Systematic Review and Meta-Analysis

Medicine®

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Association between *CASC16* rs4784227 polymorphism and breast cancer susceptibility

A meta-analysis

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Abstract

Objective: To explore whether rs4784227 polymorphism of *CASC16* is correlated with risk of breast cancer.

Methods: Relevant studies up to December 24, 2020 were searched in PubMed, Embase, Web of Science, CNKI, VIP, and WANFANG databases. Data were analyzed by using Stata 12.0. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and country-based subgroup analyses were conducted. Sensitivity analysis was conducted to assess the stability of the results. Publication bias was assessed by using the Egger regression asymmetry test and visualization of funnel plots.

Results: Seven case-control studies enrolling 4055 breast cancer cases and 4229 controls were included. rs4784227 was found significantly associated with increased risk of breast cancer in a dominant (OR = 1.301, 95% CI = 1.190–1.423, $P < .001$), a recessive (OR = 1.431, 95% CI = 1.216–1.685, $P < .001$), and an allele model (OR = 1.257, 95% CI = 1.172–1.348, $P < .001$), while an over-dominant model showed that rs4784227 was correlated with decreased breast cancer risk (OR = 0.852, 95% CI = 0.778–0.933, $P = .001$).

Conclusion: The rs4784227 polymorphism of *CASC16* gene is correlated with breast cancer susceptibility.

Abbreviations: FOXA1 = forkhead box O1, TOX3 = TOX high-mobility box protein group family member 3.

Keywords: breast cancer, *CASC16*/ TOX high-mobility box protein group family member 3, meta-analysis, rs4784227, SNP

1. Introduction

Breast cancer is a malignant tumor occurring in the breast epithelium or ductal epithelium. It is one of the most common malignant tumors in women, accounting for 30% of female cancers, and the main cause of death in women aged 20 to 59 years.[1] In China, with the development of social economy and the change of people's lifestyle, the incidence and death rates of breast cancer are increasing year by year, and more than 300,000 women are diagnosed with breast cancer every year.[2] The etiology is not completely clear yet, and it may be ascribed to genetic factors, breast cancer related gene mutations, reproductive factors, sex hormones, nutrition, and dietary and environmental factors.

In 2007, the Breast Cancer Association Collaboration reported 5 susceptibility sites associated with the occurrence of breast cancer for the first time through a three-stage GWAS study.[3] Thereafter, accumulating GWAS studies were carried out and risk single nucleotide polymorphic sites have been identified. The role of rs4784227 of *CASC16*, also known as *TOX3* (TOX high-mobility box protein group family member 3), in the regulation of tumor biological function has attracted much attention.[4,5] The rs4784227 is located in the intron region of *LOC643714*, which is upstream of *CASC16*.[6]*TOX3* encodes the TOX high-mobility box protein group family member 3, a protein involved in changes in chromatin structure, with 3 nucleotide repeat motifs and a putative gene *LOC643714*.[7] The clinical significance of CASC16 and its role in the development and invasion of breast cancer have been demonstrated in several studies.[8,9]

Studies have shown that rs4784227T allele can reduce luciferase activity and change DNA-protein binding, regulate chromatin affinity for *FOXA1* (forkhead box O1), and lead to allele-specific gene expression.[10–12] Similarly in breast cancer cell lines, different genotypes at rs4784227 can affect the affinity of *CASC16* promoter for *FOXA1* transcription factor and regulate the expression of *CASC16* thus affecting the occurrence and development of breast cancer.[3,13–15] Zheng et al first

Editor: Ning Zhang.

XSL and JLM contributed equally to this work.

Supported by the Sanming Project of Medicine in Shenzhen (No. SZSM201811057). Guangdong Medical Science and Technology Research Fund (No. B2021240).

The authors have no conflicts of interests to disclose.

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

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How to cite this article: Liang XS, Mo JL, Hu LM, Gong CM, Liu T, Hong WX, Yin JY, Liu ZQ, Zhou HH. Association between CASC16 rs4784227 polymorphism and breast cancer susceptibility: a meta-analysis. Medicine 2021;100:28(e26215).

Received: 22 March 2021 / Received in final form: 13 May 2021 / Accepted: 17 May 2021

http://dx.doi.org/10.1097/MD.0000000000026215

identified rs4784227 as a genetic susceptibility locus for breast cancer in European and Asian populations,[10,16] However, the studies of Cai Q and Antoniou AC did not find an association between rs4784227 and breast cancer.[17,18] Therefore, here we conduct a meta-analysis of the published relevant articles to comprehensively analyze the correlation between *CASC16* rs4784227 polymorphism and breast cancer risk.

2. Materials and methods

2.1. Literature retrieval strategy

We systematically searched the electronic databases (PubMed, Embase, Web of Science, CNKI, VIP, and WANFANG DATA) to identify related studies published up to December 24, 2020. The terms used for search were ("breast cancer *" OR "breast neoplasms *" OR "mammary cancer *") AND ("rs4784227*" OR "*TOX3* *" OR "*CASC16**") AND ("gene*" OR "polymorphism*" OR "mutation*" OR "single nucleotide polymorphism*" OR "SNP*" OR "variant*"). The reference lists of relevant articles were checked to identify additional eligible studies not included.

2.2. Inclusion and exclusion criteria

Eligible articles evaluating the association between *CASC16* gene rs4784227 polymorphism and breast cancer risk should meet the following inclusion criteria:

1. Patients in the case group should be diagnosed with breast cancer;
2. Case-control studies analyzing *CASC16* gene rs4784227 polymorphism and breast cancer susceptibility;
3. Studies providing the frequency distribution or enough data to calculate the frequency distribution of rs4784227 genotype.

Exclusion criteria are as follows: not enough data are included. In the case of conference abstract, if the data of animal model, cell experiments and case reports overlap, studies with more subjects will be included.

2.3. Data extraction and quality assessment

Two investigators (Liang Xiongshun and Hu Liming) extracted data from the included studies independently, and when there were inconsistences in the data, the differences were resolved through discussion with a third investigator (Mo Junluan). Data extracted from eligible studies included: first author, year of publication, journal, country, sample size, mean age, number or frequency of genotypes and alleles, and Hardy-Weinberg equilibrium (HWE) status. Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the studies included in the Meta-analysis. Studies with NOS score ≥6 were considered of high quality.

2.4. Statistical analysis

The OR value and 95% CI of different gene models were calculated by STATA/SE 12.0 to evaluate the association between rs4784227 polymorphism of *CASC16* and breast cancer susceptibility. The significance of OR was determined according to *Z* test. The combined results of the dominant, recessive, over-dominant and allele models were evaluated respectively. I^2 statistics and corresponding *P* values were used to evaluate the heterogeneity between studies. When there was heterogeneity, a random effect model ($P<.1$ and/or $I^2>50\%$) was used to combine the results, otherwise a fixed effect model ($P\geq.1$ and/or $I^2\leq 50\%$) was used.[19,20] The genotype Hardy-Weinberg equilibrium in the control group was calculated by the Chi-Squared test, and $P>.05$ was considered to meet the Hardy-Weinberg equilibrium. Funnel plots and Egger regression were used to assess publication bias, and sensitivity analysis was used to evaluate the stability of the results.

2.5. Ethics and dissemination

Since this is a protocol for meta-analysis, all data in this study come from published studies and do not involve patients, so ethical approval is not required. Findings of this research will be disseminated in a peer-reviewed journal or conference presentations.

3. Result

3.1. Basic data of the included literature

According to the above inclusion criteria, 7 case-control studies were finally included in this meta-analysis[21–27] (Fig. 1). All 7 studies were conducted in Asian populations, including 5 in China and 2 in Iran. A total of 4055 cases and 4229 controls were included for analysis. The basic data of the included studies are shown in Table 1.

3.2. Heterogeneity assessment of included literature

As can be seen from the comparison of results between Figure 2 and Figure 3, the study by Ali Hajizadeh et al[28] was the source of heterogeneity. Before the study was excluded, the subgroup in which the study was located $P=.274$, $I^2=92.9\%$. After the exclusion of this study, $P<.001$, $I^2=0$.

3.3. Meta-analysis of association between rs4784227 polymorphism of CASC16 gene and breast cancer risk

Rs4784227 was significantly associated with breast cancer in a dominant model (OR = 1.301, 95% CI = 1.190–1.423, $P<.001$), recessive model (OR = 1.431, 95% CI = 1.216–1.685, $P<.001$), allele model ($R=1.257$, 95% CI = 1.172–1.348, $P<.001$) and over-dominant model (OR = 0.852, 95% CI = 0.778–0.933, $P=.001$). The results of the meta-analysis are shown in Table 2. From the analysis of the total study population, the 4 models were statistically significant. The results showed that the rs4784227T allele of *CASC16* gene significantly increased the risk of breast cancer compared with the C allele.

3.4. Subgroup analysis

Subgroup analysis by country was performed (Table 2). In the Chinese population, 5 studies were included with a total of

3443 cases and 3571 controls. Rs4784227 was significantly associated with breast cancer in dominant model (OR = 1.274, 95% CI = 1.155–1.404, $P < .001$), recessive model (OR = 1.303, 95% CI = 1.079–1.572, $P = .006$), allele (OR = 1.219, 95% CI = 1.128–1.317, $P < .001$) and over-dominant model (OR = 0.837, 95% CI = 0.758–0.924, $P < .001$). These results suggest that the polymorphism of rs4784227 locus of *CASC16* gene may be a risk factor for breast cancer in Chinese women. In the

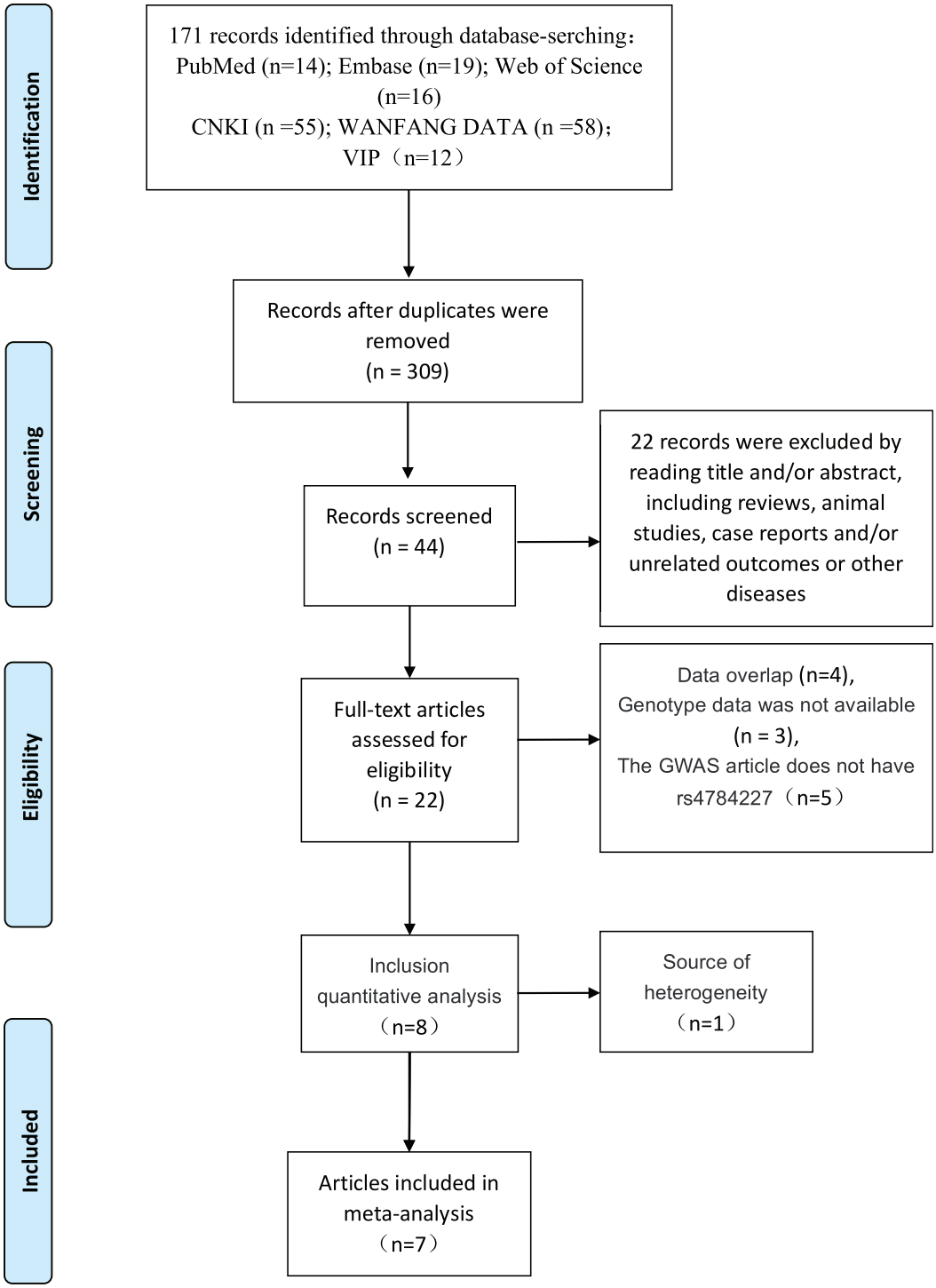

Figure 1. Flowchart of literature selection.

Table 1

Characteristics of studies included in the meta-analysis.

SNPs	Author and reference	Year	Country	Ethnicity	Case	Control	Sample size		Mean age (years)		Genotype		Allele (M/m)*		NOS	OR (95% CI) HWE
							Case	Control	Case	Control	Case	Control	Dominant model	Allelic model		
rs4784227 (C>T)	Yao Sun	2020	China	Asian	503	503	52.04±9.52	51.90±9.55	266/199/38	292/180/31	275/731	242/764	1.23 (0.96–1.58)	1.19 (0.97–1.45)	6	0.644135
	Nehle Jamali	2020	Iran	Asian	107	91	53.51±5.16	52.51±5.97	31/46/30	36/49/6	106/108	61/121	1.61 (0.89–2.90)	1.95 (1.30–2.93)	7	0.046983
	Xiaoxiao Zuo	2020	China	Asian	681	680	50.58±9.84	50.63±9.71	353/270/52	394/240/41	374/976	322/1028	1.28 (1.03–1.59)	1.22 (1.03–1.45)	6	0.581859
	Amir Tajbakhsh	2019	Iran	Asian	505	567	50.52±12.29	43.45±12.21	209/218/78	285/222/60	374/636	342/792	0.52 (0.42–0.66)	1.49 (1.26–1.77)	6	0.092861
	Zhiping Deng	2016	China	Asian	551	577	49.09±11.022	48.790±8.294	123/102/13	340/205/36	128/348	277/885	1.38 (1.02–1.86)	1.19 (0.98–1.44)	6	0.495311
	Yuxiang Lin	2014	China	Asian	702	794	47.8±10.9	48.7±9.7	331/302/68	424/313/57	438/964	427/1161	1.27 (1.03–1.56)	1.24 (1.06–1.45)	7	0.941233
	Ali Hajizadeh	2017	Iranian	Asian	126	160	–	–	75/35/16	54/96/10	67/185	116/204	0.22 (0.095–0.549)	–	6	0.000162
	Furu Wang	2020	China	Asian	1006	1017	51.59±11.14	51.54±11.18	500/415/83	569/385/61	581/1415	507/1523	1.27 (1.06–1.52)	–	7	0.69847

* M/m: major/minor allele

Genotype presented as wild type/heterozygous/homozygous; –, not available; SNP = single nucleotide polymorphisms, OR = odds ratio, 95% CI = 95% confidence interval, NOS = Newcastle–Ottawa quality assessment scale, HWE = Hardy–Weinberg equilibrium.

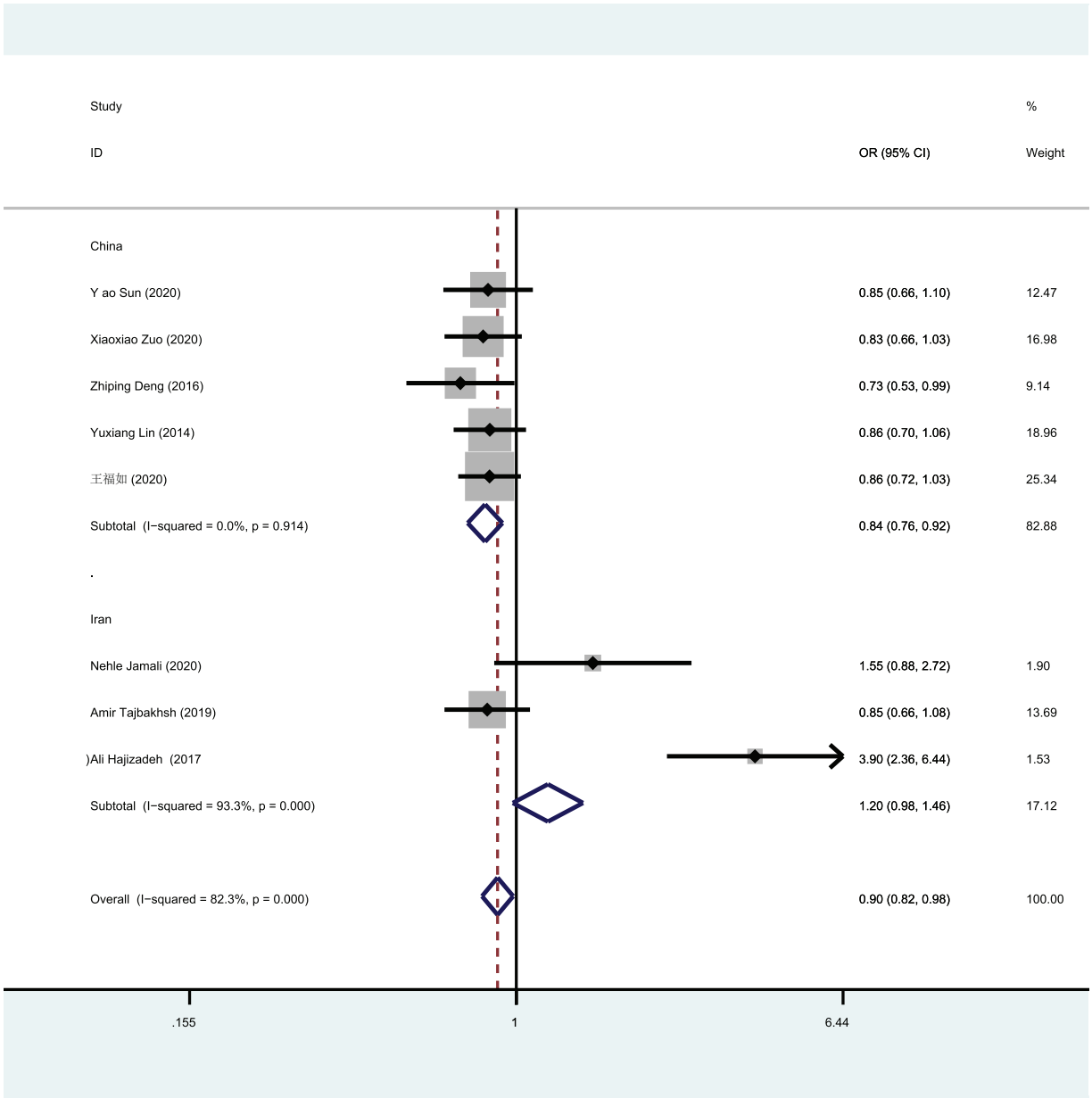

Figure 2. Meta-analysis forest map.

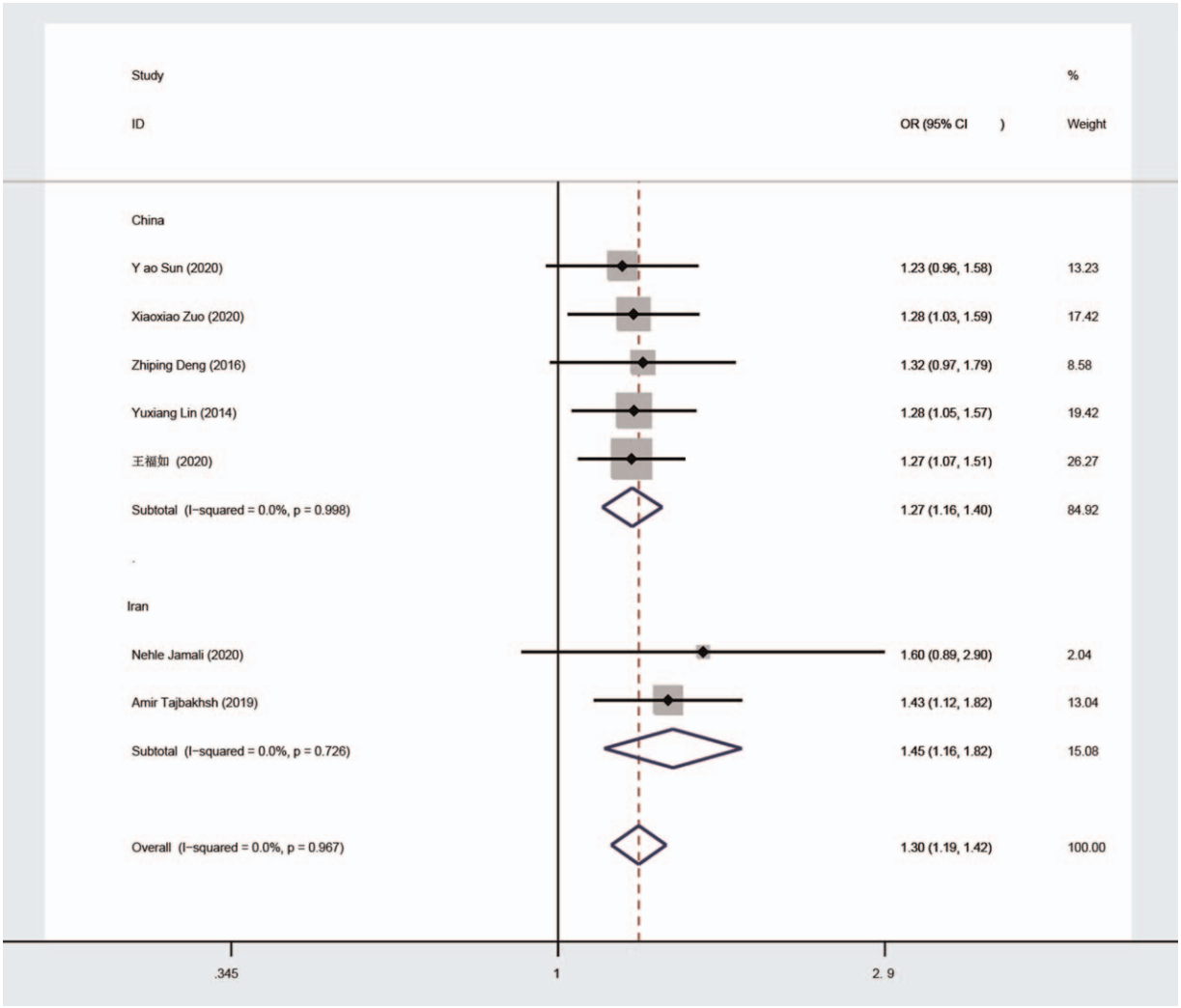

Figure 3. Eliminate a paper with heterogeneity.

Iranian population, 2 studies were included with a total of 612 cases and 658 controls. According to results from the dominant model (OR = 1.455, 95% CI = 1.163–1.820, $P = .001$), the recessive model (OR = 1.897, 95% CI = 1.365–2.636, $P < .001$), the allele (OR = 1.444, 95%CI = 1.225–1.702, $P < .001$), and the hyperdominant model (OR = 0.933, 95%CI = 0.746–1.166, $P < .54$), rs4784227 was significantly associated with breast cancer susceptibility, suggesting that the polymorphism of rs4784227 locus of *CASC16* gene may be a risk factor for breast cancer.

3.5. Sensitivity analysis

Sensitivity analysis was used to assess the impact of individual studies on the pooled results. Removing any of the studies had no significant effect on the results, indicating that the results were statistically stable and reliable.

Table 2

Association of rs4784227 polymorphism in *CASC16* gene with breast cancer risk.

		Sample size		Dominant model				Recessive model				Allelic model				Over-dominant model			
SNPs	Number of study	case	control	OR (95% CI)	I^2 (%)	P_H	P_Z	OR (95% CI)	I^2 (%)	P_H	P_Z	OR (95% CI)	I^2 (%)	P_H	P_Z	OR (95% CI)	I^2 (%)	P_H	P_Z
rs4784227																			
Total	7	4055	4229	1.301 (1.190–1.423)	0.0	.998	<.001	1.431 (1.216–1.685)	45.60%	0.088	<0.001	1.257 (1.172–1.348)	0.0	.424	<.001	0.852 (0.778–0.933)	0.0	.491	.001
China	5	3443	3571	1.274 (1.155–1.404)	0.0	.726	<.001	1.303 (1.079–1.572)	0.00%	0.769	0.006	1.219 (1.128–1.317)	0.0	.995	<.001	0.837 (0.758–0.924)	0.0	.914	<.001
Iran	2	612	658	1.455 (1.163–1.820)	0.0	.726	.001	1.897 (1.365–2.636)	84.20%	0.012	<0.001	1.444 (1.225–1.702)	59.5	.116	<.001	0.933 (0.746–1.166)	73.0	.054	.54

M/m*: major/minor allele

Genotype presented as wild type/heterozygous/homozygous; –, not available; 95% CI = 95% confidence interval, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa quality assessment scale, OR = odds ratio, SNPs = single nucleotide polymorphisms.

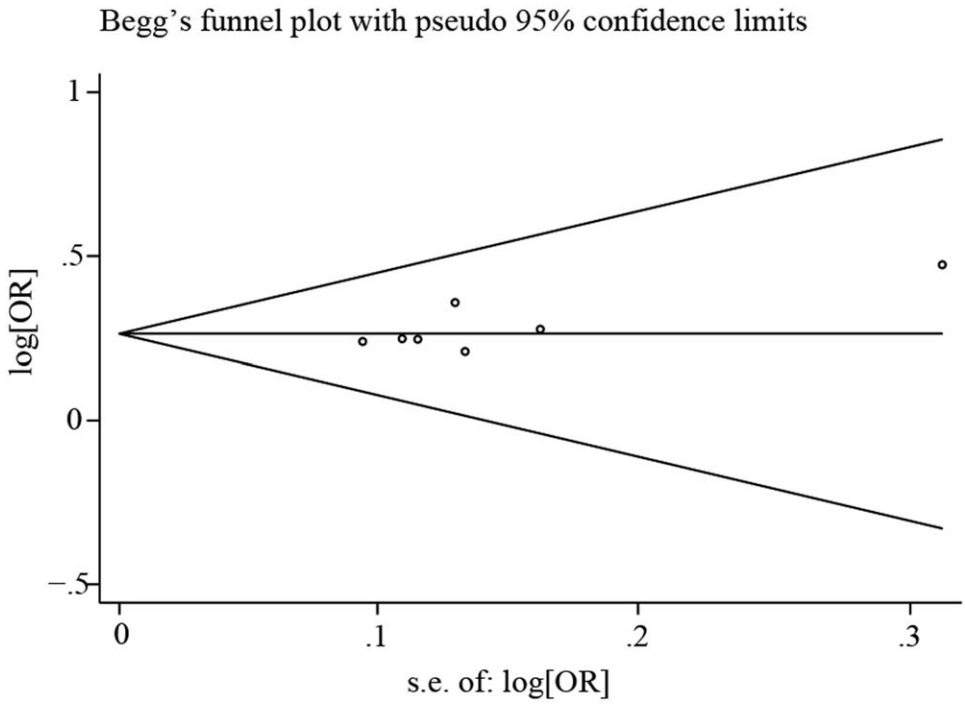

Figure 4. Publication bias analysis of included literatures.

3.6. Publication bias

Begg funnel plot and Egger regression asymmetry test were used to evaluate publication bias. No publication bias was found in the dominant model ($P > .05$), as shown in Figure 4.

4. Discussion

Breast cancer has replaced lung cancer as the world's leading cancer, according to the latest data on the global cancer burden for 2020 released by International Agency for Research on Cancer. Behind the increasing incidence rate of breast cancer, Single nucleotide polymorphisms are a major factor for the occurrence of cancer, accounting for 27% of the total risk of breast cancer.[29]

CASC16 is mainly expressed in the brain, but studies have shown high CASC16 expression in tumor tissues. It induces transcription of the estrogen response (ER) and Bcl-2.[7,8] To date, studies have shown contradictory results in terms of the association of *CASC16* rs4784227 with breast cancer susceptibility.[22] In this meta-analysis, a total of 7 studies were included, including 4055 cases and 4229 controls. The results of combination and subgroup analysis from dominant model, recessive model, allele model and over-dominant model were statistically significant. These results suggest that gene polymorphism at rs4784227 of *CASC16* gene may increase the risk of breast cancer, which is consistent with the research results of Zheng et al.[10,16] The study by Ali et al is the source of heterogeneity. This heterogeneity may be due to the relatively small sample size of the study, the genetic differences among different regions and nationalities, and the other possibility is the difference of linkage imbalance, so this study was not included in the final meta-analysis.

Single nucleotide polymorphisms in related risk genes are one of the important causes of disease susceptibility. In recent years, the association between *CASC16* rs4784227 C>T gene polymorphism and the risk of breast cancer has been increasingly studied.[3] For example, Udler et al found that rs4784227 polymorphism was associated with the expression of Retinoblastoma-like protein 2 protein, increasing the risk of breast cancer.[30] Meyer et al found that rs4782447 could lead to changes in FOXA1-binding sequence, which may increase its affinity and thus enhance the binding of *FOXA1* to *CASC16* gene promoter. In various in vitro experiments, this SNP has been identified as a functional genetic risk mutation site for breast cancer.[31,32] Zou et al found that rs4784227 was associated with an increased risk of lymph node metastasis in individuals with breast cancer.[26] RS4784227 is enriched in *FOXA1* and regulates the affinity between chromatin and FOXA1 on the distal regulatory elements, leading to changes in the ability of FOXA1 to bind DNA. The binding site of *FOXA1* can form chromatin rings with the promoter of *CASC16* gene, and alterations in FOXA1-binding DNA sequence will directly affect the expression of *CASC16* gene.[22,32]*CASC16* is a nuclear protein chromatin structure that can be modified,[33] and its high expression can affect the methylation of breast cancer 1 promoter, resulting in the reduction of breast cancer 1expression, thus improving proliferation, invasion, and survival ability of breast cancer cells in vivo.[34] Therefore, we predict that rs4784227 C>T gene polymorphism changes the affinity between *FOXA1* and *CASC16* promoter, thereby promoting the high expression of *CASC16* and accelerating lymph node metastasis of breast cancer.

In general, genetic polymorphisms at rs4784227 of *CASC16* gene are associated with risk of breast cancer. However, the biological mechanism by which rs4784227 is involved in the

occurrence of breast cancer is still unclear. More functional studies may help to increase our understanding of the biological characteristics of breast cancer. This study has certain limitations, the sample size is not large enough and only studies from China and Iran were included, thus our study fails to answer whether there is a similar association of rs4784227 with breast cancer susceptibility in patients with other ethnicities. In addition, the impact of lifestyle, environmental exposures, and other diseases on the results could not be assessed.

Author contributions

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Writing – original draft: Xiong-Shun Liang.
Writing – review & editing: Xiong-Shun Liang, Wen-Xu Hong.

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