

Association of *Hypoxia-Inducible Factor 1 α* Gene Polymorphisms With Breast Cancer Susceptibility: A Meta-Analysis

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PURPOSE Overexpression of the *hypoxia-inducible factor 1 α* (*HIF1A*) gene is significantly associated with different types of cancers, including breast cancer. In this study, the effects of single-nucleotide polymorphisms rs11549465, rs11549467, and rs2057482 of the *HIF1A* gene and their association with breast cancer were systematically investigated through meta-analysis.

MATERIALS AND METHODS After a systematic review, nine case-control studies of the *HIF1A* rs11549465 C/T polymorphism, six case-control studies of the *HIF1A* rs11549467 G/A polymorphism, and one case-control study of the *HIF1A* rs2057482 C/T polymorphism were included in this meta-analysis. The summary pooled odds ratios with 95% CIs were evaluated to detect the relationship between *HIF1A* polymorphisms and breast cancer susceptibility.

RESULTS Subgroup-stratified analyses showed that the T and TT genotypes of the *HIF1A* rs11549465 C/T polymorphism were significantly associated with increased breast cancer risk in the Asian population under three genetic models (allele, homozygous, and recessive). *HIF1A* rs11549467 G/A analyses indicated that the A and AA genotypes were significantly associated with increased breast cancer risk in the Asian population under allele and dominant models. However, no association with breast cancer was observed in the White population for the *HIF1A* rs11549465 C/T and rs11549467 G/A polymorphisms. In addition, the *HIF1A* rs2057482 C/T polymorphism showed no association with breast cancer under any genetic models or by ethnicity-stratified analyses.

CONCLUSION The results of this meta-analysis suggested that the *HIF1A* rs11549465 C/T and rs1154946 G/A polymorphisms were significantly associated with increased breast cancer risk in the Asian population, but no associations were found in the White population. Thus, *HIF1A* could be an important biomarker for population-based breast cancer screening.

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INTRODUCTION

Worldwide, breast cancer is the most commonly diagnosed cancer in women, accounting for more than 2 million new cases and around 627,000 estimated deaths from breast cancer in 2018.¹ About one in 20 females will be diagnosed with breast cancer in their lifetime.^{2,3} The risk of developing breast cancer varies among women significantly by country, and recent studies have provided more evidence of genetic susceptibility with an increased risk of cancer.⁴⁻⁶ Several genome-wide association studies (GWASs) have already identified approximately 100 common variants associated with breast cancer risk.⁷⁻⁹

Breast cancer is a heterogeneous complex disease,¹⁰⁻¹³ in which cellular adaptation to hypoxia has been identified as a crucial step in cancer progression.^{14,15}

For patients with cancer, intratumoral hypoxia denotes higher metastasis risk, poorer prognosis, and lower response to radiotherapy and chemotherapy.¹⁶⁻¹⁹ Hypoxia-inducible factor 1 α (*HIF1A*) is an oxygen-sensitive transcription factor that plays a crucial role in facilitating cells to adapt to hypoxia through regulating more than 100 genes involved in angiogenesis, erythropoiesis, metabolic reprogramming, metastasis, etc.^{20,21} In recent years, studies have demonstrated the influence of *HIF1A* polymorphisms with different cancer susceptibilities, such as lung, breast, pancreatic, and gastric.^{22,23} The most frequently reported *HIF1A* single-nucleotide polymorphisms (SNPs) in association with cancers were the two missense mutation loci rs11549465 and rs11549467 on *HIF1A* and a micro-RNA binding locus rs2057482 regulating *HIF1A* expression.²²⁻²⁴ In the literature, some studies

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Hypoxia-inducible factor 1 α (HIF1A), a transcription factor, regulates 100s of genes and plays a crucial role in different cancer progression. The three most prevalent single-nucleotide polymorphisms: rs11549465, rs11549467, and rs2057482, of this oxygen-sensing transcription factor play a vital role in the development of breast cancer. A key question that needs to be addressed is whether the *HIF1A* gene polymorphisms associated with breast cancer are ethnicity-based or is it an incidence common to all populations.

Knowledge Generated

In this systematic review and meta-analysis, stratified analyses by ethnicity data showed that the *HIF1A* rs11549465 C/T and rs11549467 G/A polymorphisms were significantly associated with increased breast cancer risk in the Asian population, but no such association was observed in the White population.

Relevance

Results from this study indicated that the *HIF1A* gene polymorphisms rs11549465 and rs11549467 could be an important biomarker for screening, early detection, and diagnosis in Asian ethnicity.

have reported no significant association of the *HIF1A* rs11549465 C/T polymorphism with breast cancer in the White population²⁵⁻²⁷ or the Asian population,²⁸ whereas other studies on the Asian population showed a significant association between the *HIF1A* rs11549465 C/T polymorphism and breast cancer risk.²⁹⁻³³ Similarly, for the *HIF1A* rs11549467 G/A polymorphism, Naidu et al,²⁹ Kim et al,³³ and Sharma et al²⁸ found no significant association with breast cancer in the Asian population and Apaydin et al²⁵ and Ribeiro et al²⁷ reported the same in White ethnicity. However, a recent study by Shan et al³⁴ concluded a significant association in the Chinese population. Thus, several studies have investigated the impact of *HIF1A* polymorphisms on breast cancer risk in different populations; however, the available studies are heterogeneous in their design and operational quality and reported various

TABLE 1. Characteristics of the Eligible Studies Included in the Meta-Analysis

Study	Year	Country	Ethnicity	Case/Control	Source of Control	HWE
rs11549465						
Apaydin et al ²⁵	2008	Turkey	White	102/102	PB	0.415 (Yes)
Lee et al ³²	2008	Korea	Asian	1,332/1,369	PB	0.250 (Yes)
Kim et al ³³	2008	Korea	Asian	90/102	HB	0.641 (Yes)
Naidu et al ²⁹	2009	Malaysia	Asian	410/275	PB	0.922 (Yes)
Zagouri et al ²⁶	2012	Greece	White	113/124	HB	0.413 (Yes)
Ribeiro et al ²⁷	2013	Portugal	White	96/74	PB	0.001 (No)
Huang et al ³⁰	2014	Taiwan	Asian	96/120	PB	0.000 (No)
Sharma et al ²⁸	2014	India	Asian	200/200	HB	0.007 (No)
Bhushann Meka et al ³¹	2015	India	Asian	348/320	PB	0.032 (No)
rs11549467						
Apaydin et al ²⁵	2008	Turkey	White	102/102	PB	0.839 (Yes)
Kim et al ³³	2008	Korea	Asian	90/102	HB	0.059 (Yes)
Naidu et al ²⁹	2009	Malaysia	Asian	410/275	PB	0.898 (Yes)
Ribeiro et al ²⁷	2013	Portugal	White	96/74	PB	0.000 (No)
Sharma et al ²⁸	2014	India	Asian	200/200	HB	0.000 (No)
Shan et al ³⁴	2018	China	Asian	560/583	PB	0.118 (Yes)
rs2057482						
Lee et al ³²	2008	Korea	Asian	1,150/1,048	PB	0.018 (No)

NOTE. *P* values < .05 were considered as a significant departure from HWE.

Abbreviations: HB, hospital-based; HWE, Hardy-Weinberg Equilibrium; PB, population-based.

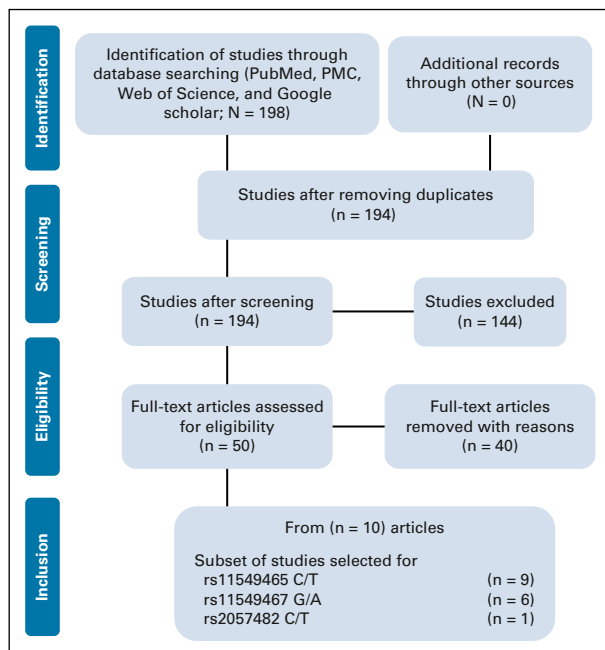


FIG 1. Flow diagram of the study selection for the HIF1A polymorphisms (rs11549465, rs11549467, and rs2057482) and breast cancer, where n is the number of corresponding studies. C/T and G/A are alleles. HIF1A, hypoxia-inducible factor 1 α ; PMC, PubMed Central.

inconclusive results across studies.²⁵⁻³⁴ As yet, there was no study exploring the association of the *HIF1A* gene polymorphisms rs11549465 C/T, rs11549467 G/A, and rs2057482 C/T with breast cancer risk together, thus, in this study, we have systematically investigated the association between these three SNPs of the *HIF1A* gene and susceptibility to breast cancer through meta-analysis.

MATERIALS AND METHODS

Search Strategy and Study Selection

To retrieve eligible peer-reviewed publications of empirical studies, PubMed, PubMed Central, Web of Science, and Google Scholar databases were searched systematically. The articles published in the English language between the years 2008 and 2019 were only considered in this investigation. The search criteria used to find out the eligible studies were as follows: (1) hypoxia-inducible factor-1A, (2) *HIF1A*, (3) SNPs, (4) polymorphisms, (5) rs11549465, (6) rs11549467, (7) rs2057482, (8) cancer, (9) case-control study, and (11) breast cancer. Advanced searches were conducted with the combination of phrases using Boolean operators (AND, OR, and NOT). The references of the related reviews and articles were further searched manually for incorporating additional relevant publications.

Eligibility Criteria and Data Extraction

Two investigators independently screened the titles and abstracts of all the research articles on the basis of the inclusion and exclusion criteria. Full texts were assessed

when it is difficult to make the selection just on the basis of the abstract. Only case-control studies of breast cancer with *HIF1A* gene polymorphisms, GWAS, and human research were included for the final review. The published articles in the English language were only considered for this study, and any discrepancies in extracting data were resolved by discussion. Editorials, reviews, meta-analyses, and non-human research were excluded. In addition, the studies with the following criteria were excluded: (1) study in nonhuman participants or in vitro studies, (2) study with duplicate or overlapping data, (3) articles without full text available, (4) articles with incomplete data on population ethnicity, (5) articles with incomplete allele frequencies data, and (6) articles without the timeline of the study clearly defined. Studies for the final review included: (1) authors name, (2) year of publication, (3) country, (4) ethnicity, (5) allele frequency data, (6) sample size, and (7) sources of control (Table 1).

Meta-Analysis

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.³⁵ From the final 10 included articles, the case-control studies of the *HIF1A* gene polymorphisms: (1) rs11549465 C/T comprising a sample size of 5,473, (2) rs11549467 G/A of sample size 2,794, and (3) rs2057482 C/T with a sample size of 2,198, were included in this meta-analysis.

Statistical Analysis

Meta-analysis of the *HIF1A* gene polymorphisms (rs11549465 C/T, rs11549467 G/A, and rs2057482 C/T) and breast cancer susceptibility was evaluated using an odds ratio (OR) with a 95% CI. The OR measures the association between exposure and outcome. The strength of association was measured by the magnitude of OR. In case-control studies, OR > 1.0 indicates an increased occurrence of an event.³⁶ In the calculation of ORs, to avoid the computation of reciprocal of zeros among observed values (if present), a slightly adjusted estimator of OR was used.³⁶ The I^2 statistic³⁷ and χ^2 test³⁸ were used for heterogeneity among studies assessment ($I^2 \geq 50\%$ indicating the presence of heterogeneity). If the study is heterogeneous, pooled ORs with 95% CIs were calculated using a random-effects model incorporating the inverse variance-weighted method^{39,40}; otherwise, a fixed-effects model was adopted,⁴¹ and a P value < .05 was considered statistically significant. Subgroup analyses were stratified by ethnicity. The Hardy-Weinberg Equilibrium (HWE) test was performed on the control group for each study. Studies with control not in HWE ($P < .05$) were supervised with sensitivity analysis. Furthermore, publication bias in the eligible studies was assessed by Begg's⁴² funnel plot and Egger's⁴³ test. All statistical analyses were performed using Stata 13.0 software (Stata Corporation, College Station, TX).

TABLE 2. Meta-Analysis of the *Hypoxia-Inducible Factor 1 α* rs11549465 C/T, rs11549467 G/A, and rs2057482 C/T Polymorphisms Associated With Breast Cancer

Ethnicity ^a	Study No.	Sample Size	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
rs11549465			TT v CC		CT v CC		TT + CT v CC		TT v CT + CC		T v C	
Overall	9	5,473	1.87 (0.86 to 4.08)	.114	1.13 (0.84 to 1.52)	.409	1.32 (0.90 to 1.93)	.156	1.80 (0.89 to 3.65)	.105	1.35 (0.91 to 2.00)	.134
Asian	6	4,862	2.97 (1.83 to 4.83)	< .001	1.20 (0.84 to 1.74)	.318	1.58 (0.97 to 2.57)	.064	2.72 (1.68 to 4.42)	< .001	1.69 (1.03 to 2.77)	.038
White	3	611	0.44 (0.16 to 1.22)	.114	0.95 (0.63 to 1.44)	.810	0.86 (0.58 to 1.29)	.474	0.45 (0.17 to 1.23)	.121	0.80 (0.55 to 1.14)	.217
rs11549467			AA v GG		GA v GG		AA + GA v GG		AA v GA + GG		A v G	
Overall	6	2,794	1.29 (0.58 to 2.87)	.525	1.26 (0.95 to 1.68)	.106	1.29 (0.98 to 1.70)	.073	1.27 (0.58 to 2.82)	.551	1.29 (1.00 to 1.68)	.054
Asian	4	2,420	1.40 (0.59 to 3.34)	.448	1.31 (0.99 to 1.75)	.064	1.34 (1.01 to 1.77)	.042	1.37 (0.57 to 3.26)	.478	1.34 (1.03 to 1.74)	.031
White	2	374	0.86 (0.12 to 6.19)	.883	0.32 (0.06 to 1.79)	.197	0.32 (0.06 to 1.79)	.197	0.88 (0.12 to 6.31)	.898	0.33 (0.06 to 1.80)	.200
rs2057482			TT v CC		CT v CC		TT + CT v CC		TT v CT + CC		T v C	
Asian	1	2,198	0.95 (0.61 to 1.47)	.815	0.93 (0.78 to 1.10)	.395	0.93 (0.78 to 1.10)	.395	0.98 (0.63 to 1.50)	.917	0.95 (0.82 to 1.09)	.457

NOTE. A, T, G, and C are alleles. AA, CCCT, GG, GA, and TT are allelic combinations.

Abbreviation: OR, odds ratio.

^aThe value of ORs for the ethnicity subgroups represents the overall breast cancer risk.

FIG 2. Forest plot of the hypoxia-inducible factor 1 α gene rs11549465 C/T polymorphism for the (A) allelic (T v C), (B) recessive (TT v CT + CC), and (C) homozygous (TT v CC) models, showing the overall association with breast cancer susceptibility. The squares and horizontal lines correspond to the individual study-specific ORs with 95% CIs. The blue areas of the squares represent the corresponding study weight. The blue diamonds reflect the pooled OR, and the lateral points of the diamonds represent the CIs of the overall analyses. The solid vertical lines are the OR of 1, which are the lines of no effect. The red dashed vertical lines show the corresponding pooled ORs of the analyses. C and T are alleles. CC, CT, and TT are allelic combinations. OR, odds ratio.

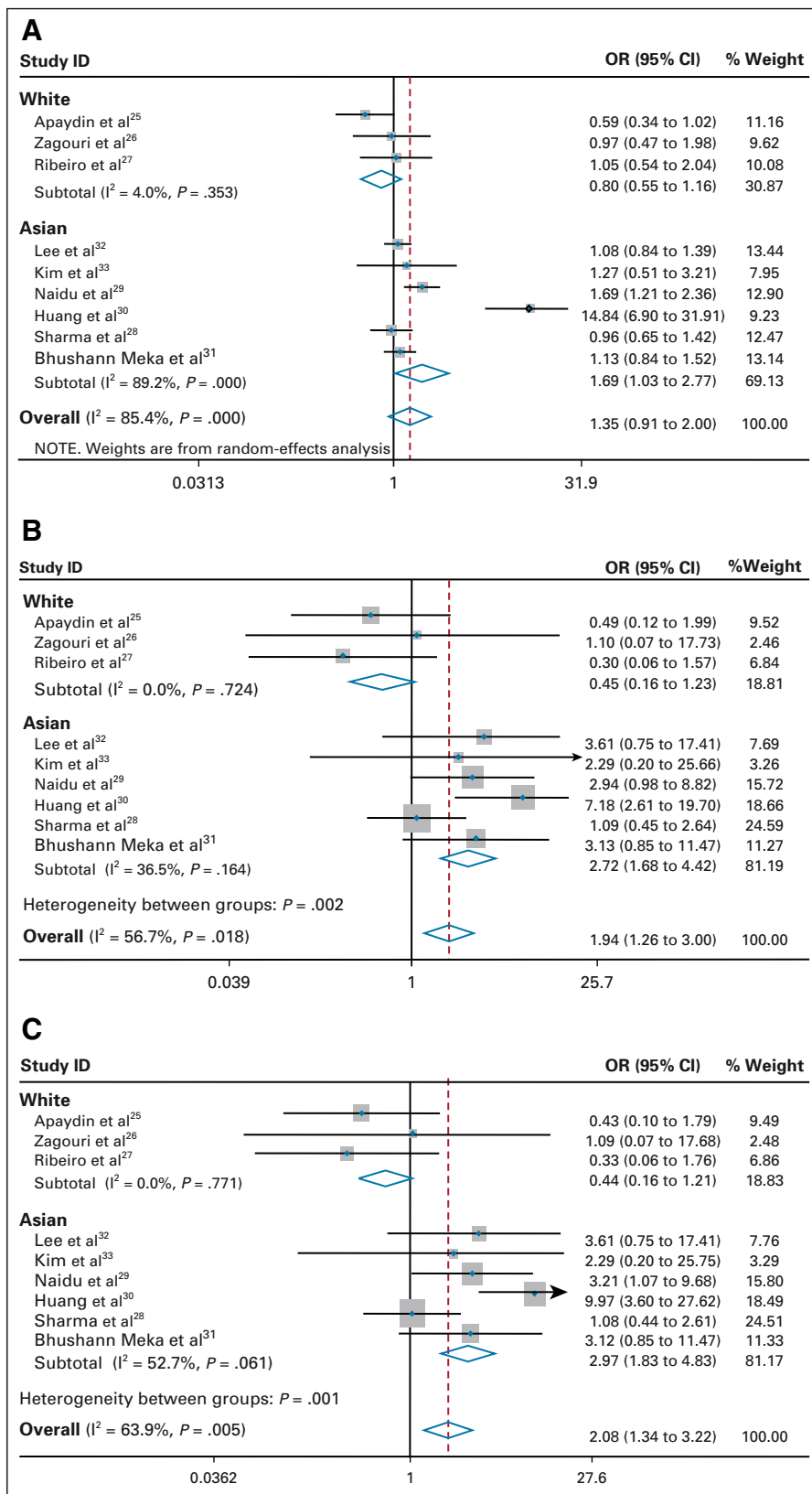


FIG 3. Forest plot of the *hypoxia-inducible factor 1α* gene rs11549467 G/A polymorphism for the (A) allelic (A v G) and (B) dominant (AA + GA v GG) models, showing the overall association with breast cancer susceptibility. The squares and horizontal lines correspond to the individual study-specific ORs with 95% CIs. The blue areas of the squares represent the corresponding study weight. The blue diamonds reflect the pooled OR, and the lateral points of the diamonds represent the CIs of the overall analyses. The solid vertical lines are the OR of 1, which are the line of no effect. The red dashed vertical lines show the corresponding pooled ORs of the analyses. A and G are alleles. AA, GA, and GG are allelic combinations. OR, odds ratio.

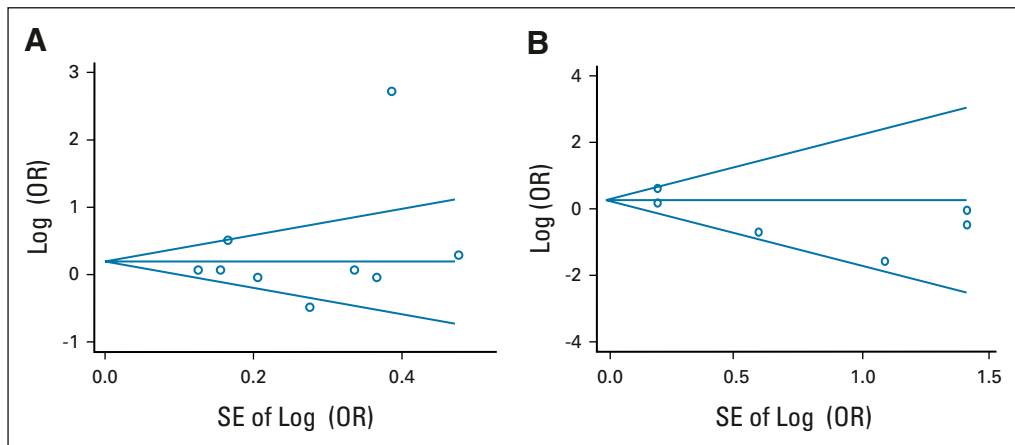
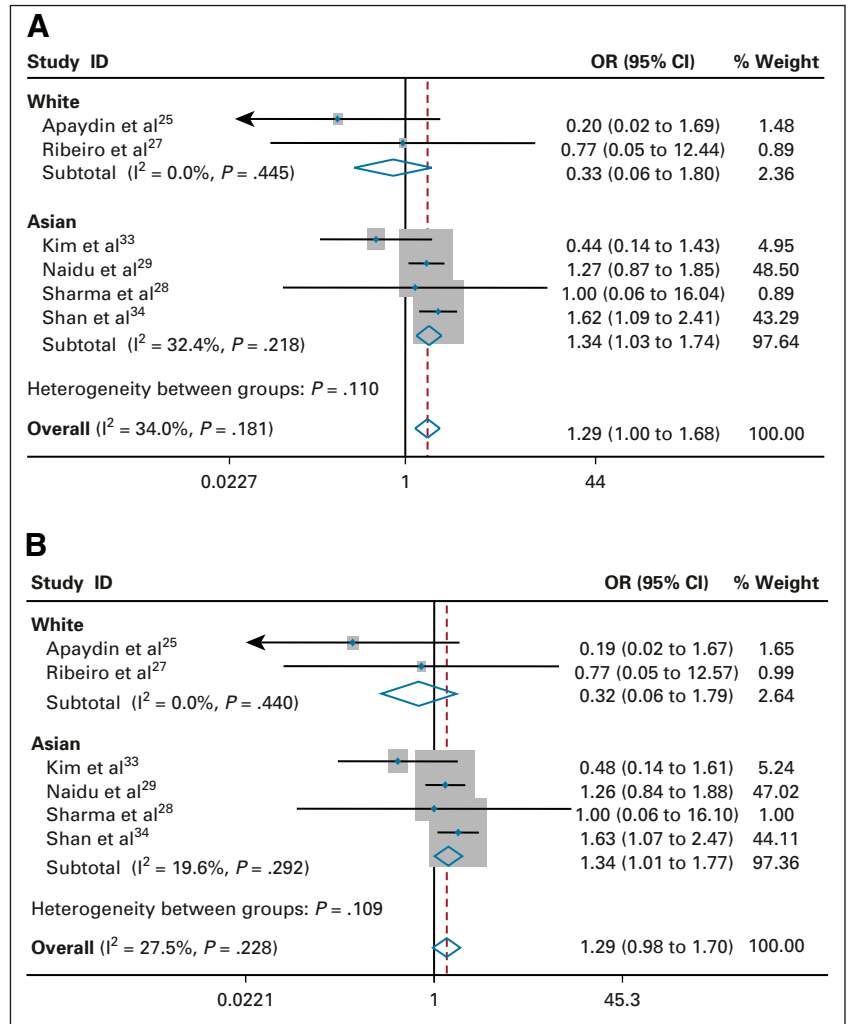


FIG 4. Funnel plots (pseudo 95% CI limits) of studies evaluating the risk of breast cancer associated with the *hypoxia-inducible factor 1α* gene polymorphisms: (A) T versus C allelic model of the rs11549465 C/T polymorphism and (B) A versus G allelic model of the rs11549467 G/A polymorphism. A, C, G, and T are alleles. OR, odds ratio.

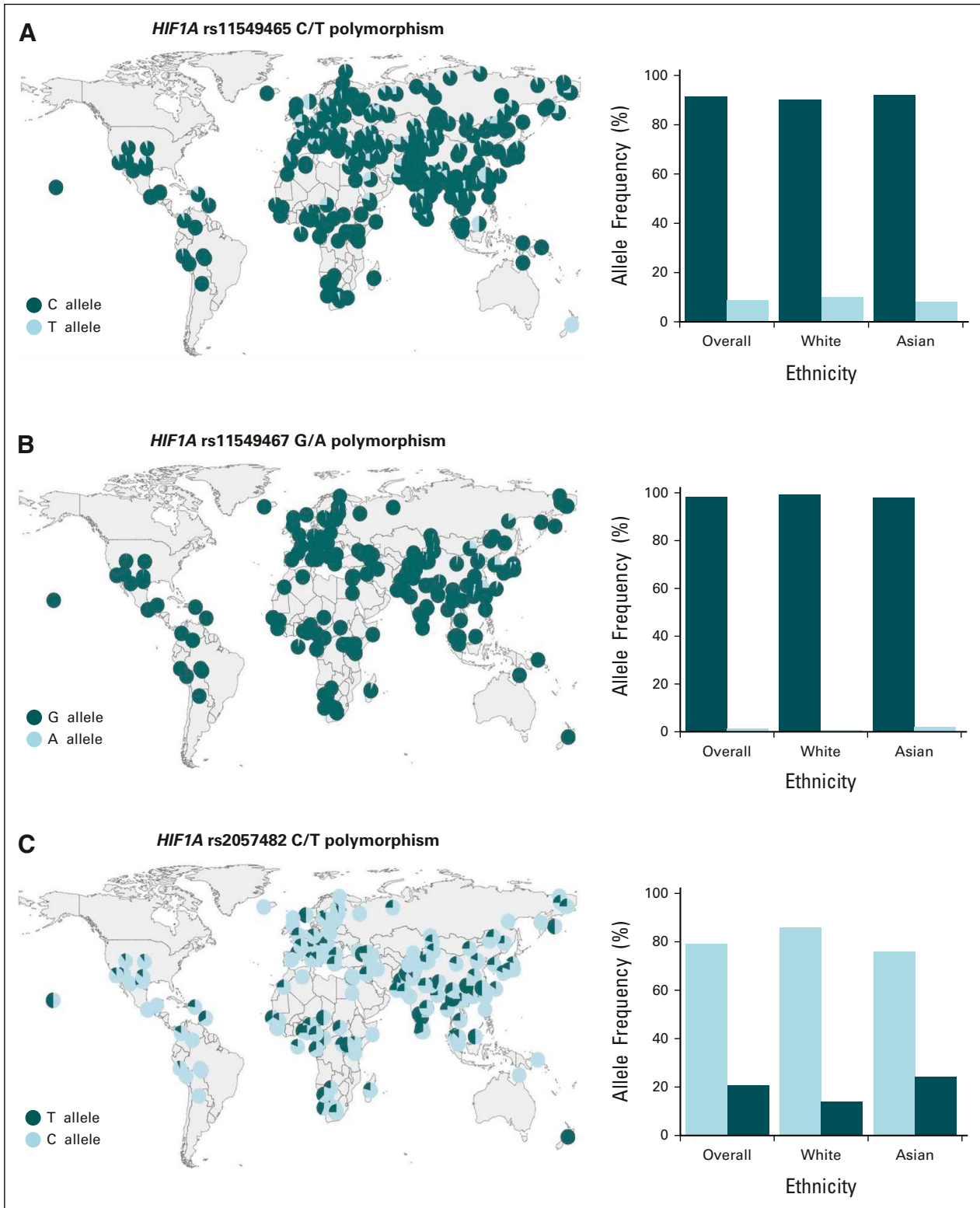


FIG 5. Worldwide prevalence of the *HIF1A* gene polymorphisms: (A) rs11549465 C/T, (B) rs11549467 G/A, and (C) rs2057482 C/T polymorphisms and allele frequency data from the 1,000 Genomes Projects (phase III). A, C, G, and T are alleles. *HIF1A*, hypoxia-inducible factor 1 α .

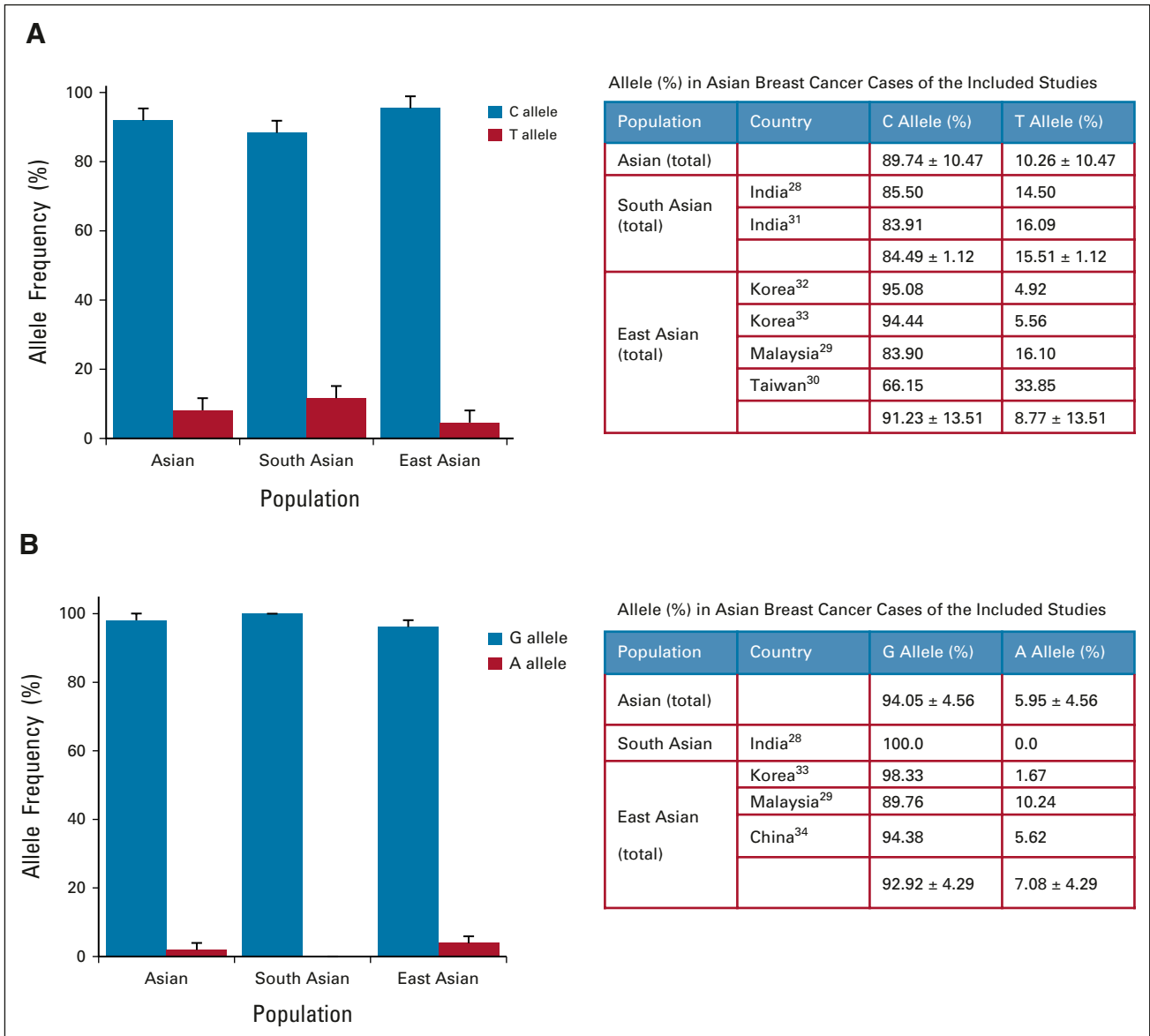


FIG 6. Prevalence of allele frequency of the *HIF1A* gene (A) rs11549465 C/T and (B) rs11549467 G/A polymorphisms in Asian populations from the 1,000 Genomes Projects (phase III) and the allele frequency in breast cancer cases from the included studies of this meta-analysis. A, C, G, and T are alleles. *HIF1A*, hypoxia-inducible factor 1 α .

Summary Measures

Pooled ORs with a 95% CI were computed from studies by allelic comparisons (T v C), dominant model (TT + CT v CC), recessive model (TT v CT + CC), homozygote comparisons (TT v CC), and heterozygote comparisons (CT v CC) for both rs11549465 C/T and rs2057482 C/T polymorphisms of the *HIF1A* gene. The genotype contrasts for the *HIF1A* rs11549467 G/A polymorphism were as follows: homozygote comparison (AA v GG), heterozygote comparison (GA v GG), dominant model (AA + GA v GG), recessive model (AA v GA + GG), and the allele comparison model (A v G). The statistical significance level was based on a Z-test with a *P* value < .05.

RESULTS

Characteristics of the Selected Studies

Initially, after the screening of the titles and abstracts, 194 articles were identified and were further assessed in full text. After the inclusion and exclusion criteria, 10 studies²⁵⁻³⁴ were finally enrolled to collect data for the meta-analysis (Fig 1 and Data Supplement). Among the 10 enrolled articles, nine case-control studies of the *HIF1A* rs11549465 C/T polymorphism, including 2,787 cases and 2,686 controls; six case-control studies of the *HIF1A* rs11549467 G/A polymorphism, including 1,458 cases and 1,336 controls; and a single case-control study of the *HIF1A* rs2057482 C/T polymorphism, comprising 1,150

cases and 1,048 controls, were included to explore the relationship with breast cancer risk. The characteristics of the included studies are shown in Table 1, and in most, the source of control was population-based (PB): seven of the included case-control studies were on the Asian population and the other three were on the White population. The sources of control were PB in seven studies and hospital-based in three studies (Table 1).

Association of the *HIF1A* rs11549465 C/T Polymorphism With Breast Cancer Risk

The pooled ORs for overall analyses suggested that the *HIF1A* rs11549465 C/T polymorphism was not significantly associated with breast cancer under any of the five genetic models (Table 2 and Data Supplement). However, the subgroup-stratified analyses data by ethnicity for the Asian population suggested that the T allele and TT genotype of *HIF1A* rs11549465 C/T polymorphism were significantly associated with increasing breast cancer risk in homozygote comparison (TT v CC: OR = 2.97; 95% CI, 1.83 to 4.83; *P* value < .001), recessive model (TT v CT + CC: OR = 2.72; 95% CI, 1.68 to 4.42; *P* value < .001), and the allele model comparison (T v C: OR = 1.69; 95% CI, 1.03 to 2.77; *P* value = .038; Fig 2 and Table 2). The magnitude of ORs > 2 and *P* values < .001 indicated a strong association between the *HIF1A* rs11549465 C/T polymorphism and breast cancer. However, the analyses data for the *HIF1A* rs11549465 C/T polymorphism suggested no significant effect on the White population.

Sources of Heterogeneity

Statistically significant heterogeneity was observed across the included studies of the *HIF1A* rs11549465 C/T polymorphism for overall cancer risk in all five genetic models (T v C: *Q* = 54.62, *df* = 8, *P* value < .001, *I*² = 85.4%; TT v CC: *Q* = 22.17, *df* = 8, *P* value = .005, *I*² = 63.9%; CT v CC: *Q* = 21.53, *df* = 8, *P* value = .006, *I*² = 62.8%; TT + CT v CC: *Q* = 40.48, *df* = 8, *P* value < .001, *I*² = 80.2%; and TT v CT + CC: *Q* = 18.49, *df* = 8, *P* value = .018, *I*² = 56.7%). However, when stratified on the basis of subgroup analysis by ethnicity, heterogeneity disappeared in the White population. The results suggested that the studies in Asian ethnicity were the main sources of heterogeneity (Data Supplement).

Association of the *HIF1A* rs11549467 G/A Polymorphism With Breast Cancer

The pooled ORs for the overall analyses suggested no significant association between the *HIF1A* rs11549467 G/A polymorphism and breast cancer under any genetic model (Table 2 and Data Supplement). However, the subgroup-stratified analyses by ethnicity for the Asian population suggested that the A allele and the AA genotype of *HIF1A* rs11549467 G/A polymorphism were significantly associated with increased breast cancer risk in the allele model (A v G: OR = 1.34; 95% CI, 1.03 to 1.74; *P* value = .031) and the dominant model comparisons (AA + GA v GG:

OR = 1.34; 95% CI, 1.01 to 1.77; *P* value = .042; Fig 3; Table 2). The magnitude of the OR > 1 and *P* values < .05 indicated a significant association of the *HIF1A* rs11549467 G/A polymorphism with breast cancer. The analyzed data from studies on White ethnicity revealed no significant association between the rs11549467 G/A polymorphism and breast cancer risk.

Sources of Heterogeneity

No significant heterogeneity was observed in the *HIF1A* rs11549467 G/A polymorphism analyses under any of the genetic model comparisons for overall cancer (Data Supplement).

Association of rs2057482 C/T Polymorphism With Breast Cancer Development

The results of the pooled ORs indicated no significant association between the *HIF1A* rs2057482 C/T polymorphism and breast cancer risks under any of the five genetic models (Table 2).

Publication Bias

The evidence of publication bias within this meta-analysis of the *HIF1A* rs11549465 C/T polymorphism for T versus C allele and the *HIF1A* rs11549467 G/A polymorphism for A versus G allele was assessed using both Begg's funnel plot and Egger's test. Funnel plot shapes demonstrated symmetrical distribution, and no publication bias was detected for the *HIF1A* rs11549465 C/T (T v C allele: *Z* = 0.94, *P* value = .348) polymorphism and the *HIF1A* rs11549467 G/A (A v G allele: *Z* = 0.38, *P* value = .707) polymorphism (Fig 4 and Data Supplement). In addition, Egger's linear regression analyses suggested no evidence of significant publication bias for the *HIF1A* rs11549465 C/T polymorphism (T v C allele: *t* = 0.71, *P* value = .50) and for the *HIF1A* rs11549467 G/A polymorphism (A v G allele: *t* = -2.01, *P* value = .115; Fig 4 and Data Supplement).

Sensitivity Analysis

To evaluate the stability of the acquired pooled ORs of the *HIF1A* rs11549465 C/T and rs11549467 G/A polymorphisms, the sensitivity analysis was carried out by excluding the studies that were not in HWE. The results demonstrated no significant fluctuations in the pooled ORs by omitting any individual study that was not in HWE (Data Supplement). Thus, none of the studies influenced the combined overall results substantially in this meta-analysis and confirmed that the obtained results of the meta-analysis were stable and robust.

DISCUSSION

The results of this meta-analysis showed no significant association between the *HIF1A* rs2057482 C/T polymorphism and breast cancer risk. For the two missense SNP variants of the *HIF1A* genes rs11549465 C/T and rs11549467 G/A, although the overall pooled ORs showed no association with breast cancer, the subgroup stratified

by ethnicity analyses showed a significant association between the *HIF1A* rs11549465 C/T polymorphism and increasing breast cancer risk in the homozygote, recessive, and allele model comparisons for the Asian population. In addition, a significant association between the *HIF1A* rs11549467 G/A polymorphism and increasing breast cancer risk was observed under the allele and dominant model comparisons in the Asian population. However, the subgroup analyses by ethnicity for the White population showed no association with rs11549465 C/T or rs11549467 G/A polymorphisms of the *HIF1A* gene.

To understand this Asian ethnicity-based association with breast cancer propensity, we interrogated three publicly available databases: 1000 Genome browser phase III,⁴⁴ NCBI variation database dbSNP,⁴⁵ and PGG.SNV,⁴⁶ to review the current knowledge of allele frequency for the *HIF1A* variants rs11549465 C/T, rs11549467 G/A, and rs2057482 C/T in the overall worldwide population and then compared that with the subgroup of the Asian and White ethnicity (Fig 5). Furthermore, we interrogated the 1000 Genome browser (phase III) for the allele frequency of the *HIF1A* rs11549465 C/T and rs11549467 G/A variants in the Asian population overall and then compared that with

the subgroup of the South Asian and East Asian ethnicity (Fig 6). Although only a few studies, of the South Asian and East Asian ethnicity comprising small sample sizes, were included in this meta-analysis, a comparable allele frequency picture was depicted using the 1000 Genome (phase III) data. A distinct variance in allele frequency of the *HIF1A* rs11549465 C/T and rs11549467 G/A polymorphisms between the South Asian and East Asian ethnicity was observed. In the future, further availability of more GWASs of the *HIF1A* polymorphisms with breast cancer and generating larger genomic data sets of different Asian ethnicity would provide a more conclusive prediction.

In conclusion, this meta-analysis has demonstrated that the *HIF1A* rs11549465 C/T and rs11549467 G/A polymorphisms are significantly associated with increased risk of breast cancer, especially among Asian women, whereas there is no significant association with increased breast cancer risk in the White population. Taken together, this study suggested that *HIF1A* could be a PB reliable biomarker for early breast cancers screening and detection. In the future, the availability of more experimental data with a larger sample size of different ethnic groups would help to validate and confirm the findings.

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No potential conflicts of interest were reported.

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