

Original article

Association of VEGF gene polymorphisms and breast cancer susceptibility: An updated systematic review and meta-analysis

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Abstract

Background: Breast cancer is among the most common malignancies in women worldwide, with genetic predispositions and environmental factors. Low-penetrance genes such as breast cancer (BRCA)1 and BRCA2 have been identified with implications in breast cancer susceptibility. Vascular endothelial growth factor (VEGF) polymorphisms that code for the VEGF protein play an important part in carcinogenesis by modulating angiogenesis required for tumor growth, invasion, and metastasis. There are five polymorphisms associated with the *VEGF* gene: 936 C > T, 2578 C > A, 634 G > C, 460 T > C, and 405 C > G, which have been linked to altered cancer risk.

Objective: This study aimed to clarify the associations between VEGF polymorphisms and breast cancer risk by conducting a meta-analysis.

Methods: A systematic review and meta-analysis were performed and reported in accordance with the PRISMA 2020 guidelines. Twenty-five eligible articles contributed 53 polymorphism-specific case-control datasets that included five *VEGF* polymorphisms. Statistical analyses were performed using Metagenyo software.

Results: the results revealed a significant association. The 2578 C > A and 460 T > C polymorphisms were associated with increased risks, while 936 C > T and 634 G > C were not. Subgroup analyses also revealed that Asian populations are more susceptible than Caucasians in the overall five polymorphisms. The 405 C > G polymorphism exhibited significance in the dominant and over-dominant models. In the sensitivity analysis, all the effects remained the same except for 405 C > G, which was influenced by a single study. The publication bias was low in all the data.

Conclusion: The present study suggest that *VEGF* polymorphisms may serve as population-specific genetic biomarkers for breast cancer risk stratification. These variants may also help identify patient subgroups that are more likely to benefit from VEGF-targeted or other anti-angiogenic therapies by influencing VEGF expression and angiogenic activity. However, their clinical utility for treatment selection and prediction of therapeutic response requires validation in larger, ethnically diverse cohorts and in prospective pharmacogenomic studies.

Keywords: Angiogenesis, breast cancer, cancer, gene polymorphism, VEGF.

Breast cancer remains one of the most prevalent malignancies affecting women worldwide. ⁽¹⁾ A complex interplay of genetic predisposition and environmental influences drives its development. While high-penetrance genes, such as breast cancer (*BRCA*)1 and *BRCA*2, substantially increase the risk in hereditary cases, numerous low-penetrance

variants, together with lifestyle and environmental exposures, also contribute to overall susceptibility. ⁽²⁾ Angiogenesis, the formation of new blood vessels from existing vasculature, is a fundamental biological process that supports tumor progression by supplying essential nutrients and oxygen. ⁽³⁾ This process is tightly regulated through the balance of proteolytic enzymes, angiogenic stimulators, and endogenous inhibitors. Among these regulators, vascular endothelial growth factor (VEGF) is recognized as a key mediator of angiogenesis. ⁽⁴⁾ The overexpression of VEGF has been documented in numerous malignancies, including breast cancer, where it promotes tumor growth, invasion, and metastasis. Extensive studies have

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clarified the VEGF signaling pathway, reinforcing its vital role in pathological angiogenesis, tumor aggressiveness, and patient prognosis.⁽⁵⁾ Given its biological importance, VEGF has emerged as an important target for anti-angiogenic therapies, and preclinical models have demonstrated the therapeutic potential of VEGF inhibition. Multiple single-nucleotide polymorphisms (SNPs) in the *VEGF* gene are known to influence VEGF expression levels, thereby altering its angiogenic activity. Several *VEGF* variants, particularly 2578 C/A, 405 C/G, 460 T/C, 634 G/C, and 936 C/T, have been widely investigated for their potential roles in modulating cancer susceptibility, tumor progression, and metastatic behavior.⁽⁶⁻⁸⁾ However, despite considerable research, relatively fewer studies have specifically evaluated the association between VEGF polymorphisms and breast cancer risk. Current epidemiological findings have often been inconsistent, largely due to small sample sizes, limited statistical power, and variations in study design or genotyping quality. Our previous meta-analysis also suffered from these constraints; the associations involving the 460 T > C and 405 C > G polymorphisms were particularly inconclusive due to insufficient sample sizes.⁽⁶⁾

Since that time, several new studies have been published with larger cohorts, improved genotyping methodologies, and more diverse populations. These additions offer an essential opportunity to re-evaluate the evidence with greater statistical precision. Therefore, an updated meta-analysis was undertaken to enhance the robustness of the conclusions, incorporate higher-quality datasets, and explore potential subgroup effects more comprehensively.

The expanded sample size in this updated analysis enables detailed subgroup stratification by ethnicity and specific VEGF variants, which is critical for identifying population-specific associations. Ultimately, this revised meta-analysis aims to provide more accurate estimates of effect sizes and clarify the role of *VEGF* gene polymorphisms in breast cancer susceptibility.

Methods

Protocol registration

This systematic review and meta-analysis was not prospectively registered in PROSPERO; therefore, no registration number is available. The eligibility criteria, search strategy, data-extraction items, and statistical analysis plan were defined before study selection and quantitative synthesis were performed.

Design of study

This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 guidelines.⁽⁹⁾ The review focused on five prespecified gene polymorphisms that have been most frequently investigated in relation to breast cancer susceptibility, namely 936 C > T, 2578 C > A, 634 G > C, 460 T > C, and 405 C > G. The study selection process, including identification, screening, eligibility assessment, and inclusion, is summarized in **Figure 1**.

Search strategy

To collect relevant literature, a structured and exhaustive database search was conducted in Google Scholar, ScienceDirect, and PubMed, covering publications through June 2025. Keywords and search phrases included combinations of terms such as “vascular endothelial growth factor,” “breast neoplasm,” “breast cancer,” “single nucleotide polymorphism,” “SNP,” and “risk” or “association.” Boolean operators (AND/OR) were used to enhance search sensitivity. Furthermore, additional manual screening of references cited in retrieved papers and reviews ensured comprehensive coverage. No restrictions were applied regarding publication year. The unit counted during the PRISMA selection process was the article or report. However, because individual articles could report data for more than one VEGF polymorphism or more than one case–control cohort, each eligible polymorphism-specific comparison was treated as a separate dataset in the quantitative analysis. Subsequently, the 25 included articles contributed 53 polymorphism-specific case–control datasets.

Inclusion criteria and exclusion criteria

Studies were eligible when they (i) used a case–control design; (ii) evaluated the association between breast cancer susceptibility and at least one of the five prespecified *VEGF* polymorphisms 936 C > T, 2578 C > A, 634 G > C, 460 T > C, or 405 C > G; and (iii) reported genotype frequencies for cases and controls or provided sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Control data were extracted from the control groups of the eligible published case–control studies. The controls were required to be free from breast cancer, originate from the same underlying population as the cases, and provide sufficient genotype data for analysis. Articles were excluded if they lacked original data, were not peer-reviewed (e.g., conference proceedings or editorials), duplicated previously

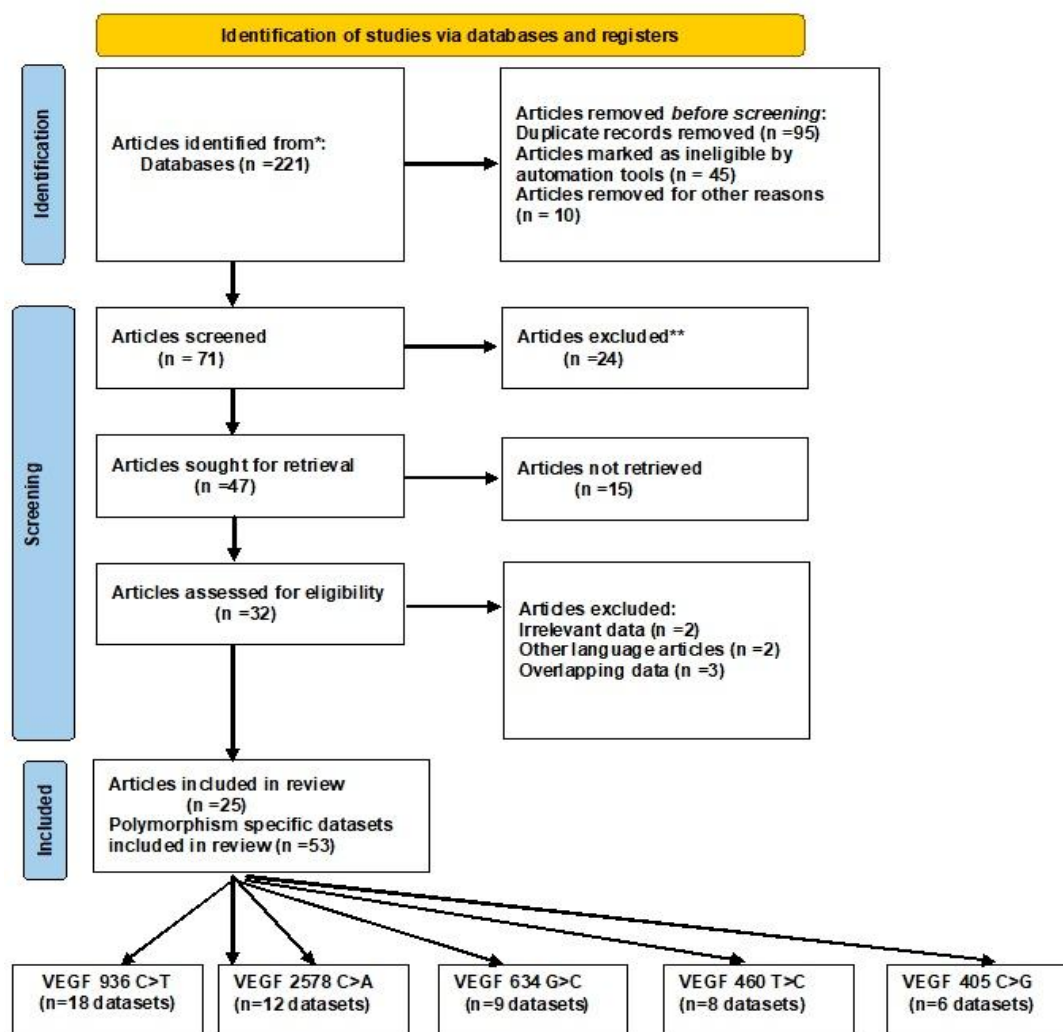


Figure 1. PRISMA 2020 flow diagram showing the identification, screening, eligibility assessment, and inclusion of articles examining VEGF gene polymorphisms and breast cancer susceptibility. The 25 eligible articles contributed 53 polymorphism-specific case-control datasets: *VEGF* 936 C>T (n = 18), *VEGF* 2578 C>A (n = 12), *VEGF* 634 G>C (n = 9), *VEGF* 460 T>C (n = 8), and *VEGF* 405 C>G (n = 6). Multiple independent cohorts reported within one article were treated as separate datasets and identified by country. VEGF, vascular endothelial growth factor.

published datasets, or presented control group genotypes not conforming to Hardy-Weinberg Equilibrium (HWE) without clarification.

Data extraction

For each eligible dataset, the following information was extracted: first author, publication year, country, ethnicity, VEGF polymorphism, case and control sample sizes, control source (population-based or hospital-based with matching characteristics), genotype frequencies in cases and controls, genotyping method, and HWE status of the control group. When a single publication reported more than one independent case-control cohort, each cohort was entered separately in the meta-analysis. Cohorts originating from the same publication were identified by first author, publication year, and country, rather than by numerical suffixes.

Quality of study

The methodological quality of the included studies was assessed using the RoB2 (Risk of Bias 2.0) tool, which evaluates five key domains: (1) the randomization process; (2) adherence to intended interventions; (3) completeness of outcome data; (4) outcome measurement; and (5) selective reporting of outcomes.⁽¹⁰⁾ Each study received an overall rating of “low risk,” “some concerns,” or “high risk of bias,” based on the cumulative assessment across all domains. This structured evaluation ensured a systematic appraisal of study rigor and helped identify potential sources of bias that may influence the meta-analysis outcomes.

Statistical analysis

The meta-analysis was conducted in MetaGenyo, an online bioinformatics tool specifically designed to gather and analyze information from genetic association studies.⁽¹¹⁾ Genotype–phenotype analysis was performed to investigate the association of *VEGF* polymorphisms with breast cancer risk in allelic, dominant, recessive, and over-dominant genetic models. The pooled ORs and 95% CIs were computed for each comparison. Between-study heterogeneity was tested with Cochran's Q test and the I^2 statistic. For studies with $I^2 > 50.0\%$ (high heterogeneity), we used the random-effects model; for others, we used the fixed-effects model. Subgroup analysis stratified by ethnicity, control source, and study quality was performed to differentiate potential population-based and methodological effects. For sensitivity analysis, we conducted an exploratory analysis by excluding one study at a time and recalculating the summary estimates. Investigation of publication bias was performed using Egger's regression test and visual inspection of the funnel plots; $P < 0.05$ was considered significant. Other exploratory analyses excluded studies with control-group deviation from HWE to confirm that this was not driven by deviations from HWE in the main results.

Results

Search strategy

A total of 221 records were identified through database searching. Before screening, 150 records were removed; these included 95 duplicates, 45 were identified as ineligible through automated screening, and 10 were removed for other reasons. Of the remaining 71 records, 24 were excluded following title and abstract screening. Forty-seven reports were sought for retrieval, of which 15 could not be retrieved. The remaining 32 full-text reports were assessed for eligibility, and seven were excluded because of irrelevant data ($n = 2$), non-English publication or unavailable extractable information ($n = 2$), or overlapping datasets ($n = 3$). Thus, 25 articles were included in the systematic review (**Figure 1**). As several articles evaluated multiple *VEGF* polymorphisms or reported more than one cohort, these articles contributed 53 polymorphism-specific case–control datasets to the meta-analysis: 18 for *VEGF* 936 C > T, 12 for *VEGF* 2578 C > A, nine for *VEGF* 634 G > C, eight for *VEGF* 460 T > C, and six for *VEGF* 405 C > G. In summary, these studies collectively evaluated the effect of *VEGF* gene

polymorphisms on breast cancer risk. The primary features of the included case–control studies are shown in **Tables 1–5**, highlighting the variability in polymorphic variants and their distribution across populations.

Of the included studies, 25 were conducted in Asian populations due to their specific genetic background.^(12–25) Twenty-two studies included Caucasian groups^(26–34), and six papers involved African populations.^(35, 36) Evidence was obtained from various racial groups to investigate the impact of *VEGF* polymorphisms on breast cancer development. The small number of studies, however, did not permit extensive subgroup analyses within African settings.

Jin Q, *et al.* (2005) reported three independent case–control cohorts from Poland, Germany, and Sweden. These cohorts were analyzed separately and are identified by name followed by a different number. Differences in sample size across the *VEGF* polymorphisms reflect variation in the availability or successful genotyping of individual SNPs.

Risk of bias

The risk of bias for all included studies was evaluated using the Cochrane ROB 2 tool (**Figure 2A and 2B**). In the figure, each row corresponds to an individual study, while each column represents a specific potential bias domain. A color-coded scheme was applied to summarize the overall judgment: red indicates high risk, yellow reflects some concerns or uncertainty, and green denotes low risk of bias. Overall, most studies exhibited strong methodological quality, with most receiving low-risk ratings across the key domains.

Quantitative analysis

A detailed literature survey identified 18 independent studies examining the *VEGF* 936 C/T polymorphism, which collectively encompassed 5,241 individuals with breast cancer and 5,249 cancer-free controls, thereby providing a robust dataset for assessing variant distribution. The *VEGF*–2578 C/A variant was assessed in 12 studies, including 3,067 cases and 3,266 controls. Similarly, nine studies explored the *VEGF* 634 G/C polymorphism, contributing data from 3,044 cases and 3,049 controls. The *VEGF* 405 C/G locus was analyzed in six investigations, covering 2,429 patients with breast cancer and 2,453 healthy participants. In addition, eight studies reported on the *VEGF* 460 T/C polymorphism, incorporating 2,759 cases and 2,842 controls.

Table 1. The distribution of the *VEGF* 2578 C > A allele and genotype among breast cancer cases and controls, HWE score.

Study	Ethnicity	CC	CT	TT	CC	CT	TT	HW-P value
		Cases			Controls			
Li Z, <i>et al.</i> 2021	Asian	150	94	15	153	101	10	0.3113
Madrid-Paredes A, <i>et al.</i> 2020	Caucasian	28	37	15	34	51	38	0.1788
Al-Mohaya MA, <i>et al.</i> 2021	Asian	30	53	21	36	58	6	0.072
Sambyal V, <i>et al.</i> 2021	Asian	69	114	67	88	129	33	0.3113
Jin Q, <i>et al.</i> 2005	Caucasian (Poland)	104	195	112	106	207	110	0.7233
Jin Q, <i>et al.</i> 2005_1	Caucasian (Germany)	44	75	34	50	72	40	0.3113
Jin Q, <i>et al.</i> 2005_2	Caucasian (Sweden)	258	449	232	257	451	232	0.3345
Ajaz S, <i>et al.</i> 2019	Asian	37	65	16	66	93	41	0.5651
Al Balawi IA, <i>et al.</i> 2018	Asian	37	45	18	54	37	9	0.5651
Rahoui J, <i>et al.</i> 2014	African	32	28	10	90	40	11	0.1596
Jacobs EJ, <i>et al.</i> 2006	Caucasian	139	245	139	129	245	114	0.9112
Abdulhussein HA, <i>et al.</i> 2024	Asian	12	27	21	35	26	14	0.1596

Jin Q, *et al.* (2005) reported three independent case-control cohorts from Poland, Germany, and Sweden. These cohorts were analyzed separately and are identified by name followed by different numbers. Differences in sample size across VEGF polymorphisms reflect variation in the availability or successful genotyping of individual SNPs. HWE, Hardy-Weinberg Equilibrium; SNP, single-nucleotide polymorphisms; VEGF, vascular endothelial growth factor.

Table 2. The distribution of the *VEGF* 936 C>T allele and genotype among breast cancer cases and controls, HWE score.

Study	Ethnicity	CC	CA	AA	CC	CA	AA	HW-P-value
		Cases			Controls			
Li Z, <i>et al.</i> 2021	Asian	183	68	8	174	92	7	0.5529
Sambyal V, <i>et al.</i> 2021	Asian	207	42	1	213	36	1	0.827
Bricia M, <i>et al.</i> 2024	Caucasian	89	140	2	120	74	7	0.5552
Nobuhiko K, <i>et al.</i> 2006	Asian	744	334	31	793	351	51	0.5529
Peter K, <i>et al.</i> 2003	Caucasian	412	79	9	353	137	10	0.6483
Balasubramanian S, <i>et al.</i> 2007	Caucasian	624	204	20	531	165	12	0.8915
Abdelhamid H, <i>et al.</i> 2015	African	52	64	36	52	32	16	0.0729
Ajaz S, <i>et al.</i> 2019	Asian	101	16	1	119	20	0	0.6483
Luo T, <i>et al.</i> 2013	Asian	446	210	24	426	204	50	0.0072
Rodrigues P, <i>et al.</i> 2012	Caucasian	366	76	5	332	99	11	0.5552
Oliveira C <i>et al.</i> 2011	Caucasian	190	43	2	176	52	7	0.5529
Lin G, <i>et al.</i> 2009	Asian	155	59	6	211	117	6	0.1404
Kapahi R, <i>et al.</i> 2014	Asian	155	36	1	171	20	1	0.7987
Absenjer G, <i>et al.</i> 2013	Caucasian	371	138	12	580	201	20	0.7987
Jin Q, <i>et al.</i> 2005	Caucasian (Poland)	298	10	14	297	114	11	0.9877
Jin Q, <i>et al.</i> 2005_1	Caucasian (Germany)	120	31	2	128	31	4	0.5529
Jin Q, <i>et al.</i> 2005_2	Caucasian (Sweden)	708	204	12	720	203	11	0.6483
Jakubowska A, <i>et al.</i> 2008	Caucasian	245	67	7	202	81	7	0.8302

Jin Q, *et al.* reported three independent case-control cohorts from Poland, Germany, and Sweden. These cohorts were analyzed separately and are identified by name followed by different numbers. Differences in sample size across VEGF polymorphisms reflect variation in the availability or successful genotyping of individual SNPs. HWE, Hardy-Weinberg Equilibrium; SNP, single-nucleotide polymorphisms; VEGF, vascular endothelial growth factor.

Table 3. The distribution of the *VEGF* 634 G > C allele and genotype among breast cancer cases and controls, HWE score.

Study	Ethnicity	Cases			Controls			HW- <i>P</i> -value
		GG	GC	CC	GG	GC	GG	
Li Z, <i>et al.</i> 2021	Asian	80	121	58	105	132	36	0.6585
Rahoui J, <i>et al.</i> 2014	African	26	33	11	36	30	4	0.6227
AbdElhamid H, <i>et al.</i> 2015	African	25	98	29	1	72	27	0
Maghsoodi M, <i>et al.</i> 2023	Caucasian	30	40	62	51	37	44	0
Madrid-Paredes A, <i>et al.</i> 2020	Caucasian	11	30	39	11	60	52	0.419
Luo T, <i>et al.</i> 2013	Asian	338	205	137	341	204	135	0
Oliveira C <i>et al.</i> 2011	Caucasian	95	102	38	82	129	24	0.0214
Jin Q, <i>et al.</i> 2005	Caucasian	488	363	85	492	367	82	0.419
Jacobs EJ, <i>et al.</i> 2006	Caucasian	232	221	47	221	222	52	0.7332

HWE, Hardy-Weinberg Equilibrium; VEGF, vascular endothelial growth factor.

Table 4. The distribution of the *VEGF* 460 T > C allele and genotype among breast cancer cases and controls, HWE score.

Study	Ethnicity	Cases			Controls			HW- <i>P</i> -value
		TT	TC	CC	TT	TC	CC	
Li Z, <i>et al.</i> 2021	Asian	146	98	15	152	103	18	0.9221
Ibrahim A, <i>et al.</i> 2020	Asian	54	51	5	31	71	8	0.0008
Sambyal V, <i>et al.</i> 2021	Asian	75	117	58	81	137	32	0.0723
Nobuhiko K, <i>et al.</i> 2006	Asian	616	418	89	665	479	78	0.6719
Rahoui J, <i>et al.</i> 2014	African	27	25	18	16	39	15	0.5408
Balasubramanian S, <i>et al.</i> 2007	Caucasian	134	248	111	141	251	106	0.8813
Rezaei M, <i>et al.</i> 2016	Asian	69	148	33	66	131	18	0
Kapahi R, <i>et al.</i> 2014	Asian	61	92	51	72	105	27	0.4824

HWE, Hardy-Weinberg Equilibrium; VEGF, vascular endothelial growth factor.

Table 5. The distribution of the *VEGF* 405 C > G allele and genotype among breast cancer cases and controls, HWE score.

Study	Ethnicity	Cases			Controls			HW- <i>P</i> -value
		CC	CG	GG	CC	CG	GG	
Sambyal V, <i>et al.</i> 2021	Asian	15	105	130	25	121	104	0.4666
Nobuhiko K, <i>et al.</i> 2006	Asian	192	508	395	182	598	418	0.4666
Balasubramanian S, <i>et al.</i> 2007	Caucasian	57	207	226	209	225	64	0.8129
AbdElhamid H, <i>et al.</i> 2015	African	32	103	17	34	66	0	0
Rezaei M, <i>et al.</i> 2016	Asian	47	102	101	36	106	73	0.8129
Kapahi R, <i>et al.</i> 2014	Asian	11	77	104	24	94	74	0.7273

HWE, Hardy-Weinberg Equilibrium; VEGF, vascular endothelial growth factor.

–2578 C/A

A significant association with breast cancer susceptibility was observed in the allelic and recessive models ($P < 0.05$), whereas the dominant and over-dominant models did not achieve significance ($P > 0.05$) (**Figure 3**). Ethnicity-based subgroup analysis revealed a notably higher risk among Asian populations, while no meaningful association was detected in Caucasian cohorts. Due to the limited number of studies, conclusions could not be drawn for African populations.

936 C/T

This variant did not exhibit a significant association with breast cancer risk across all evaluated genetic

models (recessive, allelic, dominant, and over-dominant) ($P > 0.05$) (**Figure 4**). Subgroup comparisons, however, suggested a comparatively elevated risk among Asians relative to Caucasians. The scarcity of studies from African populations precluded reliable subgroup assessment.

634 G/C

This polymorphism revealed no significant association with breast cancer across any of the analyzed genetic models ($P > 0.05$) (**Figure 5**). Similarly, ethnicity-stratified analyses revealed no detectable risk in either Asian or Caucasian groups. African populations could not be examined due to insufficient data.

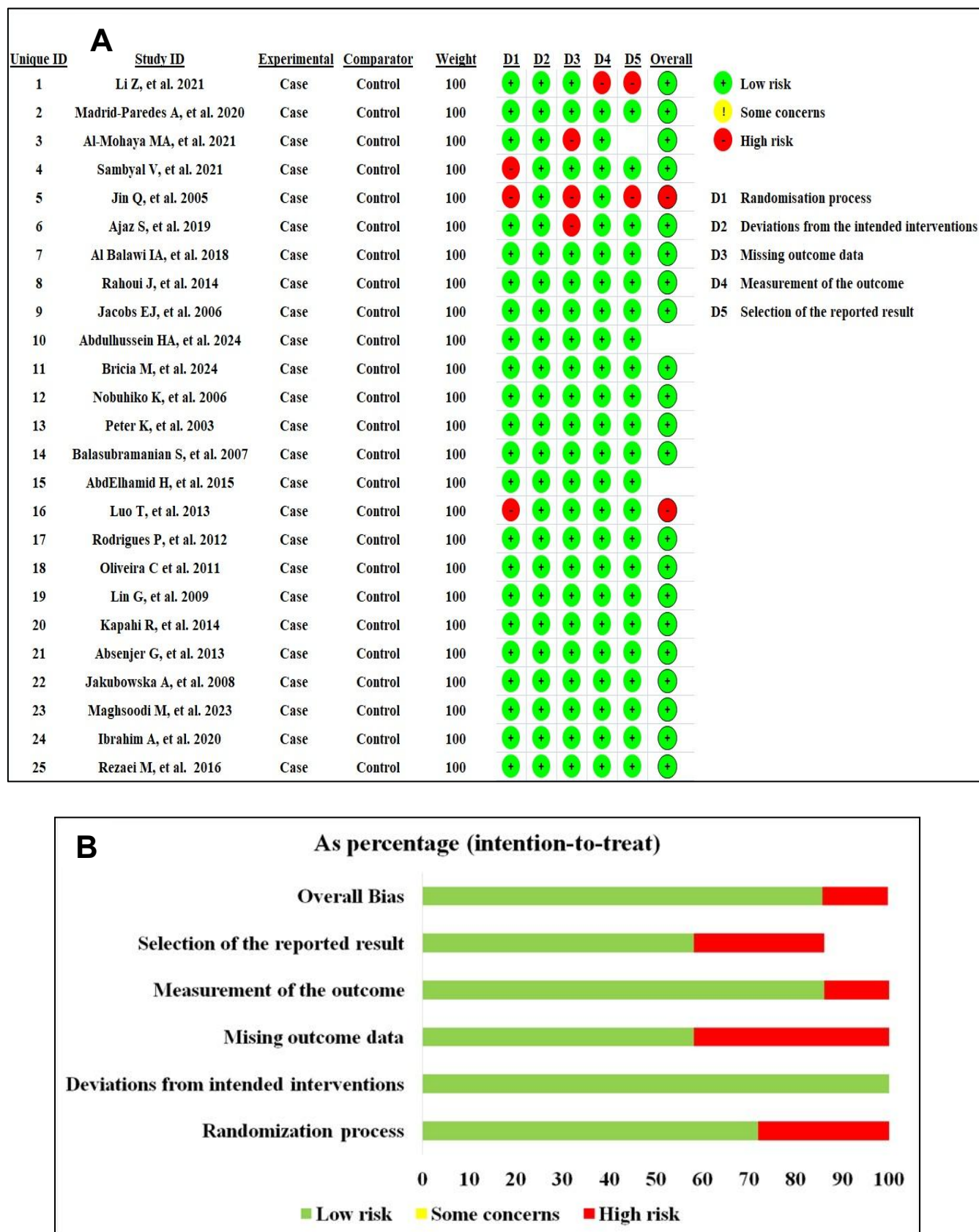


Figure 2. (A)Traffic-light plot showing the risk-of-bias assessment across individual included studies and domains,(**B**) summary plot showing the percentage distribution of risk-of-bias judgments across individual domains and overall bias.

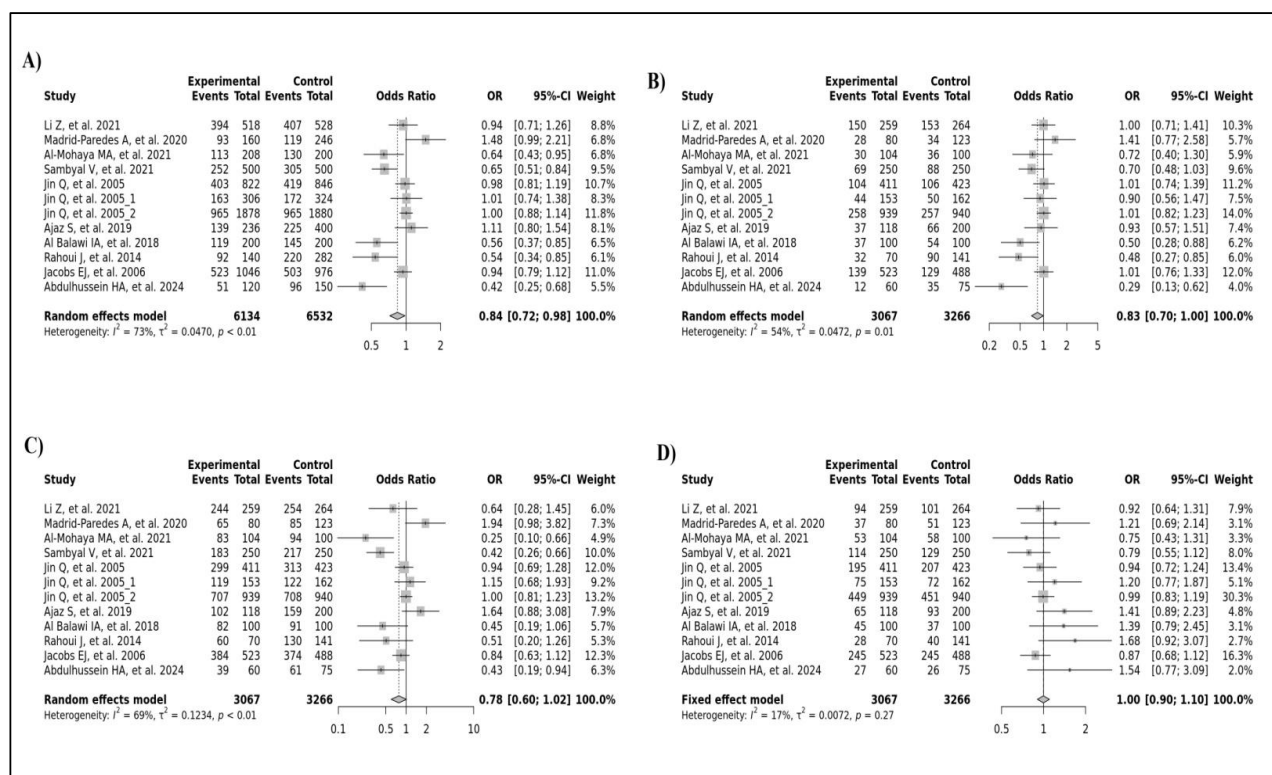


Figure 3. Forest plot for the association of *VEGF* 2578 C>A gene polymorphism with breast cancer risk under A) allelic, B) recessive, C) dominant, and D) over dominant models. Name followed by numbers were added to distinguish the independent Polish (Jin Q, *et al.* 2005), German (Jin Q, *et al.* 2005_1), and Swedish ((Jin Q, *et al.* 2005_2) cohorts reported within Jin Q, *et al.* (2005). These labels represent separate study populations from one publication, not duplicate publications. CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

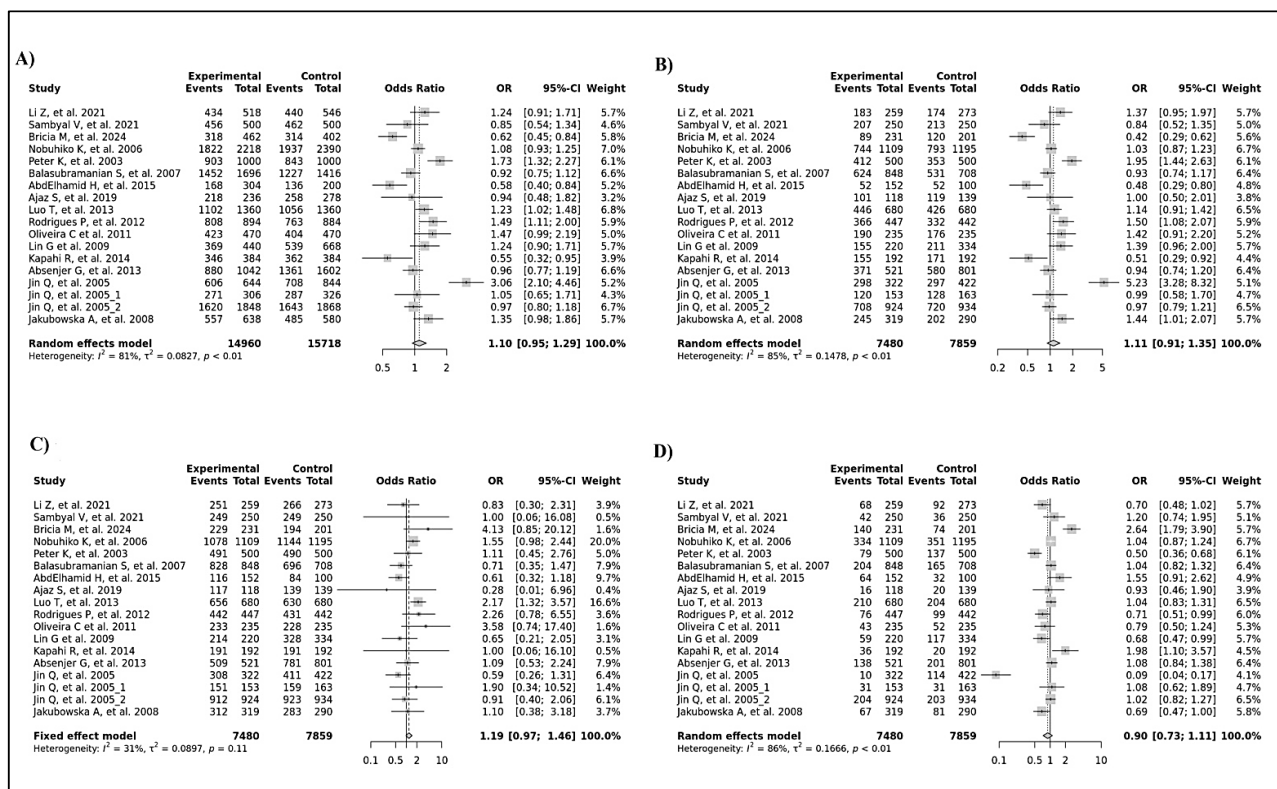


Figure 4. Forest plot for the association of *VEGF* 936 C>T gene polymorphism with breast cancer risk under (A) allelic, (B) recessive, (C) dominant, and (D) over dominant models. Name followed by numbers were added to distinguish the independent Polish (Jin Q, *et al.* 2005_1), German (Jin Q, *et al.* 2005_2), and Swedish ((Jin Q, *et al.* 2005_3) cohorts reported within Jin Q, *et al.* These labels represent separate study populations from one publication, not duplicate publications. CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial

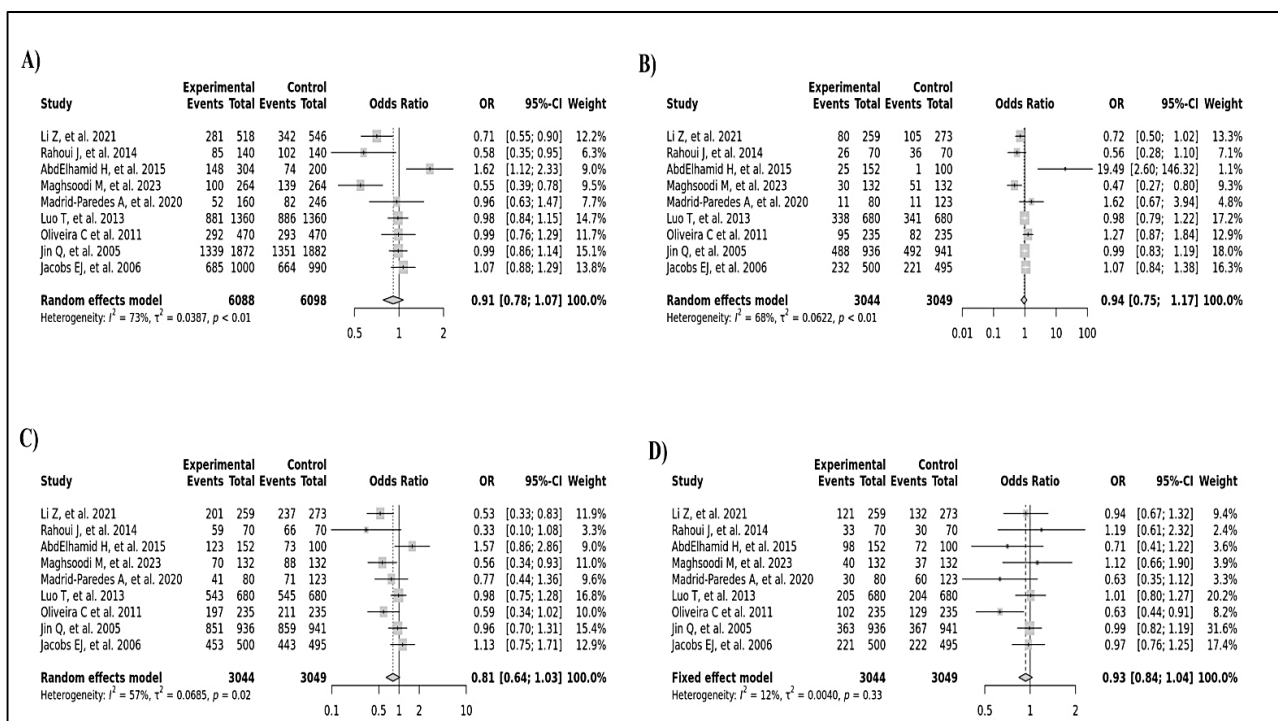


Figure 5. Forest plot for the association of *VEGF* 634 G > C gene polymorphism with breast cancer risk under (A) allelic, (B) recessive, (C) dominant, and (D) over dominant models. CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

460 C/T

Significant relationships were identified for the dominant and over-dominant models ($P < 0.05$), indicating a potential effect of this variant on breast cancer susceptibility (Figure 6). However, as only a few studies included Caucasian or African participants, subgroup analyses were not feasible.

405 C/G

This variant demonstrated a significant association with breast cancer in the dominant and over-dominant models ($P < 0.05$). In contrast, the allelic and recessive models did not reveal significant results ($P > 0.05$) (Figure 7). Similar to *VEGF* 460 C/T, subgroup evaluation for Caucasian and African populations was not performed due to inadequate representation in the available studies.

Heterogeneity, sensitivity analysis, and publication bias

The outcomes of the HWE assessment for fixed- and random-effect models, together with the results from ethnicity-based subgroup analyses, are presented in

Tables 6–10. These tables provide a comprehensive summary of the genetic distribution patterns and population-specific differences associated with the *VEGF* polymorphisms and breast cancer risk. Study heterogeneity was quantified using the I^2 statistic. Analyses with an $I^2 < 50.0\%$ were interpreted using a fixed-effect model, whereas those $>50.0\%$ were evaluated using a random-effects model to account for between-study variability.

To further illustrate heterogeneity, forest plots were constructed for each of the *VEGF* variants included in the meta-analysis. A sensitivity analysis was performed for all polymorphisms to assess the robustness of the pooled results (Figure 8). For most variants, the overall effect size remained stable when individual studies were omitted. The exception was *VEGF* 405 C/G, where the exclusion of a single study distinguished by a much larger sample size resulted in noticeable changes in the summary estimate. To assess the presence of publication bias, funnel plots were generated for all *VEGF* polymorphisms (Figure 9). The plots appeared largely symmetrical, thus indicating that the likelihood of major publication bias influencing the results was low.

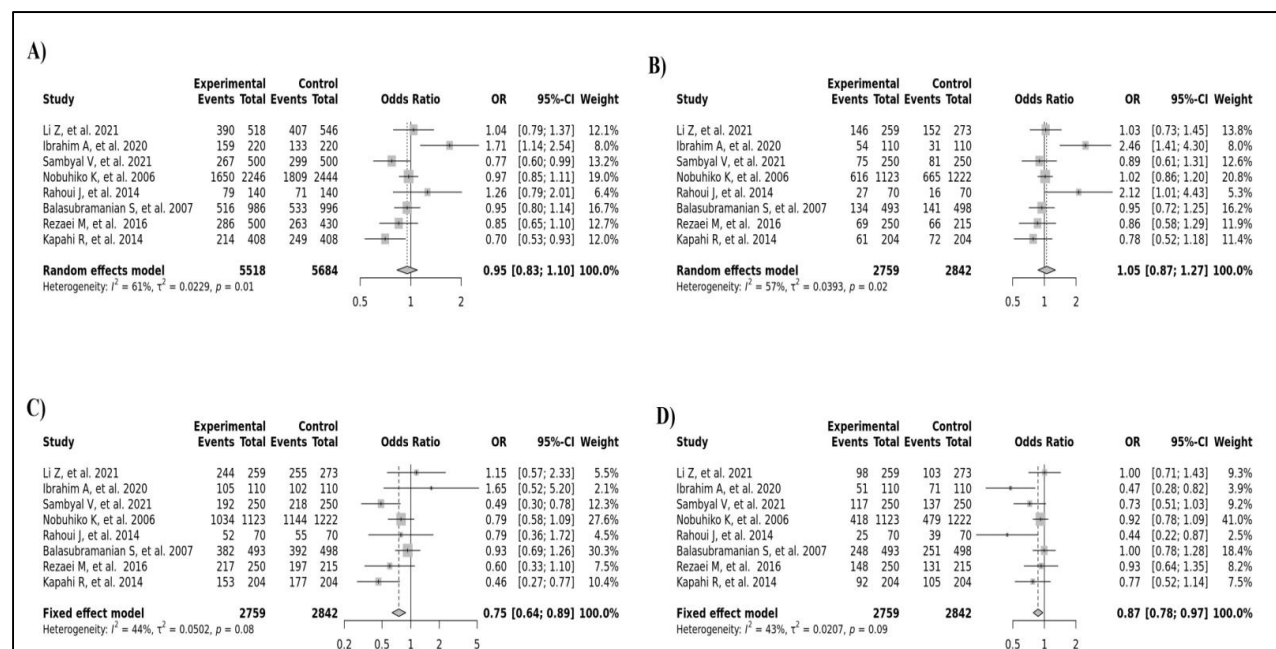


Figure 6. Forest plot for the association of *VEGF* 460 T > C gene polymorphism with breast cancer risk under (A) allelic, (B) recessive, (C) dominant, and (D) over dominant models. CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

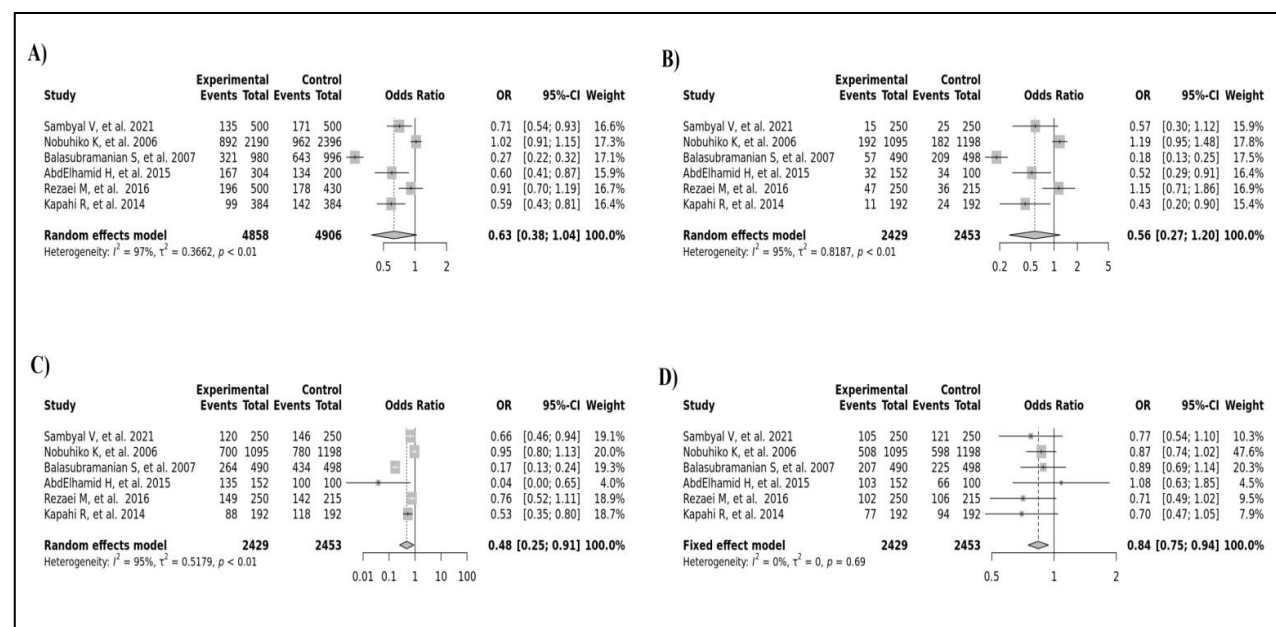


Figure 7. Forest plot for the association of *VEGF* 405 G/C gene polymorphism with breast cancer risk under (A) allelic, (B) recessive, (C) dominant, and (D) over dominant models. CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Table 6. Summary estimates for ORs and 95% CI in different ethnicities of *VEGF* 2578 C>A gene polymorphism with risk of breast cancer.

Model	Ethnicity	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95% CI	P-value	P-value	I ²	P-value (Egger's test)
Allele contrast (A vs. a)	Overall	12	0.84	[0.72 0.98]	0.02	0	0.7289	0.09
	Asian	6	0.71	[0.54 0.92]	0.00	0.0038	0.713	0.32
	Caucasian	5	1.00	[0.92 1.09]	0.981	0.3793	0.0482	0.23
Recessive model (AA vs. Aa+aa)	Overall	12	0.83	[0.70 0.99]	0.04	0.0125	0.5427	0.02
	Asian	6	0.69	[0.51 0.94]	0.01	0.045	0.5591	0.06
	Caucasian	5	1.02	[0.89 1.16]	0.81	0.8518	0	0.46
Dominant model (AA+Aa vs. aa)	Overall	12	0.78	[0.60 1.02]	0.06	0.0002	0.6941	0.21
	Asian	6	0.54	[0.32 0.93]	0.02	0.0059	0.6946	0.83
	Caucasian	5	0.98	[0.86 1.13]	0.81	0.2481	0.2601	0.19
Overdominant (Aa vs. AA + aa)	Overall	12	0.99	[0.90 1.10]	0.96	0.2721	0.175	0.06
	Asian	6	1.00	[0.83 1.20]	0.99	0.1552	0.3764	0.20
	Caucasian	5	0.98	[0.87 1.10]	0.69	0.683	0	0.27

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Table 7. Summary estimates for ORs and 95% CI in different ethnicities of *VEGF* 936 C>T gene polymorphism with risk of breast cancer.

Model	Ethnicity	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95% CI	P-value	P-value	I ²	P-value (Egger's test)
Allele contrast (A vs. a)	Overall	18	1.10	[0.95 1.29]	0.2	0	0.8068	0.97
	Asian	7	1.11	[1.01 1.22]	0.04	0.1191	0.4079	0.25
	Caucasian	10	1.22	[0.96 1.56]	0.10	0	0.8639	0.18
Recessive model (AA vs. Aa+aa)	Overall	18	1.11	[0.91 1.35]	0.31	0	0.8507	0.87
	Asian	7	1.06	[0.89 1.27]	0.51	0.0769	0.4734	0.55
	Caucasian	10	1.26	[0.91 1.74]	0.16	0	0.9017	0.32
Dominant model (AA+Aa vs. aa)	Overall	18	1.19	[0.97 1.46]	0.09	0.1071	0.3054	0.66
	Asian	7	1.52	[1.13 2.06]	0.01	0.3548	0.0973	0.08
	Caucasian	10	1.07	[0.79 1.45]	0.65	0.2864	0.1702	0.00
Overdominant (Aa vs. AA + aa)	Overall	18	0.90	[0.73 1.11]	0.31	0	0.8571	0.45
	Asian	7	0.98	[0.80 1.20]	0.86	0.0339	0.5602	0.95
	Caucasian	10	0.78	[0.55 1.11]	0.16	0	0.9103	0.25

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Table 8. Summary estimates for ORs and 95% CI in overall population of *VEGF* 634 G>C gene polymorphism with risk of breast cancer.

Model	Ethnicity	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95% CI	P-value	P-value	I ²	P-value (Egger's test)
Allele contrast (A vs. a)	Overall	9	0.91	[0.78 1.07]	0.27	0.00	0.73	0.42
Recessive model (AA vs. Aa+aa)	Overall	9	0.94	[0.75 1.17]	0.58	0.00	0.68	0.79
Dominant model (AA+Aa vs. aa)	Overall	9	0.81	[0.64 1.03]	0.09	0.02	0.57	0.21
Overdominant (Aa vs. AA + aa)	Overall	9	0.93	[0.84 1.04]	0.19	0.33	0.12	0.30

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Table 9. Summary estimates for ORs and 95% CI in overall population of *VEGF* 460 T>C gene polymorphism with risk of breast cancer.

Model	Ethnicity	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95% CI	P-value	P-value	I ²	P-value (Egger's test)
Allele contrast (A vs. a)	Overall	8	0.95	[0.83 1.10]	0.50	0.01	0.60	0.59
Recessive model (AA vs. Aa+aa)	Overall	8	1.05	[0.87 1.28]	0.60	0.02	0.57	0.32
Dominant model (AA+Aa vs. aa)	Overall	8	0.73	[0.57 0.94]	0.01	0.08	0.44	0.97
Overdominant (Aa vs. AA + aa)	Overall	8	0.83	[0.71 0.98]	0.02	0.09	0.43	0.03

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Table 10. Summary estimates for ORs and 95% CI in overall population of *VEGF* 405 C>G gene polymorphism with risk of breast cancer.

Model	Ethnicity	Number of studies	Test of association		Test of heterogeneity		Publication bias	
			OR	95% CI	P-value	P-value	I ²	P-value (Egger's test)
Allele contrast (A vs. a)	Overall	6	0.63	[0.38 1.04]	0.07	0	0.97	0.52
Recessive model (AA vs. Aa+aa)	Overall	6	0.56	[0.27 1.20]	0.14	0	0.95	0.56
Dominant model (AA+Aa vs. aa)	Overall	6	0.48	[0.26 0.91]	0.02	0	0.95	0.32
Overdominant (Aa vs. AA + aa)	Overall	6	0.84	[0.75 0.94]	0.00	0.69	0.00	0.58

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

Discussion

Breast cancer is a complex disease influenced by the interplay of genetic predisposition and environmental exposure.⁽³⁷⁾ Among the biological pathways implicated in its development, VEGF plays a crucial role because of its regulatory function in angiogenesis. Aberrant VEGF expression is frequently observed in malignancies, including breast cancer, where it contributes to tumor vascularization, growth, and metastatic spread. As VEGF-driven angiogenesis is critical for sustaining tumor progression, variations in the VEGF gene have garnered considerable interest as potential genetic determinants of breast cancer susceptibility.

Several SNPs within the VEGF gene, namely 936 C > T, 2578 C > A, 634 G > C, 460 T > C, and 405 C > G, have been investigated in different populations.⁽⁶⁻⁸⁾ However, individual studies have produced inconsistent findings, likely due to limited sample sizes, ethnic heterogeneity, and methodological differences. This meta-analysis was performed to consolidate the available evidence and provide a more precise estimate of the association between these VEGF variants and breast cancer risk.

Among the investigated variants, VEGF -2578 C > A (rs699947) revealed a significant association with breast cancer susceptibility in the allelic and recessive models. This finding is supported by Kapahi R, *et al.*, who reported that the VEGF -2578 AA genotype and A allele were associated with increased breast cancer risk in a North Indian population.⁽¹⁸⁾ The reported ORs were 2.87 for the AA genotype and 1.65 for the A allele. Similarly, Rezaei M, *et al.* observed increased breast cancer susceptibility among Iranian women carrying the CA or AA genotype in the dominant model and among carriers of the A allele.⁽²²⁾ Furthermore, a Saudi Arabian case-control study reported an association between the VEGF -2578 C > A variant, particularly the AA genotype, and breast cancer susceptibility. These findings suggest that rs699947 may influence breast cancer risk in certain populations.⁽²⁴⁾

Nevertheless, the evidence is not uniform across populations. Jacobs *et al.* found no overall association between the investigated VEGF polymorphisms, including VEGF -2578 C > A, and breast cancer risk in the Cancer Prevention Study II cohort.⁽³⁴⁾ Such discrepancies may reflect the ethnic differences in allele distribution and linkage disequilibrium,

differences in the sample size and control selection, or interactions with environmental and hormonal risk factors. Therefore, the association observed in the present meta-analysis should be interpreted as population- and genetic-model-dependent rather than as a universally increased risk.

In the present analysis, the VEGF -460 T > C polymorphism (rs833061) was significantly associated with breast cancer in the dominant and over-dominant models. Kapahi, *et al.* reported that the CC genotype and C allele were associated with increased breast cancer risk in North Indian women, with ORs of 2.23 and 1.42, respectively.⁽¹⁸⁾ A study in a Saudi Arabian population also found a significant association between -460 T > C genotype variation and breast cancer susceptibility.⁽²⁴⁾ These observations support the potential contribution of this promoter-region variant to breast cancer development.

In contrast, the population-based Shanghai Breast Cancer Study found no significant association between the VEGF -460 T > C polymorphism and breast cancer risk, and Rezaei M, *et al.* similarly reported no significant association for rs833061 in their Iranian population.⁽²²⁾ These conflicting results emphasize the importance of ethnicity, genotype coding, reference-allele selection, and the genetic model applied. Because -2578 C > A and -460 T > C are both located in the VEGFA promoter region, sequence variation at these sites may potentially alter the transcriptional regulation and VEGF-mediated angiogenic activity. However, larger multiethnic studies that combine genotype data with VEGF expression measurements are required to establish the biological and clinical importance of these associations.

One of the prominent observations of this meta-analysis was the variation in genetic risk across ethnic groups. Subgroup analyses revealed that Asian populations exhibited stronger associations between VEGF polymorphisms, particularly 2578 C/A and 460 T/C, and breast cancer risk compared with Caucasian populations. These differences may arise from distinct allele frequencies, varying linkage disequilibrium patterns, or different environmental exposures. Genetic architecture across populations may thus modulate the influence of VEGF variants on cancer susceptibility.

However, the lack of sufficient studies from African populations remains a major limitation. The inability to perform subgroup analyses for this group underscores a considerable gap in the literature.

Expanding genetic association studies to include underrepresented populations will enhance the clarity and global relevance of research on VEGF polymorphisms.

This meta-analysis possesses several notable strengths. The inclusion of a large cumulative sample size and a broad range of studies substantially increases the statistical power, thereby improving the ability to detect genuine associations between *VEGF* polymorphisms and breast cancer risk. Furthermore, the application of rigorous statistical approaches, including fixed- and random-effects models, minimizes the influence of inter-study variability and enhances the reliability of the pooled estimates. In addition, the incorporation of studies from multiple ethnic populations allows for more comprehensive and generalizable conclusions regarding the contribution of *VEGF* genetic variants to breast cancer susceptibility.

Nevertheless, several limitations should be acknowledged. Considerable heterogeneity exists among the included studies, likely arising from differences in study design, demographic characteristics, genotyping techniques, and clinical variables. Although subgroup analyses mitigated some of these inconsistencies, additional stratification, such as by menopausal status, hormone receptor subtypes, or other clinical parameters, could yield more precise insights into the population-specific genetic risk factors. Another important limitation is the underrepresentation of African populations. The small number of available studies from this group prevented meaningful subgroup comparisons, thereby limiting the ability to draw firm conclusions about VEGF polymorphisms in African individuals. Future research incorporating larger and more diverse patient cohorts is essential to ensure that genetic risk assessments are inclusive and applicable across global populations.

Conclusion

This updated and comprehensive meta-analysis provides robust evidence that specific VEGF gene polymorphisms contribute to breast cancer susceptibility. Among the five evaluated variants, *VEGF* -2578 C/A, 460 T/C, and 405 C/G demonstrated significant associations with increased risk across various genetic models, suggesting that these loci may influence VEGF expression and thereby modulate angiogenic activity, which is central to breast tumor development. In contrast, the *VEGF* 936 C/T

and 634 G/C variants showed no meaningful association with disease risk, indicating that their biological contribution to breast carcinogenesis may be limited or context-dependent. Ethnicity emerged as an important modifier of genetic risk, with Asian populations showing stronger associations than Caucasian groups across several of the *VEGF* variants. These findings emphasize the relevance of population-specific genetic architecture and the necessity for diverse representation in cancer genetics research. However, the paucity of data from African populations remains a notable gap, limiting the generalizability of conclusions for these groups. Despite some heterogeneity among studies, rigorous sensitivity analyses, large pooled sample sizes, and low publication-bias indicators strengthen the credibility of the present findings. Collectively, this meta-analysis enhances our current understanding of *VEGF*-mediated genetic susceptibility to breast cancer and highlights the importance of integrating angiogenesis-related genetic markers into future risk prediction models. Large, multiethnic, well-characterized cohort studies with standardized genotyping approaches are strongly recommended to clarify VEGF's role further.

Author contributions

SKY contributed substantially to the concept and design of this study, data acquisition and analysis, the literature review, and drafting the manuscript. SSK contributed to data acquisition and helped draft the manuscript. VN contributed to data interpretation and analysis.

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Conflict of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. All authors declare that they have no conflicts of interest.

Data sharing statement

All data generated or analyzed in the present study are included in the published article. Further details are available for non-commercial purposes from the corresponding author upon reasonable request.

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