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Association between miR-27a rs895819 polymorphism and breast cancer susceptibility

Evidence based on 6118 cases and 7042 controls

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Abstract

Background: Polymorphism in miR-27a rs895819 has been associated with breast cancer (BC) risk, but studies have reported inconsistent results. This meta-analysis investigated the possible association between miR-27a rs895819 polymorphism and BC risk.

Methods: PubMed, EMBASE, Google Scholar, and the Chinese National Knowledge Infrastructure (CNKI) databases were systematically searched to identify relevant studies in English and Chinese. Meta-analyses were performed to examine the association between miR-27a rs895819 and BC susceptibility.

Results: A total of 16 case–control studies involving 6118 cases and 7042 controls were included. Analysis using five genetic models suggested no significant association between miR-27a rs895819 polymorphism and BC risk in the total population, or specifically in Asian or Chinese subpopulations. In the Caucasian subpopulation, however, the G-allele and AG genotype at rs895819 were significantly associated with decreased BC risk according to the allelic model (OR 0.90, 95% CI 0.84–0.97, $P = .004$) and heterozygous model (OR 0.89, 95% CI 0.81–089, $P = .02$), while the wild-type AA genotype was significantly associated with increased BC risk according to the dominant model (OR 1.13, 95% CI 1.03–1.24, $P = .007$).

Conclusion: These results indicate that among Caucasians, the wild-type AA genotype at rs895819 may confer increased susceptibility to BC, while the G-allele and AG genotype may be protective factors. These conclusions should be verified in large, well-designed studies.

Abbreviations: ARMS = amplification refractory mutation system, BC = breast cancer, HB = hospital-based control group, HRM = high-resolution melting, HWE = Hardy-Weinberg equilibrium, miRNA = microRNA, OR = odds ratio; 95%CI, 95% confidence interval, PB = population-based control group, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.

Keywords: miR-27, polymorphism, breast cancer, meta-analysis

1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of cancer death among females. Based on GLOBOCAN, ~2.1 million women were newly diagnosed with BC in 2018, accounting for almost 1 in 4 cancer cases among women.[1] Causes of sporadic BC are not yet clearly understood, and it is regarded as the more complex form of the disease.

MicroRNAs (miRNAs) are short, noncoding RNA molecules 18 to 25 nucleotides long. A single miRNA can bind to as many as 200 gene targets, and miRNAs are involved in various physiological and pathological cellular pathways, such as acute lymphoblastic leukemia, liver cancer, lung cancer, and BC development.[2–5] Altogether miRNAs may regulate the expression of approximately one third of protein-coding mRNAs.

The miR-27a is a 78-bp oncogenic miRNA located on chromosome 19, extending from nucleotide 13,836,440 to 13,836,517 (locus 19q13.13). A common polymorphism (rs895819) has been found in the coding genome site of the miR-27a, and it has been associated with many cancers, including BC.[6] Numerous studies[7–22] have suggested an association between miR-27a rs895819 polymorphism and BC, but those relatively small studies have reported inconsistent results about

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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this association. Therefore, we conducted the present meta-analysis including 16 case–control studies involving 6118 cases and 7042 controls to evaluate the possible association between the miR-27a rs895819 polymorphism and BC risk. To the best of our knowledge, this is the largest meta-analysis so far to investigate miR-27a rs895819 polymorphism and BC risk.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of First Affiliated Hospital of Guangxi Medical University.

2.2. Search strategy

All clinical and experimental case–control studies of miR-27a rs895819 polymorphism and BC risk published in English and Chinese through August 12, 2020 were identified through systematic searches in PubMed, EMBASE, Google Scholar, and the Chinese National Knowledge Infrastructure (CNKI) databases. The search terms used were: *microRNA-27a; miRNA-27a; miR-27a, rs895819*; these four terms in combination with *polymorphism, polymorphisms, SNP, variant, variants, variation, genotype, genetic* or *mutation*; and all the above terms in combination with *breast cancer*. Reference lists in identified articles and reviews were also searched manually to identify additional eligible studies.

2.3. Inclusion criteria

To be included in our review and meta-analysis, studies had to

use a case–control design to assess the association between the miR-27a rs895819 polymorphism and BC risk,
be available as full-text articles and report sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI), report genotype frequencies, and
be conducted in humans.

Studies were excluded if they

1. were duplicates,
2. were irrelevant to BC or the miR-27a rs895819 polymorphism,
3. did not report genotype distributions among groups, or
4. were meta-analyses.

2.4. Data extraction

Two authors (YL and YFG) independently extracted the following data from included studies: first author's family name, year of publication, ethnicity, type of BC, testing methods, P value for HWE in controls, source of the control group (hospital- or population-based), sample size, matched clinical and pathological parameters, numbers and genotypes of cases and controls, as well as frequencies of genotypes in cases and controls. Discrepancies were resolved by consensus. Only those studies that met the predetermined inclusion criteria were included.

2.4.1. Assessment of methodological quality. To assess the quality of the studies included in this analysis, the Newcastle–Ottawa Scale was applied independently by two assessors (WYL and YQZ).[23] On this scale, a full score is 9 stars, and scores of 5 to 9 stars are considered to be of generally high methodological quality, while scores of 0 to 4 stars are considered to be of poor quality.[24] The quality of all included studies is summarized in Table 2. Any disagreements about scoring were resolved through comprehensive reassessment by the other authors. Only high-quality studies were included in our meta-analysis.

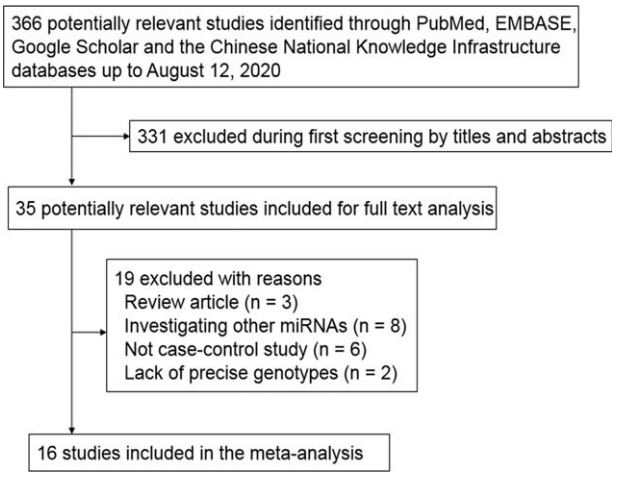

Figure 1. Flowchart showing search strategies, selection criteria, and included studies.

2.5. Description of studies

Search and selection criteria are shown in a flow diagram (Fig. 1). A total of 366 potentially relevant publications up to August 12, 2020 were systematically identified in PubMed, EMBASE, Google Scholar, and CNKI databases. We excluded 331 studies during initial screening of titles and abstracts. Nine studies (3 reviews and 6 studies) were excluded because they were not case-control studies. Another 2 articles were excluded because they did not report precise genotypes. Eight articles were excluded because they investigated polymorphisms in other miRNAs. Therefore, 16 remaining studies[7–22] were included in this meta-analysis based on our search strategy and inclusion criteria. Their characteristics and genotype distributions are summarized in Tables 1 and 2. The distribution of genotypes in controls was consistent with Hardy–Weinberg equilibrium ($P > .05$) in all but one study.[19] The overall quality of the included studies was high, with a mean score of 6.56 stars on the Newcastle–Ottawa Scale (Table 3).

2.6. Statistical analysis

The unadjusted OR with 95% CI was used to assess the strength of the association between miR-27a rs895819 polymorphism and BC risk based on the genotype frequencies in cases and controls. The significance of pooled ORs was determined using the Z test, with $P < .05$ defined as the significance threshold. Meta-analysis was conducted using a fixed-effect model when $P > .10$ for the Q test, indicating lack of heterogeneity among studies; otherwise, a random-effect model was used. All statistical tests for meta-analysis were performed using Review Manager 5.2 (Cochrane Collaboration).

Publication bias was assessed using Begg's funnel plot and Egger's weighted regression, with $P < .05$ considered statistically

Table 1

Characteristics of studies included in the meta-analysis.

First author	Year	Ethnicity	Country	Type of breast cancer	Testing method	*P* for HWE	Control source	Sample size (n)		Matched parameters
								Cases	Controls	
Hoffman[7]	2009	Caucasian	USA	–	MassArray	.654	HB	434	477	Benign breast disease
Kontorovich[8]	2010	Caucasian	Israel	–	MassArray	.905	HB	132	149	BRCA+
Yang[9]	2010	Caucasian	German	Familial, BRCA-	Sequencing	.142	PB	1189	1416	Age, residence
Zhang[10]	2011	Asian	China	–	MassArray	.605	PB	376	190	Undetermined
Zhang[11]	2012	Asian	China	–	PCR-RFLP	.122	PB	245	243	Age, sex, residence
Catucci[12]	2012	Caucasian	Italy	Familial, BRCA-	TaqMan	.051	PB	1025	1593	Age
Ma[13]	2013	Asian	China	–	MassArray	.605	HB	189	190	Age
Zhang[14]	2013	Asian	China	Sporadic	Sequencing+Syber	.446	HB	264	255	Age, sex, residence
Wang[15]	2014	Asian	China	–	PCR-RFLP	.537	HB	107	219	Undetermined
He[16]	2015	Asian	China	–	MassArray	.839	PB	450	450	Age
Qi[17]	2015	Asian	China	–	TaqMan	.141	PB	321	290	Age, sex, residence
Zhang[18]	2015	Asian	China	–	MassArray	.605	PB	376	190	Undetermined
Morales[19]	2016	Caucasian	Chile	Familial/Sporadic, BRCA-	TaqMan	.016	PB	440	807	Age, socioeconomic
Nguyen[20]	2016	Asian	Vietnam	–	HRM	.204	HB	97	100	Undetermined
Shekari[21]	2017	Asian	Iran	–	PCR-RFLP	.728	HB	120	120	Undetermined
Mashayekhi[22]	2018	Asian	Iran	–	Tetra-primers ARMS	.063	HB	353	353	Age, sex, BMI

ARMS = amplification refractory mutation system, BMI = body mass index, BRCA = breast cancer susceptibility genes, HB = hospital-based control group, HRM = high-resolution melting, PB = population-based control group, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.

significant. These tests were performed using Stata 12.0 (Stata Corp, College Station, TX).

3. Results

3.1. Quantitative data synthesis

The overall results are summarized in Table 4. On the basis of 6118 cases and 7042 controls from 16 studies,[7–22] none of the five genetic models indicated a significant association between the rs895819 polymorphism and BC risk according to any genetic model: allelic model, OR 0.92, 95% CI 0.84 to 1.00, $P=.05$; recessive model, OR 0.88, 95% CI 0.65 to 1.46, $P=.91$; dominant model, OR 1.09, 95% CI 0.97 to 1.23, $P=.14$; homozygous model, OR 0.87, 95% CI 0.73 to 1.04, $P=.12$; heterozygous model, OR 0.92, 95% CI 0.82 to 1.05, $P=.21$.

We also meta-analyzed the subgroup of 11 studies[10,11,13–18,20–22] with 2898 cases and 2600 controls from Asian populations. The results showed no evidence of a significant association between rs895819 polymorphism and BC risk for any of the five genetic models (Table 4): allelic model, OR 0.92, 95% CI 0.80 to 1.05, $P=.22$; recessive model, OR 0.86, 95% CI 0.67 to 1.12, $P=.27$; dominant model, OR 1.08, 95% CI 0.90 to 1.31, $P=.41$; homozygous model, OR 0.88, 95% CI 0.66 to 1.16, $P=.36$; or heterozygous model, OR 0.91, 95% CI 0.75 to 1.12, $P=.39$.

We also meta-analyzed the subgroup of 8 studies[10,11,13–18] involving 2328 cases and 2027 controls from the Chinese population. The results showed no evidence of a significant association between rs895819 polymorphism and BC risk for any of the five genetic models (Table 4): allelic model, OR 0.98,

Table 2

Genotype distributions of miR-27a rs895819.

First author	Year	Ethnicity	Country	Sample size (cases/controls)	No. of cases			Allele frequencies in cases		No. of controls			Allele frequencies in controls	
					AA	AG	GG	A	G	AA	AG	GG	A	G
Hoffman[7]	2009	Caucasian	USA	434/477	184	200	50	568	300	220	211	46	651	303
Kontorovich[8]	2010	Caucasian	Israel	132/149	98	78	11	274	100	101	82	15	284	112
Yang[9]	2010	Caucasian	German	1189/1416	576	486	127	1638	740	605	660	151	1870	962
Zhang[10]	2011	Asian	China	376/190	196	150	30	542	210	106	70	14	282	98
Zhang[11]	2012	Asian	China	245/243	60	144	41	264	226	75	109	59	259	227
Catucci[12]	2012	Caucasian	Italy	1025/1593	547	388	90	1432	518	803	633	157	2239	947
Ma[13]	2013	Asian	China	189/190	97	76	16	270	108	106	70	14	282	98
Zhang[14]	2013	Asian	China	264/255	152	96	16	400	128	137	103	15	377	133
Wang[15]	2014	Asian	China	107/219	78	18	11	174	40	129	76	14	334	104
He[16]	2015	Asian	China	450/450	251	165	34	667	233	232	181	37	645	255
Qi[17]	2015	Asian	China	321/290	101	159	61	361	281	95	139	56	329	251
Zhang[18]	2015	Asian	China	376/190	196	150	30	542	210	106	70	14	282	98
Morales[19]	2016	Caucasian	Chile	440/807	245	166	29	656	224	432	298	77	1162	452
Nguyen[20]	2016	Asian	Vietnam	97/100	40	45	12	125	69	49	38	13	136	64
Shekari[21]	2017	Asian	Iran	120/120	78	34	8	190	50	58	52	10	168	72
Mashayekhi[22]	2018	Asian	Iran	353/353	167	156	30	490	216	127	155	71	409	297

HWE = Hardy–Weinberg equilibrium.

Table 3

Methodological quality of studies included in the final analysis, based on the Newcastle–Ottawa Scale for assessing the quality of case–control studies.

	Selection (score)				Comparability (score)	Exposure (score)			
Study	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate*	Total Score†
Hoffman[7]	1	1	0	1	1	0	1	1	6
Kontorovich[8]	1	1	0	1	1	0	1	1	6
Yang[9]	1	1	1	1	2	0	1	1	8
Zhang[10]	1	1	1	1	0	0	1	1	6
Zhang[11]	1	1	1	1	2	0	1	1	8
Catucci[12]	1	1	1	1	1	0	1	1	7
Ma[13]	1	1	0	1	1	0	1	1	6
Zhang[14]	1	1	0	1	2	0	1	1	7
Wang[15]	1	1	0	1	0	0	1	1	5
He[16]	1	1	1	1	1	0	1	1	7
Qi[17]	1	1	1	1	2	0	1	1	8
Zhang[18]	1	1	1	1	0	0	1	1	6
Morales[19]	1	1	1	1	2	0	1	1	8
Nguyen[20]	1	1	0	1	0	0	1	1	5
Shekari[21]	1	1	0	1	0	0	1	1	5
Mashayekhi[22]	1	1	0	1	2	0	1	1	7

* One point was awarded when there was no significant difference in the response rate between the two groups based on a chi-squared test ($P > .05$).

† Total score was calculated by adding up the points awarded for each item.

95% CI 0.90 to 1.08, $P = .74$; recessive model, OR 0.94, 95% CI 0.77 to 1.15, $P = .57$; dominant model, OR 1.00, 95% CI 0.84 to 1.19, $P = .99$; homozygous model, OR 1.01, 95% CI 0.82 to 1.25, $P = .91$; heterozygous model, OR 0.96, 95% CI 0.76 to 1.20, $P = .70$.

Lastly, we meta-analyzed the subgroup of 3220 cases and 4442 controls in 5 studies[7–9,12,19] from Caucasian populations. The results showed that the G-allele and the AG genotype of rs895819 were both significantly associated with decreased BC risk according to the allelic model (OR 0.90, 95% CI 0.84–0.97,

Table 4

Overall meta-analysis of the association between breast cancer and miR-27a polymorphism.

			Heterogeneity of study design			
Genetic model	OR [95% CI]	*Z* (*P*)	c2	df (*P*)	I^2 (%)	Analysis model
miR-27a rs895819 in total population from 16 case control studies (6118 cases and 7042 controls)						
Allelic model (G-allele vs A-allele)	0.92 [0.84, 1.00]	1.95 (.05)	32.77	15 (.005)	54	Random
Recessive model (GG vs. AG+AA)	0.88 [0.74, 1.03]	1.56 (.12)	25.30	15 (.05)	41	Random
Dominant model (AA vs. AG+GG)	1.09 [0.97, 1.23]	1.49 (.14)	35.02	15 (.002)	57	Random
Homozygous model (GG vs AA)	0.87 [0.73, 1.04]	1.57 (.12)	25.40	15 (.04)	41	Random
Heterozygous model (AG vs AA)	0.92 [0.82, 1.05]	1.25 (.21)	35.45	15 (.002)	58	Random
miR-27a rs895819 in Asian population from 11 case–control studies (2898 cases and 2600 controls)						
Allelic model (G-allele vs A-allele)	0.92 [0.80, 1.05]	1.23 (.22)	26.46	10 (.003)	62	Random
Recessive model (GG vs AG + AA)	0.86 [0.67, 1.12]	1.11 (.27)	19.81	10 (.03)	50	Random
Dominant model (AA vs AG + GG)	1.08 [0.90, 1.31]	0.82 (.41)	28.02	10 (.002)	64	Random
Homozygous model (GG vs AA)	0.88 [0.66, 1.16]	0.91 (.36)	20.64	10 (.02)	52	Random
Heterozygous model (AG vs AA)	0.91 [0.75, 1.12]	0.86 (.39)	28.70	10 (.001)	65	Random
miR-27a rs895819 in Chinese population from 8 case–control studies (2328 cases and 2027 controls)						
Allelic model (G-allele vs A-allele)	0.98 [0.90, 1.08]	0.33 (.74)	5.81	7 (.56)	0	Fixed
Recessive model (GG vs AG + AA)	0.94 [0.77, 1.15]	0.56 (.57)	5.88	7 (.55)	0	Fixed
Dominant model (AA vs AG + GG)	1.00 [0.84, 1.19]	0.01 (.99)	13.08	7 (.07)	46	Random
Homozygous model (GG vs AA)	1.01 [0.82, 1.25]	0.11 (.91)	1.76	7 (.97)	0	Fixed
Heterozygous model (AG vs AA)	0.96 [0.76, 1.20]	0.38 (.70)	19.62	7 (.006)	64	Random
miR-27a rs895819 in Caucasian population from 5 case–control studies (3220 cases and 4442 controls)						
Allelic model (G-allele vs A-allele)	0.90 [0.84, 0.97]	2.85 (.004)	6.30	4 (.18)	37	Fixed
Recessive model (GG vs AG + AA)	0.93 [0.80, 1.08]	0.93 (.35)	4.30	4 (.37)	7	Fixed
Dominant model (AA vs AG + GG)	1.13 [1.03, 1.24]	2.69 (.007)	6.67	4 (.15)	40	Fixed
Homozygous model (GG vs AA)	0.88 [0.75, 1.03]	1.63 (.10)	4.64	4 (.33)	14	Fixed
Heterozygous model (AG vs AA)	0.89 [0.81, 0.98]	2.29 (.02)	6.62	4 (.16)	40	Fixed

95% CI = 95% confidence interval, OR = odds ratio.

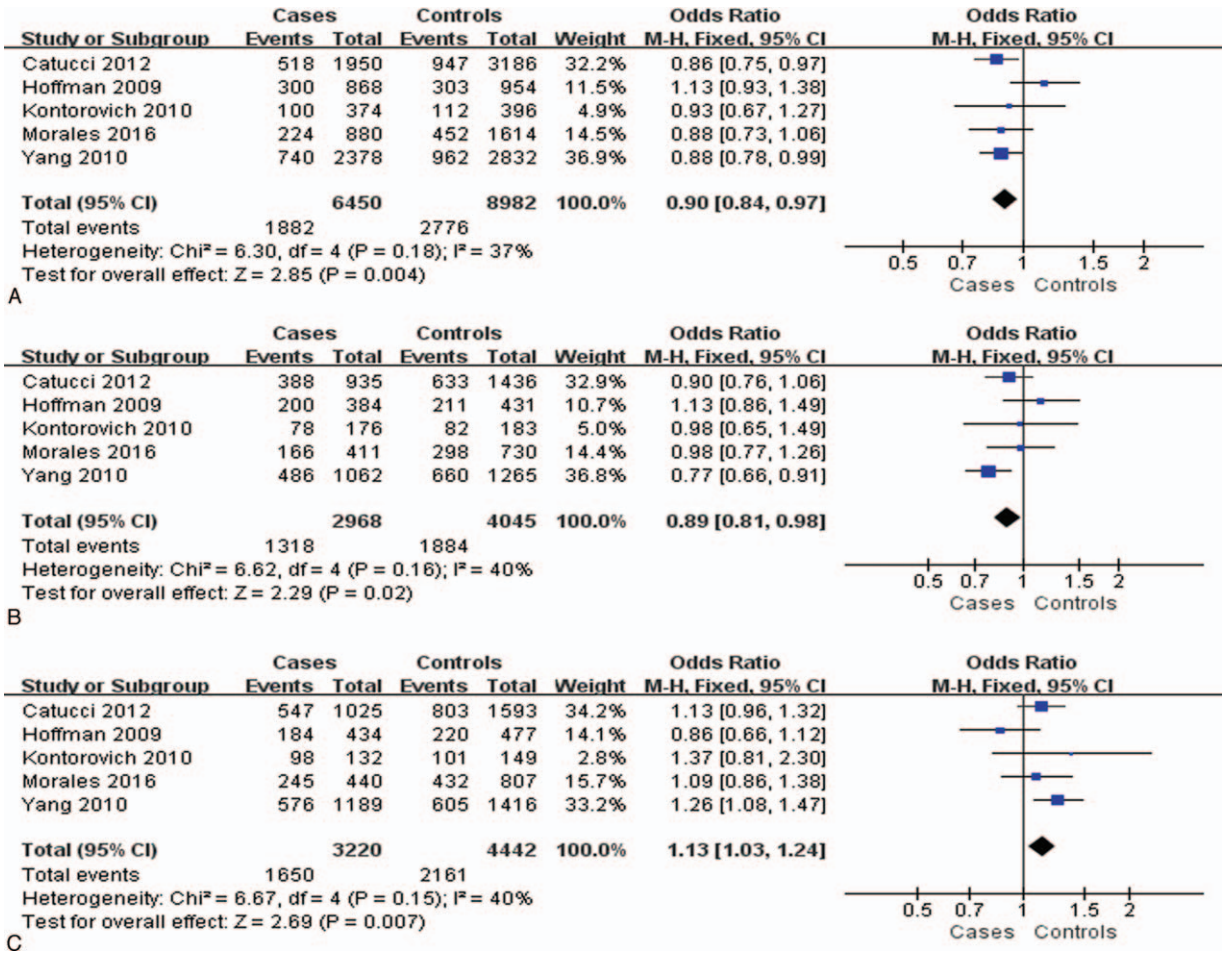

Figure 2. Forest plot showing the association between miR-27a rs895819 polymorphism and breast cancer risk in the Caucasian population, according to different genetic models: (A) allelic (G-allele vs A-allele), (B) dominant (AA vs AG+GG genotypes), and (C) heterozygous (AG vs AA genotypes).

P=.004, Fig. 2A) and heterozygous model (OR 0.89, 95% CI 0.81–089, P=.02, Fig. 2B). The wild-type AA genotype was significantly associated with increased BC risk according to the dominant model (OR 1.13, 95% CI 1.03–1.24, P=.007, Fig. 2C).

3.2. Publication bias

Begg's funnel plot and Egger's test were performed to detect potential publication bias in this meta-analysis. No obvious asymmetry was observed in any of the five genetic models based on funnel plots (Fig. 3) or Egger's test (Fig. 4), suggesting no significant publication bias.

4. Discussion

Although several meta-analyses have recently been conducted to explore the association between miR-27a rs895819 polymorphism and BC risk, the results have been inconsistent largely because of limited sample size and ethnic differences among the various populations.[25–27] Therefore, we performed a meta-analysis of all eligible studies in order to provide a more precise assessment of the association between miR-27a rs895819 polymorphism and BC risk. Our meta-analysis suggests that among Caucasians, the wild-type AA genotype at rs895819 may confer increased susceptibility to BC, while the AG genotype may be a protective factor.

A previous meta-analysis by Chen et al[25] involving 8 case–control studies with 3697 cases and 5013 controls found that the G-allele at rs895819 was significantly associated with decreased

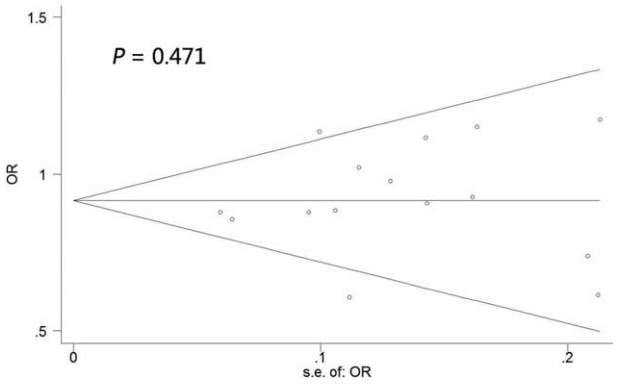

Figure 3. Begg's funnel plot to assess publication bias according to the allelic model (G-allele vs A-allele).

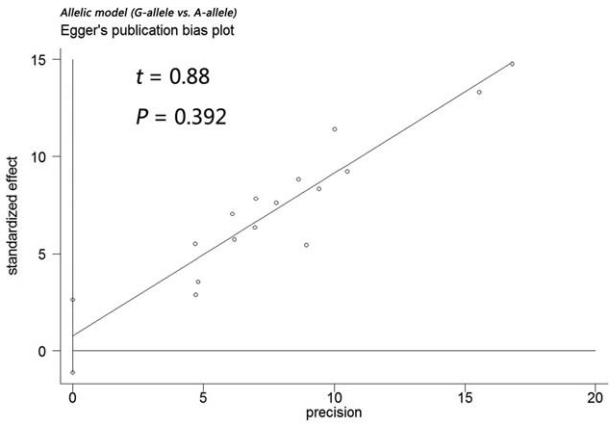

Figure 4. Egger's test to assess publication bias according to the allelic model (G-allele vs A-allele).

BC risk in the total population. Another recent meta-analysis by Zhang et al[26] including 9 case–control studies with 4191 cases and 4776 controls found that rs895819 could decrease BC risk according to the allele contrast and dominant models in the total population. In addition, a meta-analysis by Wu et al[27] including 9 case–control studies with 4499 cases and 5434 controls found that the G-allele at rs895819 is likely associated with decreased BC risk, mainly in Caucasians. A total of 11 case–control studies were included in the three meta-analyses mentioned above.[25–27] In addition to these studies, the present meta-analysis contained another 5 case–control studies,[7,8,20–22] giving a total of 16 case–control studies[7–22] involving 6118 cases and 7042 controls.

In contrast to the three previous meta-analyses,[25–27] our work showed no significant association between rs895819 polymorphism and BC risk in the total population or in Asian or Chinese subpopulations. Significant associations were, however, observed in the Caucasian subpopulation, in agreement with the meta-analysis by Wu et al.[27] We found that not only the G-allele but also the AG genotype at rs895819 decreased BC risk in Caucasians, while the wild-type AA genotype may confer increased susceptibility to BC in that ethnic group. It is possible that larger samples would allow identification of additional significant correlations.

While the current meta-analysis, to the best of our knowledge, is the largest so far to investigate the possible association between the miR-27a rs895819 polymorphism and BC risk, it is limited by the designs of the included studies. First, the *P* value for HWE in one study[19] was $<.05$, suggesting that study population may not be representative of the broader population. Second, BC risk may be affected by age, menopausal status, expression of triple antigen (ER, PR, and Her2), environmental exposure, and other factors, but most studies did not report data on those factors, making it impossible to include them in the present meta-analysis. Third, our exclusion of unpublished data and of papers published in languages other than English or Chinese may have biased our results. Fourth, the studies may show performance bias, attrition bias and reporting bias, although Newcastle-Ottawa scores were at least 5 for all 14 studies, indicating high quality. Thus, additional large and well-designed studies are warranted. Fifth, the studies that we analyzed from different regions of the world likely included mostly members of majority ethnic groups, such as Han in China, so whether our results can be generalized to ethnic minorities should be addressed in future work.

Despite these limitations, the present large meta-analysis provides strong evidence that in the Caucasian population, the wild-type AA genotype at rs895819 may confer increased susceptibility to BC, while the G-allele and AG genotype at rs895819 may be protective factors. These conclusions should be verified in large, well-designed studies.

Author contributions

Data curation: Yi-Fei Gui, Xiao-Bin Zhang, Yan-Ping Huang, Feng-Ming Wu, Zhen Huang.
Formal analysis: Wen-Yong Liao, Feng-Ming Wu, Zhen Huang.
Methodology: Yu-Qin Zhang.
Writing – original draft: Yuan Liu.
Writing – review & editing: Yuan Liu, Yun-Fei Lu.

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