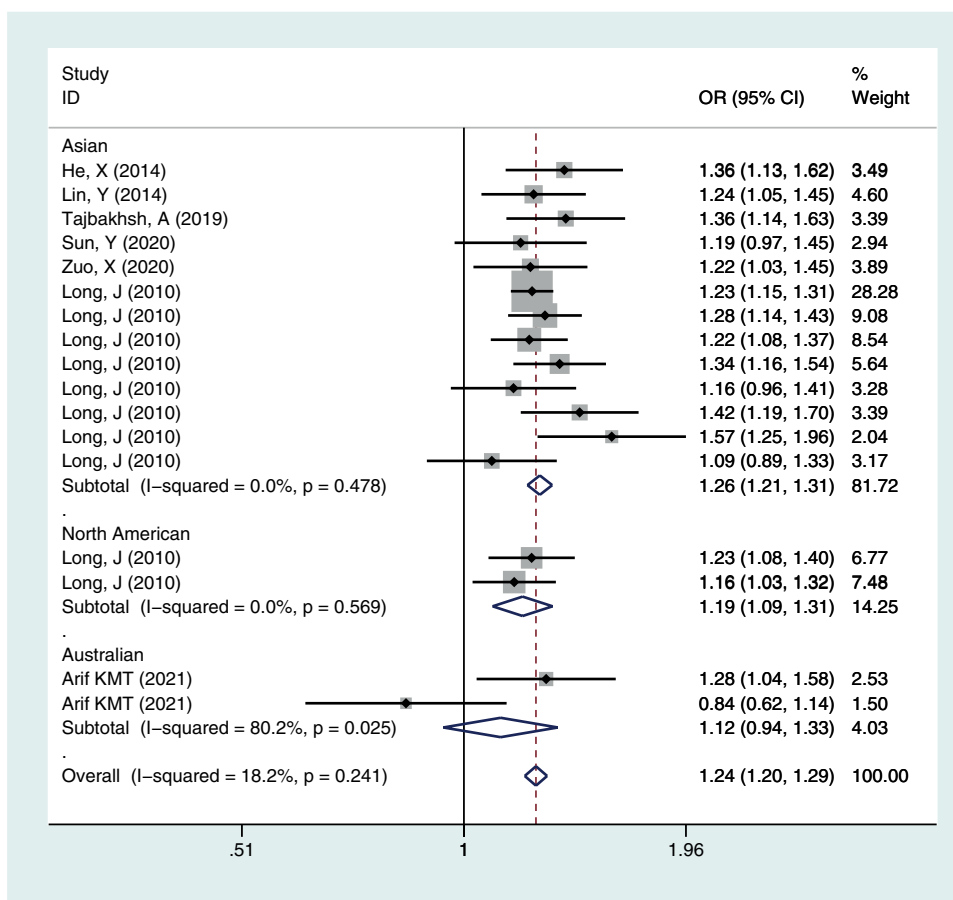
- (1) a case-control study;
- (2) an investigation of the association between the rs4784227-CASC16 polymorphism and breast cancer risk;
- (3) including sufficient data for calculating the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs);
- (4) The genotype distribution of the control group must be consistent with the Hardy–Weinberg equilibrium (HWE).

The exclusion criteria were as follows:

- (1) duplicate publication;
- (2) case reports, review articles, letters, comments, meta-analyses, irrelevant studies;
- (3) not offering sufficient data for calculation of ORs with 95% CIs.

### 2.3. Data extraction and Synthesis

Information and data were extracted carefully from all qualified independent articles by 2 independent investigators (Liping Bao and Wenji Xu), based on the inclusion and exclusion criteria above. The data included the first author, publication year, country, source of controls, number of cases and controls for each



**Figure 1.** Meta-analysis for the OR of breast cancer associated with the rs4784227-CASC16 polymorphism (T vs C). CASC16 = cancer susceptibility candidate gene 16, CI = confidence interval, OR = odds ratios.

genotype, and genotyping method. If genotype distributions were not given in the study, we calculated them from allele frequencies and number of cases and controls. When necessary, we wrote to the corresponding authors for extra information. Disagreements were resolved by discussion and consensus. If discussion and consensus were not achieved, a suggestion was offered by the third reviewer (Yao Zhong) to determine the correct selection.

**2.4. Statistical analysis**

We performed this meta-analysis based on published studies. So there is no need to conduct special ethic review, and the

ethical approval is not necessary. The OR with 95% CI was used to assess the strength of the association between rs4784227-CASC16 C/T polymorphisms and breast cancer risk in 5 genetic models (T vs C, TT vs CT + CC, CC vs CT + TT, TT vs CC, and CT vs TT). The rs4784227-CASC16 polymorphism distribution in the control group was tested for HWE using the Pearson chi-square test.<sup>[23]</sup> The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the eligible studies. Studies with NOS scores ≥ 6 were considered high quality. Between-study heterogeneities were assessed by Cochran chi-square-based Q-test and I<sup>2</sup> test. A fixed-effect model was used for analyses if the heterogeneity was not significant

**Table 1**  
**Characteristics of the studies included in the meta-analysis.**

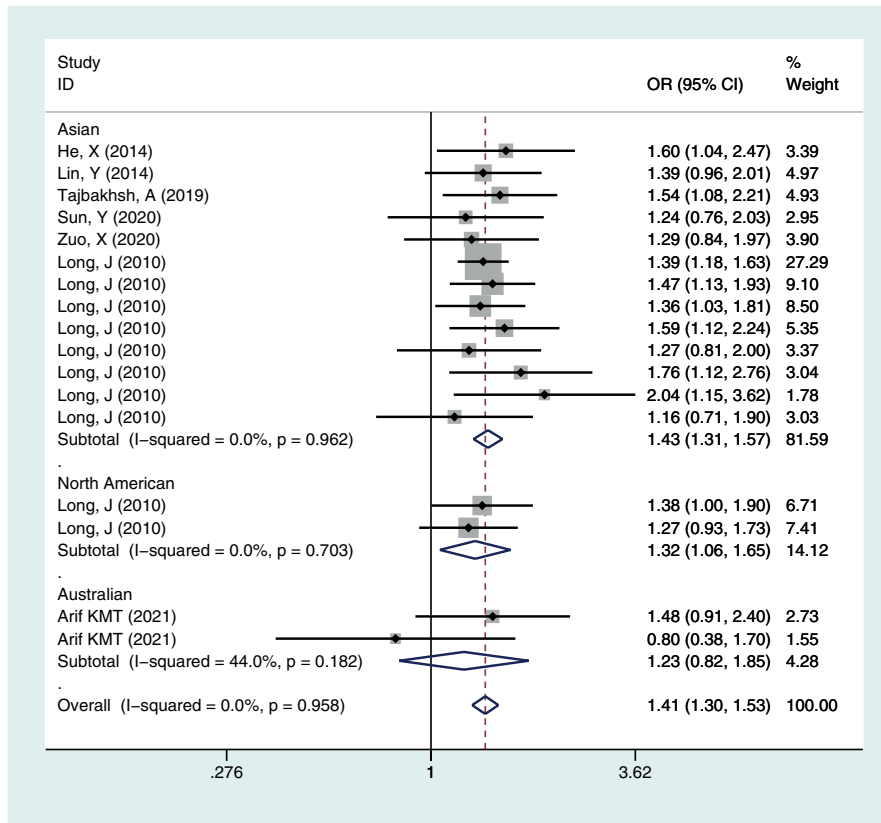
First author	Year	Country	Cases	Controls	Cases			Controls			P for HWE	NOS score
					CC	CT	TT	CC	CT	TT		
He X <sup>[19]</sup>	2014	Chinese	623	620	305	262	56	358	226	36	.966	9
Lin Y <sup>[18]</sup>	2014	Chinese Fujian	701	794	331	302	68	424	313	57	.941	9
Tajbakhsh A <sup>[17]</sup>	2019	Iranian	505	567	209	218	78	285	222	60	.092	7
Sun, Y <sup>[14]</sup>	2020	Chinese Shanxi	503	503	266	199	38	292	180	31	.644	9
Zuo, X <sup>[16]</sup>	2020	Chinese Shanxi	675	675	353	270	52	394	240	41	.581	9
Long J <sup>[20]</sup>	2010	Chinese Shanghai	6346	3921	3253	2581	512	2241	1447	233	.977	7
		Chinese Tianjin	1520	1583	747	637	136	890	594	99	.993	7
		Chinese Nanjing	1437	1437	726	591	120	808	539	90	.993	7
		Chinese Taiwan	1003	1010	500	416	87	587	366	57	.996	7
		Chinese Hong Kong	456	644	231	187	38	354	247	43	.992	7
		Japanese Nagoya	640	631	320	265	55	378	221	32	.743	7
		Japanese Nagano	403	403	196	170	37	247	137	19	.999	7
		Japanese	531	511	288	206	37	289	191	31	.940	7
		North American	1145	1142	577	472	96	643	428	71	.984	7
		North American	1357	1148	704	547	106	646	430	72	.960	7
Arif KMT <sup>[21]</sup>	2021	Australian Caucasian	369	484	173	159	37	262	188	34	.972	7
		Australian Caucasian	231	201	133	84	14	105	81	15	.908	7

HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale.

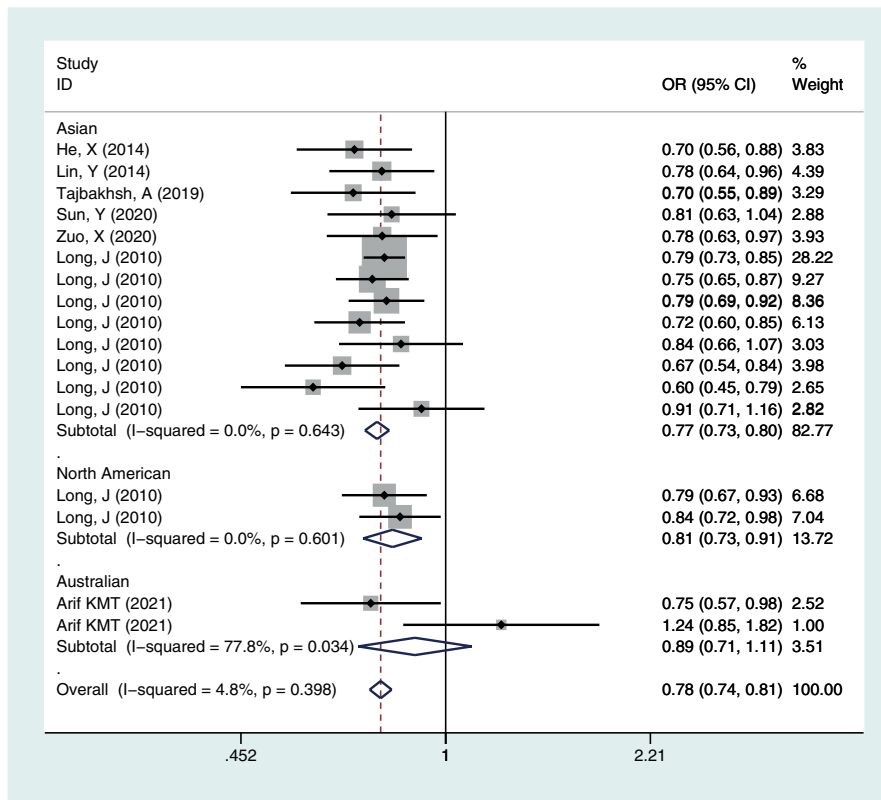
**Table 2**  
**Summary of pooled ORs in the stratified analysis association between rs4784227-CASC16 and breast cancer risk.**

	N	T vs C		TT vs CT + CC		CC vs CT + TT		TT vs CC		CT vs TT	
		OR	Ph	OR	Ph	OR	Ph	OR	Ph	OR	Ph
Total	17	1.24 (1.20–1.29)	0.241	1.41 (1.30–1.53)	0.958	0.78 (0.74–0.81)	0.398	1.54 (1.42–1.68)	0.757	1.24 (1.19–1.30)	0.772
Asian	13	1.26 (1.21–1.31)	0.478	1.43 (1.31–1.57)	0.962	0.77 (0.73–0.80)	0.643	1.58 (1.44–1.73)	0.837	1.26 (1.20–1.32)	0.890
North America	2	1.19 (1.09–1.31)	0.569	1.32 (1.06–1.65)	0.703	0.81 (0.73–0.91)	0.601	1.42 (1.13–1.79)	0.639	1.20 (1.06–1.35)	0.673
Australian	2	1.12 (0.94–1.33)	0.025	1.23 (0.82–1.85)	0.182	0.89 (0.71–1.11)	0.034	1.29 (0.85–1.97)	0.087	1.10 (0.87–1.39)	0.073

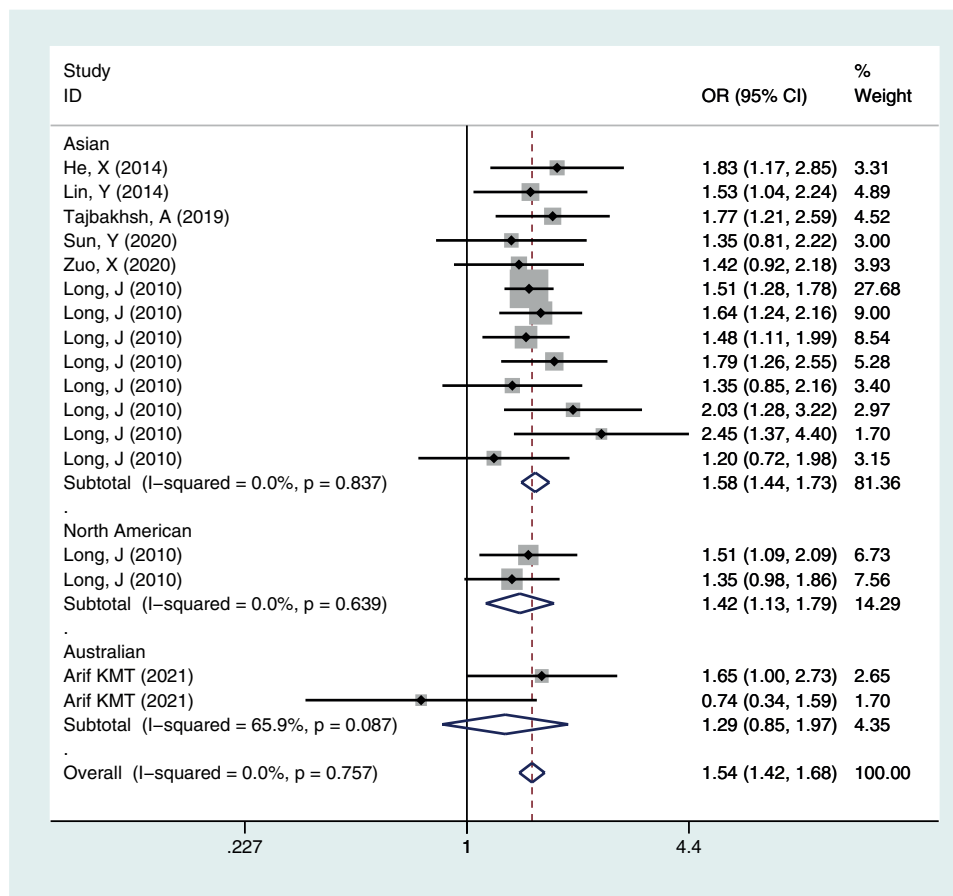
CASC16 = cancer susceptibility candidate gene 16, N = number, OR = odds ratios, Ph = P value for heterogeneity.



**Figure 2.** Meta-analysis for the OR of breast cancer associated with the rs4784227-CASC16 polymorphism (TT vs CT + CC). CASC16 = cancer susceptibility candidate gene 16, OR = odds ratios.



**Figure 3.** Meta-analysis for the OR of breast cancer associated with the rs4784227-CASC16 polymorphism (CC vs CT + TT). CASC16 = cancer susceptibility candidate gene 16, OR = odds ratios.



**Figure 4.** Meta-analysis for the OR of breast cancer associated with the rs4784227-CASC16 polymorphism (TT vs CC). CASC16 = cancer susceptibility candidate gene 16, OR = odds ratios.

( $P > .1$ ,  $I^2 < 50.0\%$ ). Otherwise, a random-effect model was used. Subgroup analyses were performed based on ethnicity. Sensitivity analysis was conducted to identify the influence of the individual data on pooled results and test the reliability of the results. Begg funnel plots and Egger tests were used to assess the existence of publication bias. All statistical analyses were conducted by Stata version 12.0 (StataCorp LP, College Station, TX).

### 3. Results

#### 3.1. Study characteristics

Figure 1 shows the literature search flowchart of our meta-analysis. A total of 22 potentially relevant citations were identified from the databases. Five duplicate records were removed. After we screened the titles and abstracts, 5 citations were removed due to irrelevant topics (not about breast cancer and rs4784227-CASC16 polymorphism). Then, the full text of the remaining 12 citations was downloaded for reading carefully; we removed 4 citations due to insufficient genotype data for extraction and 1 citation due to a  $P$  value for Hardy–Weinberg equilibrium  $< 0.05$ . All 17 case and control studies from 7 articles were included in our meta-analysis, incorporating 18,445 breast cancer cases and 16,274 controls. The populations were from Asia (China, Japan, and Iran), North America, and Australia. The characteristics of these studies and the quality scores are presented in Table 1.

#### 3.2. Overall and Subgroup analyses

We calculated the summary ORs and their 95% CIs in 5 genetic models: the allelic contrast model (T vs C), the dominant model (CC vs CT + TT), the recessive model (TT vs TC + CC), and the additive model (TT vs CC), and the heterozygous model (CT vs CC). The evaluation of the association between the rs4784227-CASC16 C > T polymorphism and breast cancer risk is presented in Table 2. Overall, there was correlation between the prevalence of the rs4784227-CASC16 polymorphism and breast cancer, and the difference was statistically significant (T vs C: OR = 1.244, 95% CI = 1.202–1.287; TT vs CT + CC: OR = 1.407, 95% CI = 1.296–1.528; CC vs CT + TT: OR = 0.777, 95% CI = 0.745–0.811; TT vs CC: OR = 1.544, 95% CI = 1.419–1.681; CT vs CC: OR = 1.244, 95% CI = 1.189–1.301).

To identify potential differences based on ethnicity, subgroup analysis was performed. In the stratified analysis by ethnicity, significant associations were found among different populations (Asian, North American, Australian) for the polymorphism in all genetic models. The results suggested that the rs4784227-CASC16 C > T gene has a certain correlation with breast cancer susceptibility in Asian and North American populations, but no significant risk in the Australian population, as shown in Figures 1–5.

#### 3.3. Sensitivity analysis

Sensitivity analysis was conducted by omitting a single study by turns to estimate the influence of the individual data on pooled results and test the reliability of the results (Fig. 6). The results

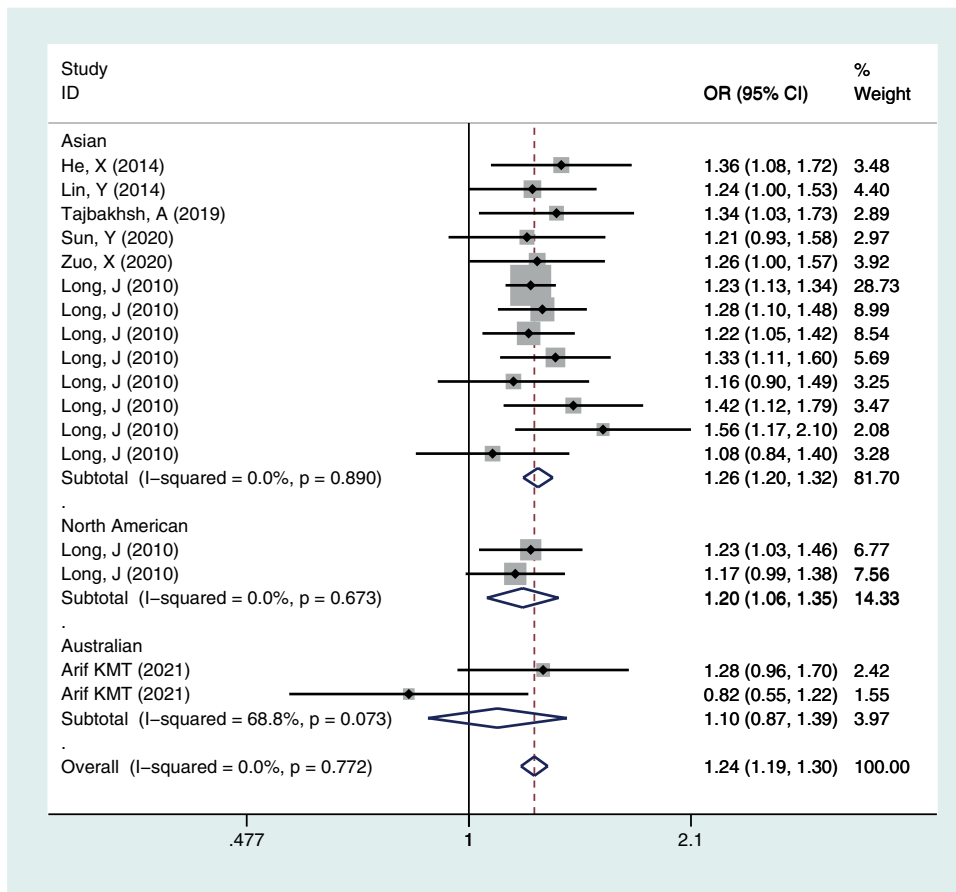


Figure 5. Meta-analysis for the OR of breast cancer associated with the rs4784227-CASC16 polymorphism (CT vs TT). CASC16 = cancer susceptibility candidate gene 16, OR = odds ratios.

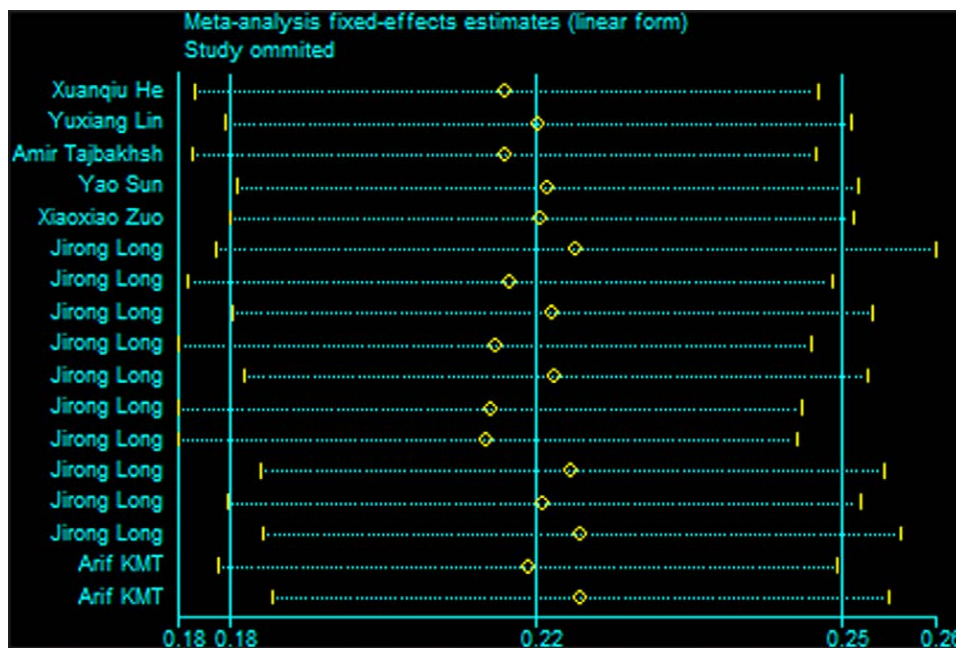
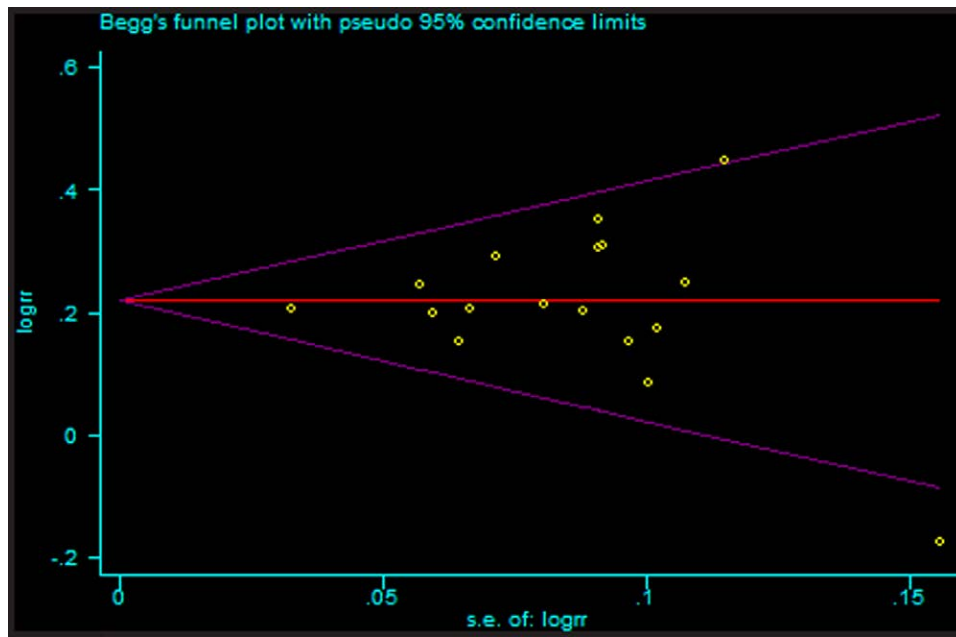


Figure 6. Sensitivity analysis of association between the rs4784227-CASC16 genetic variances and breast cancer. CASC16 = cancer susceptibility candidate gene 16.





**Figure 7.** Assessment of publication bias in the analysis of the association between the rs4784227-CASC16 gene polymorphism and breast cancer susceptibility. CASC16 = cancer susceptibility candidate gene 16.

of the sensitivity analysis showed that no individual study significantly affected the pooled OR, suggesting the stability of the meta-analyses.

**3.4. Publication bias**

We used funnel plots and Egger test to evaluate potential publication biases. The shape of funnel plots was symmetrical for every comparison, thus suggesting no publication bias among the studies included. The results did not show any evidence of publication bias based on Begg funnel plot ( $P_{Begg} = .902$ , T vs C, Fig. 7) or Egger regression test ( $P_{Egger} = 0.982$ , T vs C). Similarly, there was no publication bias for the association between rs4784227-CASC16 polymorphism and breast cancer susceptibility under the other genetic models.

**4. Discussion**

A variety of studies have focused on the association between the rs4784227-CASC16 gene polymorphism and breast cancer. However, the results obtained from such investigations have been inconclusive. Some studies have indicated that rs4784227-CASC16 may confer susceptibility to breast cancer by affecting the binding affinity of FOXA1 for the X3 gene promoter.<sup>[13]</sup> To derive a more precise estimation of the relationship, we performed this meta-analysis, combining data from similar studies to increase sample size and statistical power and achieve a more robust result.

The rs4784227-CASC16 SNP is an important SNP related to TOX3 and FOXA1, located upstream of the TOX3 gene. Meyer and Carroll suggested a tumor suppressor role for TOX3 in breast cancer.<sup>[24]</sup> FOXA1 is associated with ER and likely regulates TOX3 promoter activity. FOXA1-binding to DNA is crucial for the opening of chromatin and nucleosome positioning sequences for recruitment of transcription factors. Researchers have shown that rs4784227-CASC16 may disrupt enhancer function by FOXA1-binding affinity-modulation and, therefore, can change TOX3 expression.<sup>[13]</sup> Lupien et al<sup>[25]</sup> have demonstrated that the place for rs4784227-CASC16 on the FOXA1 genome for interaction is on the eighth position of the

FKH motif recognized via FOXA1. Moreover, a study indicated that FOXA1 is modulated by T-rs4784227-CASC16 in vivo.<sup>[25]</sup> Katika et al<sup>[26]</sup> indicated that the affinity of the DNA site for the FOXA protein was enhanced for T-rs4784227-CASC16 compared with C-rs4784227-CASC16. Another study also showed that T rs4784227-CASC16 favors FOXA1-binding affinity over the C allele.<sup>[13]</sup> The Gro/transducin-like enhancer of split (TLE) protein, as a corepressor, is bound to the DNA sequence through DNA-binding repressor proteins. FOXA1 commonly stimulates gene expression, and cobinding to DNA sequences with Gro/TLE proteins, which leads to local chromatin condensation and transcriptional repression.<sup>[27]</sup> Cowper-Sal et al<sup>[13]</sup> showed that the risk allele T-rs4784227-CASC16 led to a reduction in TOX3 gene expression by decreasing the stability of the enhancer by increasing TLE repressor affinity recruitment. Additionally, a study showed that rs4784227-CASC16 affects the risk of breast cancer by regulating the sequence of RB transcriptional corepressor-like 2 gene expression.<sup>[28]</sup>

The objective of this meta-analysis was to explore the association between the CASC16 rs4784227 polymorphism and breast cancer risk. In this meta-analysis, a total of 7 articles including 17 case and control studies were used to evaluate the association between the rs4784227-CASC16 polymorphism and breast cancer risk. To eliminate heterogeneity, we established strict inclusion and exclusion criteria, and heterogeneity was not observed in the models in our meta-analysis. Therefore, the fixed-effect model was used in the genetic models. The results indicated that the rs4784227-CASC16 polymorphism significantly increased susceptibility to breast cancer. Considering that the polymorphism frequencies might differ among ethnic groups, we performed a subgroup analysis by ethnicity (Table 2). The results demonstrated that the rs4784227-CASC16 C/T polymorphism was associated with breast cancer risk in Asian and North American populations, but not in the Australian population. Since only 2 studies were performed and the total number of cases and controls is far lower in the Australian population, it should be noted that the ethnicity-based analysis may not be reliable in regard to the Australian subgroups. Our results indicated that the rs4784227-CASC16 gene polymorphism was associated with breast cancer risk in Asian and North American populations.

The rs4784227-CASC16 T allele was a risk factor for breast cancer in Asian and North American populations.

Some potential limitations of the present meta-analysis should be considered. First, there were only 2 studies with a North American population and 2 studies with an Australian population, and the exploration of moderator variables was limited by the low number of studies. Further studies including a wider spectrum of subjects to investigate the role of this variant in other populations will be needed. Second, breast cancer is a complex disease with multiple determinants, and other risk factors were not well considered in the analysis, such as age and body mass index, which may affect the risk of breast cancer. We also need to consider the association between different types of breast cancer and the rs4784227-CASC16 polymorphism. As the limited original data contained in the study, we did not perform more hierarchical analysis, which could lead to a loss of significant evaluation subgroups.

Despite these limitations, this meta-analysis suggests that the rs4784227-CASC16 polymorphism was significantly associated with an increased risk of breast cancer in Asian and North American populations, particularly in Asian populations. Further studies including a wider spectrum of subjects in other populations and investigating multiple determinants and different types of breast cancer for breast cancer in large GWAS data are warranted.

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