RESEARCH ARTICLE

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Comprehensive Meta-Analysis of 28 miRNA-SNPs Reveals First Pooled Evidence for Five Variants Associated with Breast Cancer Susceptibility

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Abstract

Background: MicroRNA-related single nucleotide polymorphisms (miRNA-SNPs) influence post-transcriptional gene regulation and may contribute to breast cancer susceptibility. Individual case–control studies have evaluated several miRNA-SNPs, but there is limited or no pooled evidence available for many variants. **Objective:** This study aimed to conduct a comprehensive meta-analysis of miRNA-SNPs and their associations with breast cancer risk, including novel variants not previously examined in pooled analyses. **Methods:** A systematic search of PubMed, Scopus, Web of Science, and Google Scholar up to July 2024 identified eligible case–control studies. Fifty-eight studies involving 28 miRNA-SNPs were included. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated under multiple genetic models. Subgroup analyses were conducted using population and genotyping methods. Heterogeneity was explored using meta-regression, and robustness was assessed via leave-one-out sensitivity analyses. **Result:** Five previously established SNPs-rs11614913, rs895819, rs3746444, rs2910164, and rs2043556 showed significant associations with breast cancer risk. Additionally, five novel variants rs1053872, rs2018562, rs5750504, rs2682818, and rs353291-were identified as significantly associated for the first time. These SNPs are functionally linked to PI3K/AKT, NF-κB, and EGFR signaling pathways. The genotyping method was the major contributor to heterogeneity (R^2 = 41.16%). Population-specific associations were observed, with rs2910164 significant across four continents. Most associations were stable in sensitivity analyses. **Conclusion:** This meta-analysis is the first to provide pooled evidence for five novel miRNA-SNPs associated with breast cancer susceptibility. The findings confirm key genetic variants and reveal new population-specific markers that may inform polygenic risk models and precision prevention strategies.

Keywords: Genetic Predisposition to Disease- Single Nucleotide Polymorphism- MicroRNAs- Meta-Analysis

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Introduction

The discovery of microRNAs (miRNAs), a class of small non-coding RNAs that regulate gene expression post-transcriptionally, has revolutionized our understanding of gene regulation in both physiological and pathological contexts [1-3]. By binding to target messenger RNAs (mRNAs), miRNAs can repress translation or promote degradation, thereby modulating critical biological processes such as cell proliferation, apoptosis, differentiation, and immune responses [2-4]. Dysregulation of miRNA expression is now recognized as a hallmark of various cancers, including breast cancer, where specific miRNAs have been identified as potential biomarkers for diagnosis, prognosis, and therapeutic response prediction [4, 5].

Single nucleotide polymorphisms (SNPs) occurring within miRNA genes, including pri-, pre-, or mature-miRNA sequences, can influence miRNA biogenesis, stability, or binding affinity to target transcripts [6-8]. These genetic variations may consequently modify the oncogenic or tumor-suppressive potential of miRNAs, altering individual susceptibility to cancer [9]. Numerous primary studies have investigated associations between specific miRNA-SNPs and breast cancer risk across different populations. However, their findings remain inconsistent and often contradictory, possibly due to limited sample sizes, population heterogeneity, and differences in genotyping techniques. For instance, while rs2910164 in miR-146a has been reported as a protective variant in Iranian women [10, 11], other studies found no association in East Asian or European cohorts [12-14].

Although several meta-analyses have been conducted for individual miRNA-SNPs, a comprehensive and updated synthesis of all key miRNA-SNPs with sufficient data is lacking. Moreover, most existing meta-analyses

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focus on a few SNPs [15-19] and do not systematically evaluate the impact of study-level factors, such as ethnicity or genotyping method, on study outcomes and heterogeneity. Importantly, with recent advances in genotyping and population-scale studies, several SNPs previously understudied or absent in earlier reviews now have sufficient data for pooled analysis. Additionally, new statistical tools allow us to assess heterogeneity and robustness more thoroughly through meta-regression and sensitivity analysis.

This study addresses these gaps by conducting the most extensive meta-analysis to date of miRNA-SNPs and breast cancer risk, integrating data from 58 studies involving 28 SNPs across diverse populations, including Asian, European, American, Australian, and African. Unlike prior reviews that focused on a few well-known variants [15-19], we include both widely studied and understudied SNPs to identify novel variants with potential biological relevance. This study synthesizes evidence from observational case–control studies examining the association between miRNA polymorphisms and breast cancer risk. The primary outcome was the association between specific miRNA-SNP genotypes and breast cancer risk, measured by pooled odds ratios (ORs), 95% confidence intervals, and p-values under five genetic models. Furthermore, we apply subgroup and meta-regression analyses to uncover the influence of ethnicity, control source, and genotyping methodology on heterogeneity. Through this comprehensive approach, our goal is to (1) clarify inconsistent findings from the literature, (2) discover new SNPs with significant associations, and (3) provide insights into the methodological factors that may influence genetic association results. We hypothesize that specific miRNA-related SNPs are significantly associated with breast cancer risk and that heterogeneity across studies can be explained by methodological and population-level factors.

These findings are intended to inform future functional studies, enhance the development of miRNA-based diagnostics and screening tools, and ultimately contribute to personalized breast cancer risk prediction and prevention strategies.

Materials and Methods

Literature search

Two investigators trained in systematic review methodology conducted the literature search independently in the PubMed, CrossRef, and Google Scholar databases up to July 2024 using a combination of MeSH terms and free-text keywords. The MeSH terms included: "MicroRNAs" [MeSH], "Polymorphism, Single Nucleotide" [MeSH], "Breast Neoplasms" [MeSH], and "Neoplasms" [MeSH]. Free-text terms used in various combinations included: miRNA, microRNA, miR, SNP, variant, variation, breast, mammary, cancer, carcinoma, and tumor. Furthermore, manual searches were also carried out to locate further articles within the reference lists of the included studies. The search was conducted without using specific bibliographic software and no attempt was made to contact original authors for unpublished data.

Inclusion and exclusion

Studies were eligible for inclusion if they met all of the following criteria: (1) observational case–control design involving human participants; (2) investigation of the association between miRNA-SNPs and breast cancer risk; (3) availability of genotype frequency data sufficient to compute odds ratios (ORs) with 95% confidence intervals; (4) breast cancer cases confirmed by standard clinical or pathological criteria and cancer-free controls; (5) SNPs located within functionally relevant regions of miRNA genes (primary, precursor, or mature sequences); and (6) adequate methodological quality, defined as a Newcastle-Ottawa Scale (NOS) score ≥7.

Studies were excluded if they met one or more of the following criteria

(1) duplicate publications; (2) irrelevant to miRNA-SNPs or not focused on breast cancer; (3) reviews, meta-analyses, letters, meeting abstracts, editorials, or commentaries; (4) full text unavailable or not in English; (5) lack of case–control study design; (6) insufficient genotyping data for effect size estimation; (7) SNPs located outside miRNA-coding or regulatory regions; or(8) low methodological quality (NOS score <7).

Data extraction

Data from eligible studies were independently extracted by two investigators using a standardized data collection form. The extracted variables included first author, year of publication, country of origin, ethnicity, miRNA name, SNP name, SNP location within the miRNA gene, genotyping method, number of cases and controls, and genotype frequencies in both groups. Ethnicity was categorized as Asian or Caucasian, while the control sources were classified as hospital-based (HB) or population-based (PB). Studies employed various genotyping methods, including PCR-RFLP, MassARRAY, TaqMan, Tetra-Arms PCR, HRM, AS-PCR, Sanger sequencing, and Next-Generation Sequencing (NGS). To ensure consistency across studies, extracted data were cross-checked for completeness and accuracy. Any discrepancies between the two investigators were resolved through discussion and, if necessary, consultation with a third investigator.

Methodology quality assessment

The quality of the studies was independently assessed by two authors using the Newcastle-Ottawa Scale (NOS). This scale evaluates research quality based on three criteria: selection of study subjects, comparability of groups, and measurement of exposure factors [20]. The highest possible score for each study is 9, with four points allocated for selection, two for comparability, and three for outcomes [20]. A study was regarded as "low risk of bias" if its score was 7 or higher [20].

Statistical analysis

The study aimed to assess the association between miRNA-SNPs and breast cancer risk using pooled odds

ratios under five genetic models: allelic, homozygous, heterozygous, recessive, and dominant. Statistical significance was determined when the OR 95% CI did not include 1 and p-value < 0.05. Potential confounding factors, such as ethnicity, source of controls, and genotyping method, were addressed through subgroup and meta-regression analyses. Subgroup analyses were conducted to explore potential sources of heterogeneity, stratified by continent. Heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic. Meta-regression analyses were performed using continent, genotyping method, and source of controls as independent variables. The significance of moderators was determined using Q-statistic-based heterogeneity tests, R^2 values, and Tau^2 values. To assess the stability of results, sensitivity analyses were conducted by systematically excluding individual studies and re-estimating pooled ORs. Potential publication bias was evaluated using Egger's regression test when at least three studies were available. All statistical analyses were conducted using R software version 4.1.3, with meta-analyses performed using the "meta" and "metafor" packages.

Results

Study selection

The study selection process, the inclusion and exclusion criteria applied are presented in Figure 1. A total of 2,587 articles were retrieved through database searches. Following the removal of duplicates, 2,306 articles were screened based on titles and abstracts, leading to the exclusion of 2,135 studies that did not meet the inclusion criteria. Subsequently, 171 full-text articles were assessed, with 45 excluded due to the unavailability of full texts, non-English language, absence of a case-control study design, or insufficient genotyping data. Among the 126 eligible studies, 54 were further excluded due to non-specific miRNA SNP identification, SNPs located outside functionally relevant miRNA regions, or low methodological quality (Newcastle-Ottawa Scale (NOS) score <7) (Supplementary Table 1). Ultimately, 58 studies investigating 28 miRNA-SNPs were included in the final meta-analysis.

Study characteristics

The key characteristics of the eligible studies included are shown in Table 1. The included studies covered diverse geographic regions, including Asia, Australia, America, Europe, and Africa, and examined various ethnic populations. Sample sizes varied significantly, with cases ranging from 332 to 8,647 and controls from 305 to 9,971. Various genotyping methodologies were utilized, including PCR-RFLP, MassARRAY, TaqMan, Tetra-Arms PCR, HRM, AS-PCR, Sanger sequencing, and Next-Generation Sequencing (NGS), ensuring robust genetic analysis. The control groups were derived from both population-based (PB) and hospital-based (HB) sources. Detailed characteristics of the studies and 28 SNP distributions are in Supplementary Table 2.

Associations between miRNA-SNPs and breast cancer risk

Among the 28 SNPs analyzed, 10 SNPs demonstrated significant associations with breast cancer risk (Table 2). Two SNPs, rs11614913 and rs895819, were associated with an increased risk of breast cancer, with ORs ranging from 1.072–1.202 and 1.125–1.154, respectively. Conversely, eight SNPs (rs1053872, rs2018562, rs2043556, rs2682818, rs2910164, rs353291, rs3746444, and rs5750504) exhibited protective effects, with ORs ranging from 0.506 to 0.923. The details breast cancer

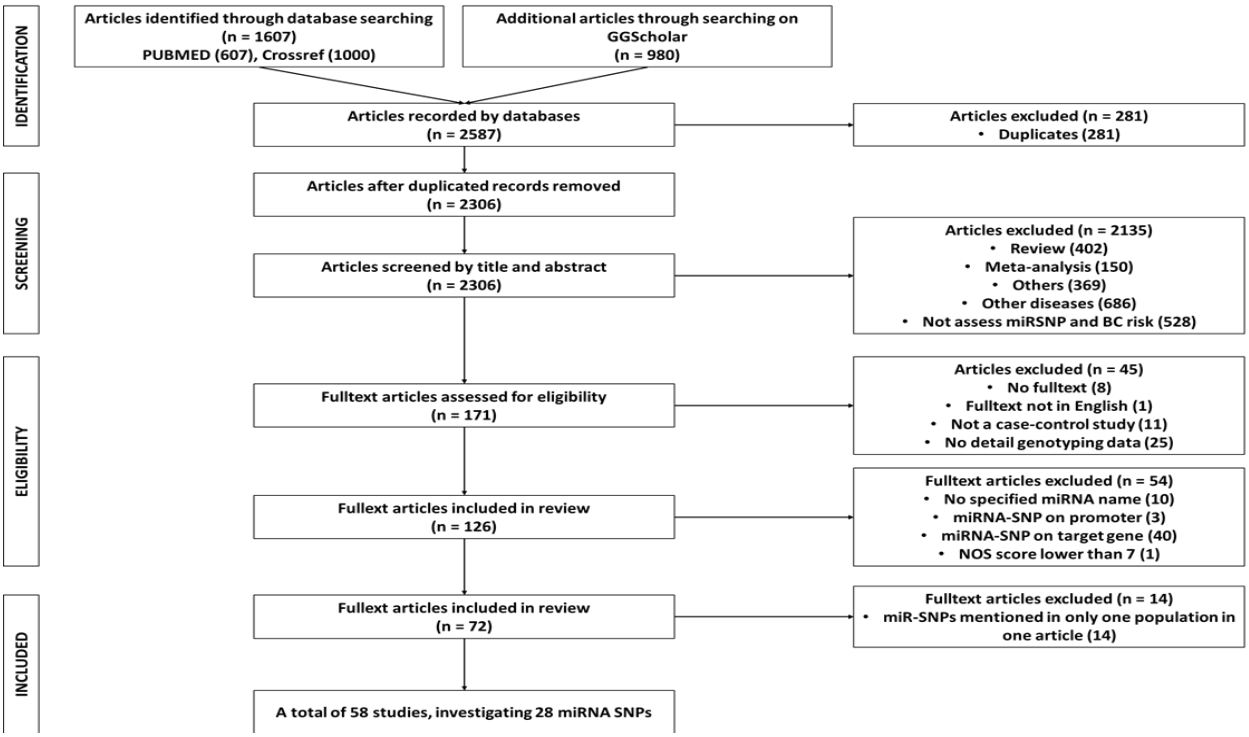

Figure 1. Flow Diagram of Study Selection

associations of 28 miR-SNPs were observed across genetic models and shown in Supplementary Table 3.

Population subgroup analysis

Subgroup analyses were conducted to evaluate population-specific genetic variations in breast cancer risk (Supplementary Table 4 and Table 3). The Asian population exhibited the highest number of significant SNPs, reinforcing the role of genetic susceptibility in this group. The African population showed only one significant SNP (rs6505162), possibly reflecting either lower genetic predisposition or limited study representation. The American population showed three significant SNPs, including rs2910164, rs5750504 and rs2018562. The Australian and European populations exhibited three and five significant SNPs, respectively, highlighting population-specific genetic factors. Four SNPs that are significantly associated with breast cancer risk in multiple populations (Table 3). Notably, rs2910164 is the most widely shared SNP, found in four subgroups, while rs2682818, rs895819, rs712, and rs6505162 are shared among two or three subgroups.

Heterogeneity and meta-regression analysis

Heterogeneity analysis indicated that most SNP models exhibited low or negligible heterogeneity ($I^2 \leq 30\%$, Q p-value > 0.10), suggesting consistency in effect size estimates. However, a subset of SNP models displayed significant heterogeneity ($I^2 > 50\%$, Q p-value < 0.10), necessitating further investigation (Table 2, Supplementary Table 3).

Meta-regression was successfully conducted for the SNPs that satisfied the required conditions, specifically those with at least two levels in the moderator variable and an adequate number of included studies. The number of eligible SNPs was 10 for the continent subgroup, 9 for source of controls, and 10 for genotyping methodology. Among the investigated moderators, genotyping methodology accounted for the greatest proportion of heterogeneity ($R^2 = 41.16\%$), followed by continent ($R^2 = 30.25\%$) and source of controls ($R^2 = 17.77\%$) (Supplementary Table 5).

In addition, the between-study variance was assessed using Tau² (τ^2) values (Supplementary Table 5). Notably, several SNPs with high I^2 also exhibited high τ^2 values, such as rs2910164, which showed τ^2 values of 0.1844 (continent), 0.1962 (source of controls), and 0.2374 (genotyping method), indicating considerable residual heterogeneity. Conversely, SNPs like rs4938723 showed low τ^2 values (< 0.01), suggesting more consistent effect sizes across studies. Incorporating τ^2 strengthens the interpretation of heterogeneity beyond I^2 and Q-statistics.

Sensitivity analysis and publication bias assessment

Sensitivity analyses confirmed the robustness of our findings, as the exclusion of individual studies did not significantly alter the overall effect estimates (Supplementary Table 6). The SNP rs11614913 exhibited the highest sensitivity, whereas rs12239077, rs12940701, and rs12983273 demonstrated stability across analyses.

Among the 28 SNPs analyzed, only 10 SNPs had data from at least three populations, allowing for a meaningful assessment of publication bias. Egger's regression test indicated no significant publication bias (P > 0.05 for 10 SNPs), corroborated by symmetrical funnel plots (Supplementary Table 7 and Figure 2).

Discussion

This meta-analysis integrated data from 58 studies on 28 miRNA-SNPs and breast cancer risk. Among six well-characterized SNPs, rs11614913, rs895819, rs3746444, rs2910164, rs2043556, and rs6505162, five showed significant associations in updated analyses, consistent with prior studies [21-33, 8, 18, 34-38]. These findings reinforce their biological relevance in breast cancer pathogenesis (Table 2).

The C allele of rs11614913 was associated with increased breast cancer risk (OR = 1.07, 95% CI: 1.03–1.12, P = 0.0016), especially in Asian populations [39, 21, 22], consistent with earlier meta-analyses [23, 21]. Functionally, this variant enhances miR-196a2 expression, leading to repression of tumor suppressors such as HOXD10 and upregulation of TOX3, which contribute to Wnt/β-catenin signaling and epithelial–mesenchymal transition (EMT), pathways closely linked to breast tumor proliferation and metastasis [24, 8, 40, 41]. Similarly, the A allele of rs895819 increased breast cancer risk

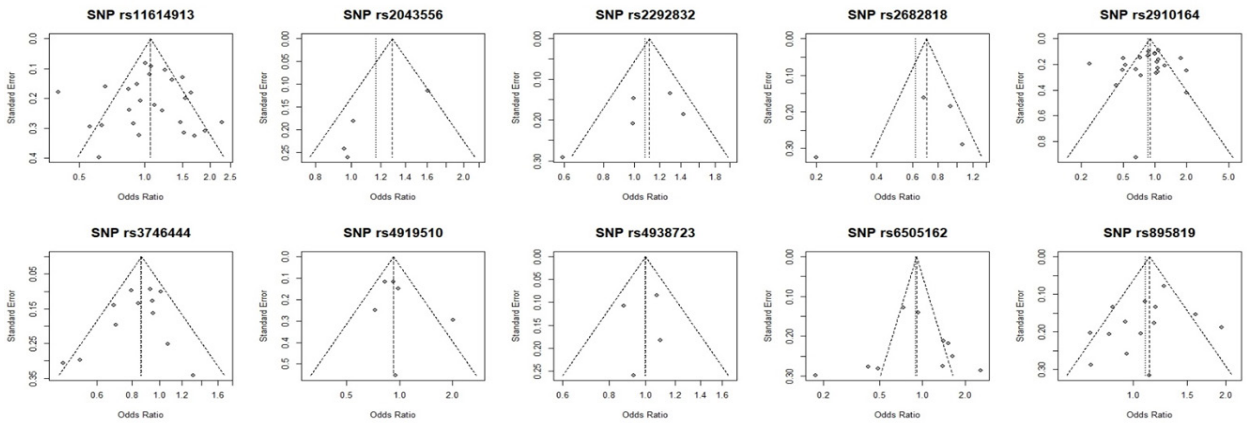

Figure 2. Funnel Plot for Assessing Publication Bias

Table 1. Characteristics of Included Studies

SNP	Alleles	miRNA	Position in miRNA	Total Studies	Cases	Controls	Continents	Population	Genotyping Method	Source of Controls
rs1053872	G/C	miR-101, miR-101-2	pri	2 [72, 73]	1161	1171	Asian	Vietnamese, Chinese	TaqMan, NGS	PB
rs11614913	C/T	miR-196a2	mature	25 [74-81, 9, 82-87, 10, 88, 13, 14, 89-93]	8647	9971	Asian, Australian, American, European	Indian, Caucasian Australian, American, Pakistani, Iranian, Saudi Arabian, Vietnamese, Chinese, Israeli, German, Italian, Chilean, Brazilian	PCR-RFLP, MassARRAY, Tetra-Arms PCR, TaqMan, HRM	PB, HB
rs12239077	G/A	miR-9-1	pri	1 [94]	1946	1747	American	African American, Caucasian American	NGS	PB
rs12940701	C/T	miR-152	pri	2 [95, 96]	332	305	Asian, Australian	Iranian, Caucasian Australian	PCR-RFLP	PB
rs12983273	C/T	miR-373	pri	2 [87, 97]	955	920	Asian, European	Chinese, German	MassARRAY, TaqMan	HB, PB
rs1501672	C/T	miR-9-2	pri	1 [94]	1946	1747	American	African American, Caucasian American	NGS	PB
rs16882131	C/T	miR-206	pri	1 [94]	1946	1747	American	African American, Caucasian American	NGS	PB
rs1834306	C/T	miR-100	pri	2 [98, 87]	455	471	Asian	Chinese, Iranian	MassARRAY, PCR-RFLP	HB, PB
rs2008591	C/T	miR-185	pri	1 [94]	1945	1747	American	African American, Caucasian American	NGS	PB
rs2018562	G/A	miR-513a-2	pri	1 [99]	802	721	American	African American, European American	NGS	PB
rs2043556	G/A	miR-605	pre	4 [98, 87, 100, 93]	1049	1722	Asian, European	Chinese, Iranian, Chilean	PCR-RFLP, MassARRAY, TaqMan	PB, HB
rs2078749	G/A	miR-185	pri	1 [94]	1944	1747	American	African American, Caucasian American	NGS	PB
rs2292832	C/T	miR-149	pre	5 [9, 83, 85, 87, 93]	2013	2080	Asian	Chinese, Israeli	PCR-RFLP, MassARRAY	PB, HB
rs2368392	C/T	miR-604	pre	2 [82, 87]	616	657	American, Asian	American, Chinese	MassARRAY	HB
rs2682818	C/A	miR-618	pre	4 [101, 88, 73, 93]	881	1235	Asian, European	Chinese, Iranian, Chilean, Vietnamese	PCR-RFLP, Tetra-Arms PCR, TaqMan, HRM	PB
rs2910164	G/C	miR-146a	mature	22 [102, 76-78, 103, 79, 81, 9, 82, 83, 87, 10, 100, 13, 14, 11, 104, 89, 105, 12, 91, 106]	7753	8883	Asian, American, Australian, European	Indian, American, Pakistani, Iranian, Saudi Arabian, Vietnamese, Chinese, Caucasian Australian, Chilean, German, Italian, Brazilian	PCR-RFLP, MassARRAY, Tetra-Arms PCR, TaqMan, HRM, AS-PCR, Sanger	PB, HB
rs353291	G/A	miR-145	pri	2 [107, 108]	930	574	Australian, Asian	Caucasian Australian, Vietnamese	MassARRAY, HRM	PB, HB
rs3746444	G/A	miR-499	mature	11 [74, 76, 77, 79-81, 9, 83, 100, 14, 89]	4972	6276	Asian, European	Iranian, Saudi Arabian, Chinese, Chilean, German, Italian, Indian	Tetra-Arms PCR, TaqMan, MassARRAY, PCR-RFLP	HB, PB
rs4541843	G/A	miR-182	pri	2 [109, 100]	605	1209	Asian, European	Iranian, Chilean	PCR-RFLP, TaqMan	PB
rs4919510	G/C	miR-608	mature	6 [80, 110-112, 87, 88]	2221	3290	Asian, European	Iranian, Chinese, Chilean, Vietnamese	PCR-RFLP, MassARRAY, TaqMan, Tetra-Arms PCR	PB, HB
rs4938723	C/T	miR-34b/c, miR-34	pri	3 [94, 113, 114]	2322	2091	Asian, American, European	Iranian, African American, Caucasian American, Greek	PCR-RFLP, NGS	PB
rs531564	C/G	miR-124-1	pri	2 [98, 87]	446	469	Asian	Chinese, Iranian	MassARRAY, PCR-RFLP	HB, PB

PB, Population-based; HB, Hospital-based; pri, primary, pre: precursor

Table 1. Continued

SNP	Alleles	miRNA	Position in miRNA	Total Studies	Cases	Controls	Continents	Population	Genotyping Method	Source of Controls
rs5750504	A/T	miR-659	pri	1 [99]	442	722	American	African American, European American	NGS	PB
rs6505162	C/A	miR-423	pre	10 [115, 9, 85, 87, 116, 88, 117, 118, 91, 119]	2044	2528	African, Asian, Australian, European	Egyptian, Vietnamese, Chinese, Saudi Arabian, Israeli, Caucasian Australian, Chilean, Iranian	TaqMan, HRM, Sanger, Tetra-Arms PCR, MassARRAY	PB, HB
rs6920648	G/A	miR-206	pri	1 [94]	1944	1746	American	African American, Caucasian American	NGS	PB
rs887205	G/A	miR-185	pri	1 [94]	1943	1747	American	African American, Caucasian American	NGS	PB
rs895819	G/A	miR-27a	pre	14 [120, 9, 82, 85, 87, 10, 88, 11, 121, 89, 122, 97, 93, 123]	4667	5240	American, Asian, European	American, Iranian, Thailand, Chinese, Saudi Arabian, Vietnamese, Israeli, Chilean, German	MassARRAY, PCR-RFLP, TaqMan, Tetra-Arms PCR, HRM	HB, PB
rs9535416	G/A	miR-16-1/15a	pri	1 [94]	1946	1747	American	African American, Caucasian American	NGS	PB

PB, Population-based; HB, Hospital-based; pri, primary; pre: precursor

(OR = 1.10, 95% CI: 1.03–1.16, P = 3.04×10^{-3}), with concordant results observed in European cohorts [25]. This SNP impairs miR-27a maturation, leading to reduced suppression of FBXW7, a tumor suppressor that regulates the Notch, mTOR, and cell cycle pathways in breast cancer [8, 42-45]. Conversely, the A allele of rs3746444 exhibited a significant protective effect (OR = 0.86, 95% CI: 0.80–0.92, P = 4.49×10^{-6}), in agreement with prior analyses [27-29], and helps preserve miR-499a-3p activity, limiting activation of the Wnt pathway, particularly relevant in triple-negative breast cancer [32, 24, 33, 8, 46]. For rs2910164, the G allele was significantly protective (OR = 0.92, 95% CI: 0.88–0.97, P = 1.22×10^{-3}), consistent with Moossavi et al. [30] and Moazeni-Roodi et al. [31]. This allele is known to upregulate miR-146a expression, thereby suppressing TRAF6 and downstream NF-κB signaling, a key driver of inflammation-associated breast tumorigenesis [24, 8, 38, 47]. The A allele of rs2043556 (miR-605) also showed a protective effect (OR = 0.76, 95% CI: 0.59–1.00, P = 0.0483) align with Chen et al. [34], particularly in Asians. rs2043556-A enhances miR-605 expression, promoting p53 activation through MDM2 inhibition, potentially restoring p53's functions and potentially leading to tumor regression in breast cancer [8, 35-37, 48]. In contrast, rs6505162 did not show a significant association in the pooled analysis (OR = 0.98, 95% CI: 0.90–1.07, P = 0.61), which is consistent with previous null findings [18, 34, 23], despite sporadic associations reported in individual studies.

Notably, this study is the first to report pooled evidence for five previously understudied SNPs, rs1053872, rs2018562, rs5750504, rs2682818, and rs353291, as significantly associated with breast cancer risk. These variants appear to influence key pathways such as PI3K/AKT, JAK/STAT, and EGFR signaling, with protective effects observed across different populations. The C allele of rs1053872 reduced breast cancer risk (OR = 0.89, 95% CI: 0.79–1.00, P = 0.044) by improving Drosha processing of pri-miR-101-3p, suppressing key breast cancer development players (STMN1, CXCR7, and JAK2), and influencing PI3K/AKT and JAK/STAT pathways [8, 49-51]. Rs2682818-C was found to be protective (OR = 0.72, 95% CI: 0.61–0.85, P = 1.29×10^{-4}) by promoting miR-618 expression and suppressing PI3K/AKT signaling via PTEN regulation, a crucial pathway for cell growth and survival in breast cancer [8, 33]. The protective effect of rs2018562-A (OR = 0.84, 95% CI: 0.73–0.98, P = 0.0286) may help preserve PR and ZFP36 expression, influencing hormone sensitivity and breast tumor phenotype [52, 33, 53, 54]. Rs5750504-A's protective effect (OR = 0.68, 95% CI: 0.51–0.91, P = 0.0085) may be due to improved pri-miR-659 processing, reducing H1F0, a transcription-related protein, which may lead to increased gene expression involved in cell proliferation and self-renewal in breast cancer [55-57]. Finally, rs353291-A is likely protective (OR = 0.80, 95% CI: 0.69–0.93, P = 0.0041) via upregulation of miR-145, which suppresses EGFR— a key oncogene linked to poor prognosis and EMT activation, and potentially inhibiting apoptosis [8, 58-63].

Table 2. Meta-Analysis and Functional Summary of Significant miRNA-SNPs.

No.	miRNAs	SNP	Model	Pool OR (95% CI.)	P_value	I2	Q_pvalue	Prior Meta-analysis	Allele Effect	Functional Impact
1	miR-101	rs1053872	Allelic (C vs G)	0.89 (0.79-1.00)	0.04	64%	9.52E-02	None	C	↑miR-101-3p → ↓STMN1, ↓CXCR7, ↓JAK2 → ↓tumor proliferation
			Homozygous (CC vs GG)	0.79 (0.62-0.99)	0.04	64%	9.48E-02			
2	miR-196a2	rs11614913	Allelic (C vs T)	1.07 (1.03-1.12)	< 0.01	69%	9.31E-08	Wu et al., 2018 [23]; Mu et al., 2017 [21]	C	↑miR-196a2 → ↓JAG1, ↓HOXD10, ↓TOX3 → ↑cancer progression.
			Dominant (CC + CT vs. TT)	1.14 (1.05-1.23)	< 0.01	59%	1.19E-04			
			Homozygous (CC vs. TT)	1.20 (1.10-1.32)	< 0.01	59%	1.30E-04			
3	miR-513a-2	rs2018562	Allelic (A vs. G)	0.84 (0.73-0.98)	0.03	59%	1.20E-01	None	A	↑miR-513a-2 → ↑PR, ↑ZFP36 → ↓tumor proliferation.
			Dominant (AA + GA vs. GG)	0.74 (0.55-0.98)	0.04	0%	4.57E-01			
			Homozygous (AA vs. GG)	0.67 (0.49-0.93)	0.02	17%	2.73E-01			
4	miR-605	rs2043556	Dominant (AA + GA vs. GG)	0.76 (0.59-1.00)	0.05	16%	3.14E-01	Chen et al.,2013 [34]	A	↑miR-605 → ↑p53, ↓MDM2 → ↑tumor suppression.
5	miR-618	rs2682818	Allelic (C vs. A)	0.72 (0.61-0.85)	< 0.01	87%	3.25E-05	None	C	↑miR-618 → ↓PTEN → ↓PI3K/AKT signaling → ↓metastasis.
			Dominant (CC + CA vs. AA)	0.60 (0.39-0.92)	0.02	69%	2.29E-02			
			Homozygous (CC vs. AA)	0.51 (0.33-0.79)	< 0.01	83%	5.33E-04			
6	miR-146a	rs2910164	Allelic (G vs. C)	0.92 (0.88-0.97)	< 0.01	84%	5.29E-19	Moazeni-Roodi et al., 2021 [31]	G	↑miR-146a → ↓TRAF6, ↓NF-κB →↓tumor growth.
			Homozygous (GG vs. CC)	0.82 (0.73-0.91)	< 0.01	79%	1.52E-12			
7	miR-145	rs353291	Allelic (A vs. G)	0.80 (0.69-0.93)	< 0.01	61%	1.10E-01	None	A	↑miR-145 → ↓EGFR → ↓cell proliferation and invasion.
			Dominant (AA + GA vs. GG)	0.74 (0.56-0.98)	0.04	52%	1.51E-01			
			Homozygous (AA vs. GG)	0.66 (0.48-0.89)	0.01	63%	1.02E-01			

OR, Odds Ratio; CI, Confidence Interval; P_value, Significance level of pooled analysis; I^2, Heterogeneity across studies; Q_pvalue, P-value of Cochran's Q test; Allele Effect, Increased or Decreased risk allele identified; Functional Impact, Known or predicted effect of the SNP on miRNA expression and cancer-related pathways.

Table 2. Continued

No.	miRNAs	SNP	Model	Pool OR (95% CI)	P_value	I2	Q_pvalue	Prior Meta-analysis	Allele Effect	Functional Impact
8	miR-499	rs3746444	Allelic (A vs. G)	0.86 (0.80-0.92)	< 0.01	55%	1.12E-02	Tan et al., 2020 [27]	A	↑miR-499 → ↓SOX2 → ↓tumor stemness and epithelial-mesenchymal transition.
			Dominant (AA + GA vs. GG)	0.75 (0.64-0.87)	< 0.01	49%	2.83E-02			
			Homozygous (AA vs. GG)	0.72 (0.62-0.85)	< 0.01	41%	6.55E-02			
9	miR-659	rs5750504	Dominant (AA + AT vs. TT)	0.68 (0.51-0.91)	0.01	14%	2.81E-01	None	A	↑miR-659 → ↓HIF0 → ↓tumor regulation.
			Homozygous (AA vs. TT)	0.72 (0.52-1.00)	0.05	77%	3.61E-02			
10	miR-27a	rs895819	Allelic (A vs. G)	1.10 (1.03-1.16)	< 0.01	64%	5.57E-04	Liu et al., 2021 [25]	A	↓miR-27a → ↓FBXW7 → ↑tumor growth.
			Homozygous (AA vs. GG)	1.15 (1.00-1.32)	0.04	61%	1.33E-03			

OR, Odds Ratio; CI, Confidence Interval; P_value, Significance level of pooled analysis; I^2, Heterogeneity across studies; Q_pvalue, P-value of Cochran's Q test; Allele Effect, Increased or Decreased risk allele identified; Functional Impact, Known or predicted effect of the SNP on miRNA expression and cancer-related pathways.

To further explore the sources of variability in SNP effects and assess the consistency of findings across subpopulations and methodologies, we conducted subgroup analyses and meta-regression. Subgroup analyses revealed population-specific genetic associations. Asian populations exhibited the highest number of significant SNPs (n = 7), including both previously known and novel variants. American populations showed associations with rs2018562 and rs5750504, while rs353291 was significant in Australians. Notably, rs2910164 demonstrated consistent associations across four continents (Asia, Europe, America, and Australia), reinforcing its potential cross-population relevance. Meta-regression analysis identified genotyping methodology as the primary source of between-study heterogeneity (R^2 = 41.16%), followed by geographic region (R^2 = 30.25%) and control source (R^2 = 17.77%) (Sup. Table 8). For instance, rs11614913 showed stronger associations when assessed by HRM (OR = 1.31, P = 0.005) and MassARRAY (OR = 1.16, P = 0.002), while PCR-RFLP and TaqMan yielded non-significant results. Similarly, rs2910164 was significant in studies using Tetra-Arms PCR and HRM (OR = 0.56, P < 0.001; OR = 1.31, P = 0.001), but weaker or inconsistent across other methods. Platform-dependent variability was also observed for rs3746444 and rs895819. In contrast, SNPs such as rs1053872, rs2018562, and rs5750504 produced consistent results with NGS, while rs353291 was significant only with MassARRAY. For rs2043556 and rs2682818, the observed associations diverged depending on the genotyping assay used, suggesting an influence of assay sensitivity and technical error rates on effect estimation. Between-study variance, quantified using Tau^2 values, supported these findings. SNPs such as rs2910164 exhibited high τ^2 across moderator variables, reflecting residual heterogeneity unexplained by measured factors. Conversely, SNPs like rs4938723 showed low τ^2 values, indicating more homogeneous effects across studies. Sensitivity analyses further validated the robustness of most results. SNPs rs2043556, rs2018562, and rs1053872 demonstrated high stability, with fewer than 10 changes during leave-one-out analysis. However, rs11614913, rs2910164, and rs3746444 showed greater sensitivity to individual studies, with 93, 73, and 52 significant deviations respectively, suggesting potential susceptibility to study-level or methodological differences. Taken together, these findings underscore the critical role of genotyping methodology in effect size estimation and highlight the need for methodological harmonization. To reduce heterogeneity and enhance reliability, we excluded studies with low-quality scores (NOS <7), non-English language publications, and those lacking sufficient genotyping data. Furthermore, although Egger's regression test and funnel plots indicated no significant publication bias, the possibility of residual bias due to unpublished negative findings cannot be fully excluded.

While this meta-analysis identified several significant associations between miRNA-SNPs and breast cancer risk, alternative explanations should be considered. Some observed associations may be influenced by

Table 3. Summary of Significant miR-SNPs Across Population Group

Population(s)	SNP(s)	Number of SNP
African	rs6505162	1
American	rs2018562, rs2910164, rs5750504	3
Asian	rs1053872, rs11614913, rs4541843, rs2682818, rs2910164, rs3746444, rs895819	7
Australian	rs353291, rs6505162, rs2910164	3
European	rs2043556, rs2682818, rs2910164, rs6505162, rs895819	5
American, Asian, Australian, European	rs2910164	4
Asian, European	rs2682818	2
Asian, European	rs895819	2
African, Australian, European	rs6505162	3

population-specific genetic backgrounds, differences in environmental exposures, or publication bias despite statistical corrections. Additionally, individual SNP effects may be modified by interactions with other variants, particularly within convergent signaling pathways such as PI3K/AKT or NF-κB. The newly identified variants may reflect tissue-specific regulatory roles or may appear breast cancer–specific due to underrepresentation in studies of other cancers [64-71]. Further research using polygenic risk models, haplotype analysis, and cross-cancer comparisons is warranted to validate these findings and clarify the underlying mechanisms.

In conclusion, this meta-analysis expands the list of miRNA-SNPs associated with breast cancer susceptibility. It confirms the significance of several previously studied variants across diverse populations (rs11614913, rs895819, rs3746444, rs2910164, rs2043556, and rs6505162) and provides the first pooled evidence for five novel miRNA-SNPs (rs1053872, rs2018562, rs5750504, rs2682818, and rs353291. These variants show significant protective associations with breast cancer risk and are linked to critical cancer-related pathways, including PI3K/AKT, NF-κB, and EGFR signaling. Their effects are population-dependent, with relevance observed in Asian, American, and Australian cohorts. The findings highlight the influence of methodological variability, particularly genotyping techniques, on effect size estimates, highlighting the need for harmonization in future genetic association studies. These robust and replicable miRNA-SNPs represent promising components for inclusion in future polygenic risk models, enhancing risk stratification, early detection, and precision prevention strategies for breast cancer.

Author Contribution Statement

Thanh Nguyen Thi Ngoc: Conceptualization, Software, Data curation, Visualization, Writing- Original draft preparation. Thuy Duong Thi Chung: Methodology, Investigation, Reviewing and Editing. Hue Nguyen Thi: Supervision, Reviewing and Editing, Final approval.

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Ethical approval and scientific oversight

This study is part of an approved research project under VNU-HCM. As the study is a systematic review and meta-analysis of previously published data, no new human or animal subjects were directly involved, and ethical approval was therefore not required.

Availability of Data

All data analyzed in this study were obtained from previously published articles included in the meta-analysis. Full data extraction sheets and summary tables are available from the corresponding author upon reasonable request.

Registration Statement

This systematic review and meta-analysis was not registered in an international review database. However, it was conducted following the PRISMA and MOOSE guidelines to ensure transparency and reproducibility.

Conflict of Interest

The authors declare no conflict of interest

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