International Journal of Comprehensive Health, Medicine, and Dentistry

IJCHMD 2026;2(1) 35-56

Original Article

Association of CYP1A1 rs1048943 Polymorphism: A Comprehensive Meta-Analysis of Case–Control Studies

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Abstract:

Breast cancer remains the most prevalent malignancy in women worldwide and its etiology involves genetic and environmental components. Among these genetic components, the CYP1A1 rs1048943 (Ile462Val) polymorphism has been shown to play a modifying role in breast cancer susceptibility based on its contribution to the metabolism of carcinogens and estrogens.

This meta-analysis objectively estimated the risk association of this polymorphism and breast cancer in 34 case-control studies including 14,166 cases and 18,912 controls Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated under various genetic models. The dominant model (GG+GA vs. AA) revealed a significant association with breast cancer risk in the overall population (OR = 1.1533, 95% CI: 1.0038–1.3250, p = 0.044). Subgroup analysis by ethnicity showed a stronger effect in Asian populations (OR = 1.2742, 95% CI: 1.0123–1.6038, p = 0.039), while a protective effect was observed

in Caucasians (OR = 0.8843, 95% CI: 0.7837–0.9979, p = 0.046). Other genetic models, including the allele contrast, recessive, over dominant, and homozygote comparisons, did not show statistically significant associations in the overall analysis. Sensitivity analyses confirmed the consistency of findings, stability of the dominant model results, and no major publication bias was detected. These findings suggest that the CYP1A1 rs1048943 polymorphism may be associated with breast cancer susceptibility, particularly among Asian populations, while ethnic differences may influence its effect.

Keywords:

Breast Cancer Susceptibility, CYP1A1 polymorphism, Meta-Analysis, Ethnic variation, Genetic Association.

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Received: 7 December 2025 **Revised:** 7 January 2026 **Accepted**: 127 January 2026

Published: 31 January 2026

Introduction:

Breast cancer is a malignant neoplasm of the lobules or ductal epithelium of the breast. It is ranked the highest incidence among all malignancies affecting women worldwide [1]. It is the most frequent malignancy to be diagnosed in women worldwide. Breast cancer has become the most common cancer diagnosed and the fifth leading cause of cancer-related death worldwide, replacing lung cancer in recent years. There were an estimated 2.3 million new cases and 685,000 deaths in 2020, and the incidence is expected to increase to 4.4 million by 2070. [2]. Associated with the loss of significant healthy life years (14.9 million DALYs), breast cancer is a major contributor to global cancer morbidity and mortality. Incidence and mortality burden increases in developed and developing nations both, making it one of the world's most serious, burdensome cancers. [3] Various studies and researches have suggested that BC incidence is highest in countries like Northern America, Australia, New Zealand and regions of Europe, that ranges between 85.8 to 91.6 cases per 100,000 while the mortality rates are highest in regions like Africa and Oceania, that ranges from 17.4 to 20.1 deaths per 100,000. [4]. Although the incidence of breast cancer among women who live in South Asia is as in the West, the mortality rates among South Asian women are disproportionately high. The disparity is primarily because of the lack of screening guidelines, poor awareness, and a lack of adequate knowledge on the part of the masses about breast cancer and early detection among this population. [5]. Breast cancer is the most prevalent cancer in Pakistani women and accounts for 34.6% of all cancers in women. One out of every nine women in Pakistan is at risk of developing the disease. Alarmingly, only 10% of them are diagnosed with the disease, and out of them, almost 75% of the diagnosed ones do not receive treatment and die of the disease within five years. This is one of the highest breast cancer rates in Asia.[6]

Breast cancer risk is influenced by a complex interplay of genetic and environmental factors. Several genes have been associated with higher risk of breast cancer including BRIPI, CHEK2, TGFB, MDM, TP53, and PTEN, BRCA2, and BRCA1. [7]. About 10% of female breast cancer cases are linked with inherited autosomal dominant mutations, which are mostly caused by germline mutations in the BRCA1 and BRCA2 genes. Gene mutations are considered to be high-risk genetic factors for breast cancer. Female patients with mutations in the BRCA1 or BRCA2 gene have a lifetime risk of 60–80% for breast cancer.[8]. While only 5 to 10% of breast cancer cases are hereditary, recent estimates indicate that 55–65% of women carrying BRCA1 mutations and around 45% of those with BRCA2 mutations will develop breast cancer by the age of 70.[9]. Demographic characteristics such as age, ethnicity, reproductive history, body mass, socioeconomic status, and geographic location also contribute to an individual's risk level. There is growing evidences that environmental exposures such as tobacco smoke, pesticides, insecticides, and food packaging bisphenol are also major causes of risk elevation for breast cancer.[10]. Based on WHO studies, at least 35% of cancer mortality worldwide can be causally attributed to potentially modifiable environmental and lifestyle risk factors. These include alcohol consumption, exposure to ultraviolet (UV) light from the sun and artificial sources of tanning beds, diet, hormone replacement, and exposure to ionizing radiation. The pattern is seen in low, middle and high-income nations.[11]. Weight gain is another major risk factor for breast cancer. The age when menstruation begins is also an important variable in the evaluation of breast cancer risk. Women who have their first menstrual period under the age of 12 are more vulnerable than those whose period occurs later since levels of estrogen increase of the girls' blood after puberty.[12].

Cytochrome P450 1A1 (CYP1A1) is a phase I enzyme that participates in the metabolism of endogenous compounds and environmental pollutants. It plays a role in cancer initiation by catalyzing procarcinogens like polycyclic aromatic hydrocarbons and estradiol. Some genetic polymorphisms of CYP1A1, such as the A2455G SNP, have also been implicated in the increased risk of breast cancer, particularly in Caucasian individuals.[13]. CYP1A1 is also involved in the metabolism of estrogen in extrahepatic tissues by catalyzing estrogen hydroxylation. [14]. The CYP1A1 gene has four common polymorphisms. The M1 variant is a T to C transition at nucleotide 3801 in the 3' noncoding region, thus generating a MspI restriction site. The M2 variant is an A to G transition at nucleotide 2455, resulting in an amino acid change from isoleucine to valine at codon 462 in the heme-binding domain of exon 7. The M3 variant is a T to C transition at nucleotide 3205 in the 3' noncoding region of intron 7, resulting in an RFLP detectable with MspI. Lastly, the M4 variant is a C to A transition at nucleotide 2453, resulting in a threonine to asparagine substitution at codon 461 in exon 2 region.[15]. CYP1A1 is a polymorphic gene, situated on chromosome 15 at position 15q22-q24 and is of 5987-bp length. It consists of 7 exons and 6 introns coding for a 512 amino acid protein. [16] [17]. The CYP1A1 gene contains a significant SNP known as CYP1A1*2C which is additionally alluded to as A2455G, the m2 allele, or rs1048943.[18]. The A2455G polymorphism can affect the level of gene expression or messenger RNA stability, leading to high inducibility of the Cytochrome P450 1A1 activity.[19]

The main objective of this meta-analysis is to assess the overall correlation of the CYP1A1 rs1048943 (A4889G) polymorphism with breast cancer risk in ethnically diverse groups. The investigation also aims to examine the interaction of ethnicity with different genetic models such as dominant, over dominant, recessive, genotype-based comparisons (e.g., homozygote vs heterozygote) and allelic models with the correlation of interest. Specifically, this study aims to quantify the strength of this association by calculating odds ratios (ORs) and 95% confidence intervals (CIs) under these genetic models. In order to provide assurance regarding the reliability and strength of the results, the study also seeks to evaluate the occurrence of publication bias and the heterogeneity among the studies included.

Materials and Methods:

Searching Strategy

The search strategy for this meta-analysis is depicted in Figure 1. Study identification and selection followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A systematic literature search was conducted up to May 2025, focusing exclusively on case-control studies. The comprehensive search encompassed several databases, including PubMed, Research Gate, Science Direct, Science Hub and Google Scholar. Relevant studies were identified using keywords such as “CYP1A1 polymorphisms in breast cancer” “A2455G polymorphism,”, “CYP1A1 M2 variation” and “rs1048943 CYP1A1 association.” In total, 34 studies examining the Ile462Val (CYP1A1*2C) polymorphism were included, each providing genotypic data from a case-control design.

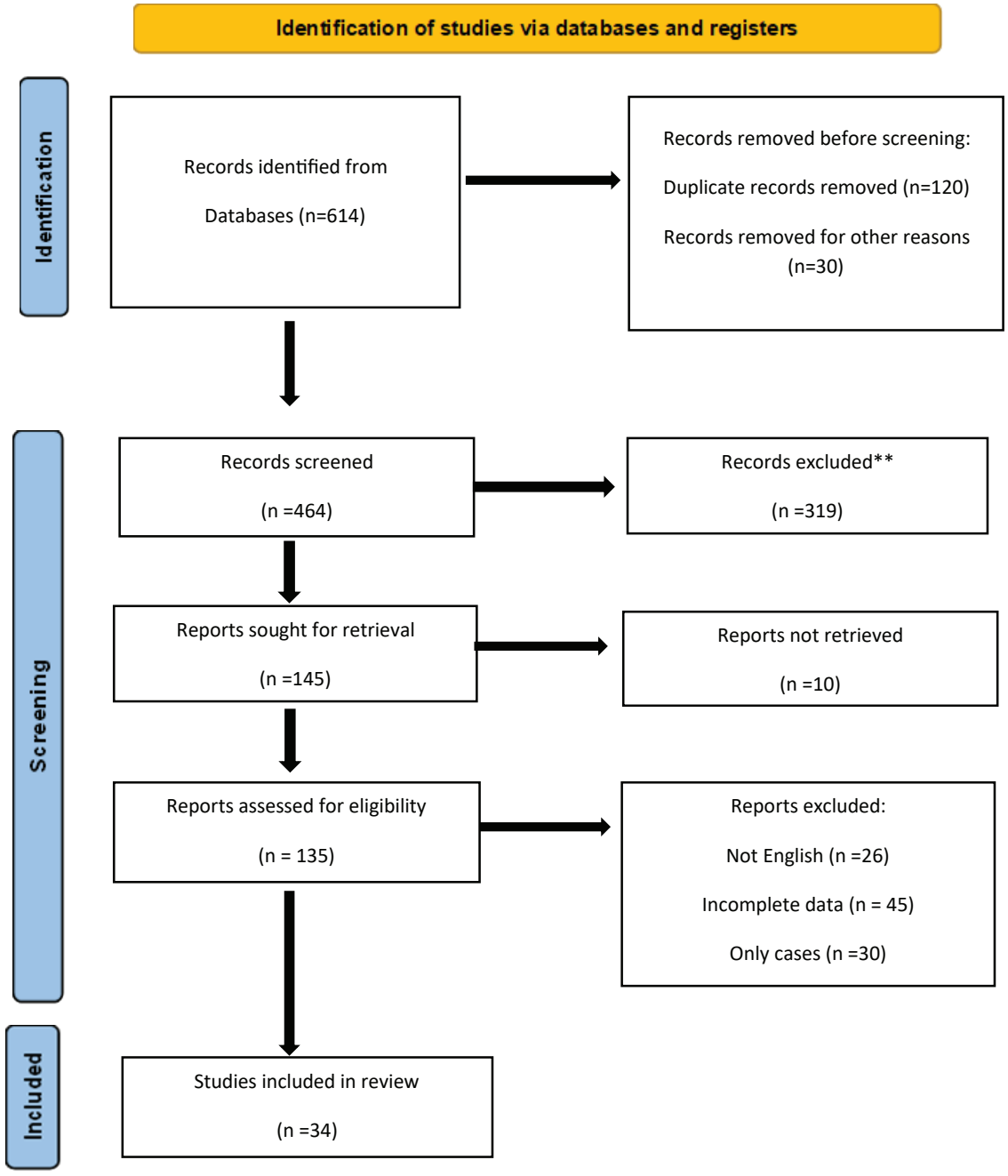

Figure 1: The PRISMA flowchart illustrating the study selection process for inclusion in the meta-analysis

Data Extraction and Quality Assessment

Data was separately retrieved into a standardized manner by two independent reviewers from the published data. The following information was included in each article: the first author's name, the year of publication, the country of origin, the sample sizes, the genotyping frequencies, the number of cases and control (Table 1). The quality of the following studies was assessed and evaluated using a standardized evaluation tool to ensure methodological consistency and reliability.

Table 1. Data inclusions and Hardy Weinberg Equilibrium (HWE) included in meta-analysis.

Study	References	Ethnicity	GG_Cases	GA_Cases	AA_Cases	GG-Controls	GA_Controls	AA_Controls	HW-P.value	HW-adjusted.P.value
Murithi et al., 2023	[20]	Mixed	2	5	61	0	0	20	1	1
Lin et al., 2022	[21]	Asian	12	92	117	12	59	75	0.9339	0.9923
Ibrahem et al., 2021	[22]	Asian	20	70	90	12	38	130	0.0005	0.0024
Zhao et al., 2021	[23]	Asian	5	55	80	9	31	100	0.0058	0.0246
Hamad et al., 2021	[24]	Mixed	16	14	70	8	5	87	0	0
Ghazaleh et al., 2019	[25]	Asian	0	21	75	2	17	91	0.2706	0.5932
Mary et al., 2019	[26]	Asian	4	36	160	2	34	164	0.8726	0.957
Wielsøe et al., 2018	[28]	Asian	17	38	20	19	38	24	0.6008	0.8881
Naif et al., 2018	[27]	Asian	97	62	40	21	65	74	0.2692	0.5932
Humberto et al., 2017	[28]	Caucasian	4	60	873	3	92	890	0.7046	0.9022
García et al., 2017	[29]	Mixed	150	409	368	161	488	338	0.4951	0.7652
Ghisari et al., 2017	[30]	Caucasian	0	4	138	1	8	187	0.0122	0.0461
Mutar et al., 2017	[31]	Asian	21	3	26	30	7	13	0	0
Parisa et al., 2016	[32]	Asian	43	13	23	27	12	40	0	0
Amrani et al., 2016	[33]	Asian	0	10	102	1	12	102	0.3492	0.6249
Borges et al., 2015	[34]	Mixed	20	195	527	15	157	570	0.2834	0.5932

Hakimeh et al., 2014	[36]	Asian	1	17	82	0	7	93	0.7168	0.9022
Martínez et al., 2013	[37]	Mixed	74	37	39	50	43	57	0	0
Wang et al., 2011	[38]	Asian	36	149	215	24	152	224	0.7897	0.9224
Moreno et al., 2010	[39]	Mixed	14	48	29	15	41	38	0.4845	0.7652
Marie, 2010	[40]	Caucasian	2	210	2934	7	378	5099	0.9984	1
Laetitia et al, 2010	[41]	Caucasian	5	52	853	5	59	932	0.0003	0.0017
Surekha et al., 2009	[42]	Asian	1	169	78	0	127	122	0	0
Shimada et al., 2009	[43]	Mixed	29	245	592	28	232	613	0.2966	0.5932
Christina et al., 2008	[44]	Caucasian	0	41	563	3	51	565	0.1225	0.3786
Shin et al., 2007	[45]	Asian	28	213	252	30	175	232	0.6982	0.9022
Sillanpää et al., 2007	[46]	Caucasian	2	53	426	1	66	412	0.3274	0.6184
Singh et al., 2006	[47]	Asian	0	25	80	5	41	70	0.743	0.9022
Sonia et al., 2005	[48]	Asian	51	421	659	73	442	694	0.8139	0.9224
Hefler et al., 2004	[49]	Caucasian	1	28	361	6	117	1570	0.0188	0.0639
Li et al., 2004	[15]	Mixed	3	41	644	2	48	652	0.2725	0.5932
Miyoshi et al., 2002	[50]	Asian	12	52	131	22	94	156	0.1499	0.4247
Huang et al., 1999	[51]	Asian	8	64	71	12	53	80	0.4491	0.7635

Inclusion and Exclusion Criteria

The inclusion criteria for this study were as follows: (1) studies that involved both breast cancer patients and healthy control groups; (2) studies that provided genotyping data; (3) studies that evaluated the association between CYP1A1 polymorphisms and breast cancer risk; and (4) only full-text articles published in English were considered. The exclusion criteria for this study were as follows: (1) studies that were not based on a case-control design; (2) duplicate publications of previously included research; (3) studies with insufficient or incomplete data; (4) studies that did not evaluate the association between CYP1A1 polymorphisms and breast cancer risk; and (5) non-original research articles, including editorials, letters, case reports, reviews, and other meta-analyses.

Statistical analysis

Statistical analyses were conducted using R Studio to estimate the pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs), a random-effects model was primarily applied to account for expected heterogeneity among studies. When heterogeneity was low, a fixed-effects model was used instead. Inter-study heterogeneity was quantified using the I^2 statistic, with values above 50% indicating substantial heterogeneity. Publication bias was assessed using Egger's test, complemented by funnel plot analysis for visual inspection. To ensure the validity of genotype distributions in control groups, the Hardy-Weinberg equilibrium (HWE) test was conducted, thereby confirming the reliability of the genetic data included in the meta-analysis.

Sensitivity Analysis

A sensitivity analysis was conducted to test the stability of our meta-analysis results and to assess the potential influence of each individual study on the overall outcome. This was done using the leave-one-out approach, in which one study was omitted at a time, and the pooled odds ratio and 95% confidence interval were recalculated for each iteration. This method allowed us to identify any single study that might disproportionately affect the combined effect estimate.

Results:

This meta-analysis examines the relationship between the CYP1A1 rs1048943 (Ile462Val) polymorphism and breast cancer susceptibility, drawing on data from 34 case-control studies involving a total of 14,166 breast cancer cases and 18,912 healthy controls.

1. Allele Contrast Model (G vs. A)

Overall Analysis

The allele contrast model included 34 studies and showed a modest but non-significant association (OR = 1.1249, 95% CI: 0.9889-1.2794, p = 0.073). The analysis used a random-effects model due to substantial heterogeneity (I^2 = 81.58%, p < 0.001), indicating significant variation between studies. No publication bias was detected (Egger's test p = 0.2559).

Ethnicity-Specific Results

• Asian Population (19 studies): Showed the strongest effect size (OR = 1.1888, 95% CI: 0.9614-1.4700, p = 0.110) with high heterogeneity (I^2 = 86.11%) but remained non-significant. No publication bias was observed (p = 0.5243).

• Caucasian Population (7 studies): Demonstrated a significant protective effect (OR = 0.885, 95% CI: 0.7874-0.9946, p = 0.040). The analysis used a fixed-effects model due to low heterogeneity (I^2 = 0%, p = 0.5754). No publication bias was detected (p = 0.2022).

• Mixed Population (8 studies): Showed a borderline significant association (OR = 1.2412, 95% CI: 0.9957-1.5472, p = 0.055) with moderate heterogeneity (I^2 = 77.99%). Potential publication bias was suggested (p = 0.071) (Figure:2).

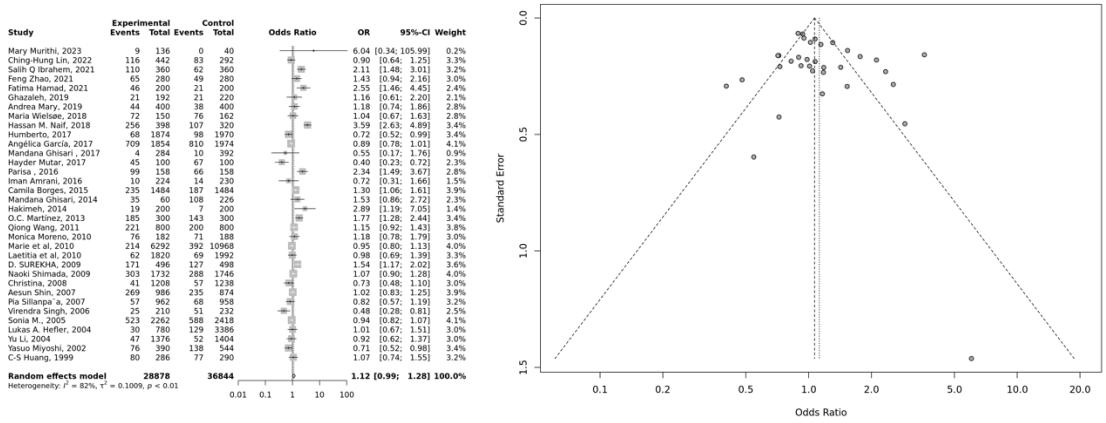

Figure 2: (A) illustrate forest plot, (B) illustrate funnel plot for G vs. A

2. Recessive Model (GG vs. GA+AA)

Overall Analysis

The recessive model analysis of 34 studies revealed no significant association (OR = 1.1409, 95% CI: 0.8972-1.4508, p = 0.282). Moderate heterogeneity was observed (I^2 = 59.95%, p < 0.001), necessitating a random-effects model. No publication bias was detected (p = 0.659).

Ethnicity-Specific Results

• Asian Population (19 studies): No significant association was found (OR = 1.0785, 95% CI: 0.7249-1.6044, p = 0.709) with high heterogeneity (I^2 = 74.17%). No publication bias was observed (p = 0.5924).

• Caucasian Population (7 studies): Showed no significant association (OR = 0.8586, 95% CI: 0.4309-1.7111, p = 0.665) with no heterogeneity (I^2 = 0%, p = 0.8035), allowing for fixed-effects analysis. No publication bias was detected (p = 0.2839).

• Mixed Population (8 studies): Demonstrated a borderline significant association (OR = 1.1695, 95% CI: 0.9759-1.4015, p = 0.090) with low heterogeneity (I^2 = 21.8%, p = 0.2561), permitting fixed-effects analysis. No publication bias was observed (p = 0.2693) (Figure:3).

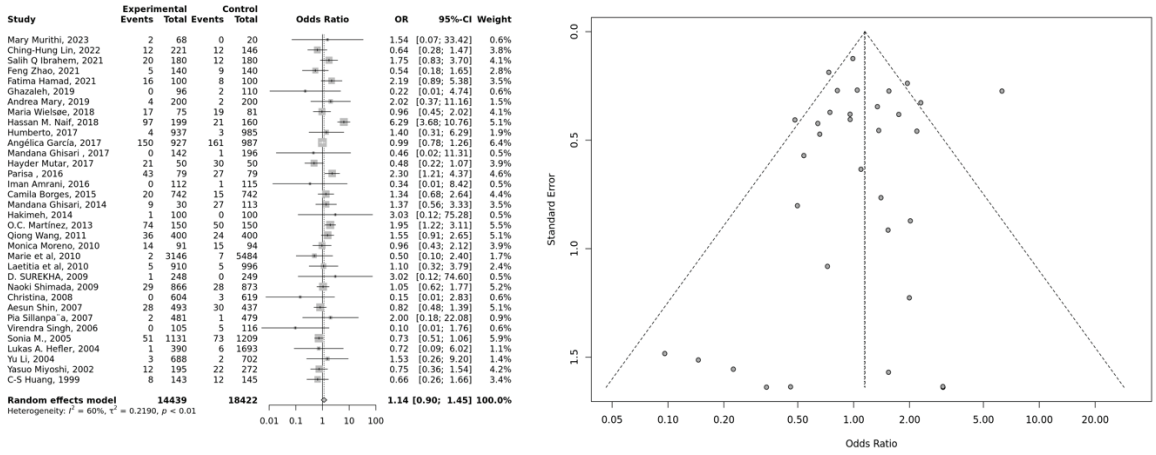

Figure 3: (A) illustrate forest plot, (B) illustrate funnel plot for GG vs. GA+AA genotype.

3. Dominant Model (GG+GA vs. AA)

Overall Analysis

The dominant model showed a significant association across 34 studies (OR = 1.1533, 95% CI: 1.0038-1.3250, p = 0.044). High heterogeneity was present (I^2 = 76.06%, p < 0.001), requiring random-effects modeling. A potential publication bias was suggested (Egger's test p = 0.0948).

Ethnicity-Specific Results

- Asian Population (19 studies): Demonstrated a significant association (OR = 1.2742, 95% CI: 1.0123-1.6038, p = 0.039) with high heterogeneity (I^2 = 80.43%). No publication bias was detected (p = 0.3062).
- Caucasian Population (7 studies): Showed a significant protective effect (OR = 0.8843, 95% CI: 0.7837-0.9979, p = 0.046) with no heterogeneity (I^2 = 0%, p = 0.5495), allowing fixed-effects analysis. No publication bias was observed (p = 0.2545).
- Mixed Population (8 studies): No significant association was found (OR = 1.2346, 95% CI: 0.9521-1.6008, p = 0.112) despite significant heterogeneity (I^2 = 74.79%, p = 0.0002). No publication bias was detected (p = 0.1031) (Figure:4).

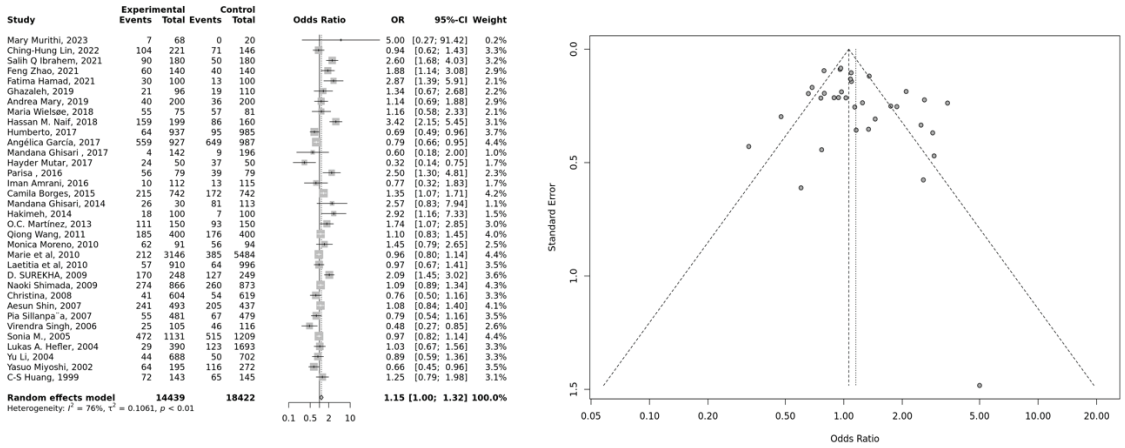

Figure 4: (A) illustrate forest plot, and (B) illustrate funnel plot for GG+GA vs. AA genotype.

4. Over dominant Model (GA vs. GG+AA)

Overall Analysis

The over dominant model analysis of 34 studies showed no significant association (OR = 1.0603, 95% CI: 0.9454-1.1891, p = 0.317). Moderate heterogeneity was observed (I^2 = 62.13%, p < 0.001), necessitating random-effects modeling. No publication bias was detected (p = 0.2766).

Ethnicity-Specific Results

- Asian Population (19 studies): No significant association was found (OR = 1.1657, 95% CI: 0.9693-1.4018, p = 0.103) with moderate heterogeneity (I^2 = 66.67%). No publication bias was observed (p = 0.5966).
- Caucasian Population (7 studies): Showed a borderline significant protective effect (OR = 0.8887, 95% CI: 0.7863-1.0046, p = 0.059) with no heterogeneity (I^2 = 0%, p = 0.51), allowing fixed-effects analysis. No publication bias was detected (p = 0.333).
- Mixed Population (8 studies): No significant association was observed (OR = 1.0718, 95% CI: 0.8580-1.3389, p = 0.541) with moderate heterogeneity (I^2 = 63.26%, p = 0.008). No publication bias was detected (p = 0.2599). (Figure:5)

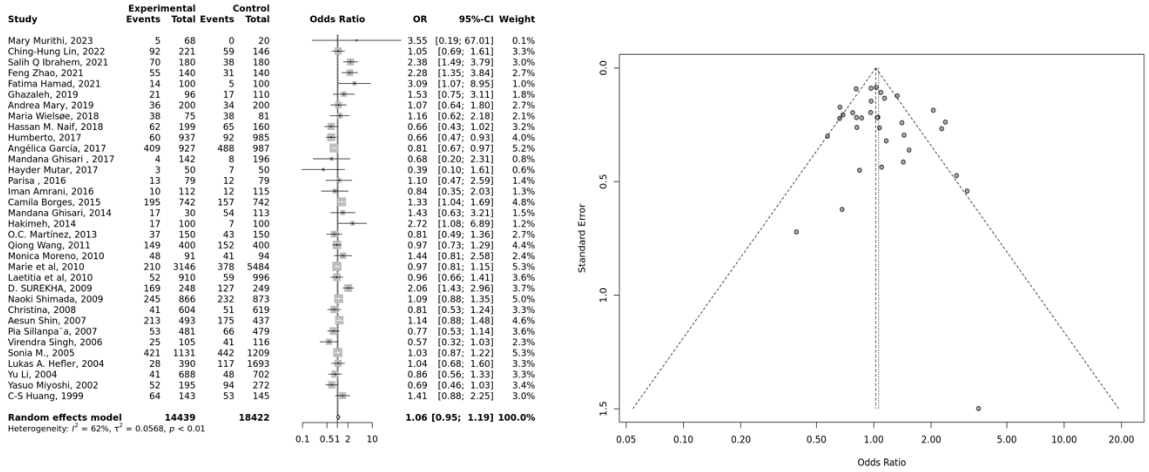

Figure 5: (A) illustrate forest plot, and (B) illustrate funnel plot for GA vs GG+ AA genotype.

5. Homozygote Comparison (GG vs. AA)

Overall Analysis

The homozygote comparison across 34 studies revealed no significant association (OR = 1.2036, 95% CI: 0.9136-1.5856, p = 0.188). Moderate heterogeneity was present (I^2 = 66.01%, p < 0.001), requiring random-effects modeling. No publication bias was detected (p = 0.8707).

Ethnicity-Specific Results

- Asian Population (19 studies): No significant association was found (OR = 1.1731, 95% CI: 0.7479-1.8401, p = 0.487) with high heterogeneity (I^2 = 77.45%). No publication bias was observed (p = 0.8795).
- Caucasian Population (7 studies): Showed no significant association (OR = 0.8486, 95% CI: 0.4258-1.6913, p = 0.641) with no heterogeneity (I^2 = 0%, p = 0.8105), permitting fixed-effects analysis. No publication bias was detected (p = 0.2736).
- Mixed Population (8 studies): Demonstrated a borderline significant association (OR = 1.3308, 95% CI: 0.9478-1.8685, p = 0.099) with moderate heterogeneity (I^2 = 47.38%, p = 0.0651). No publication bias was observed (p = 0.1142).(Figure:6)

A B

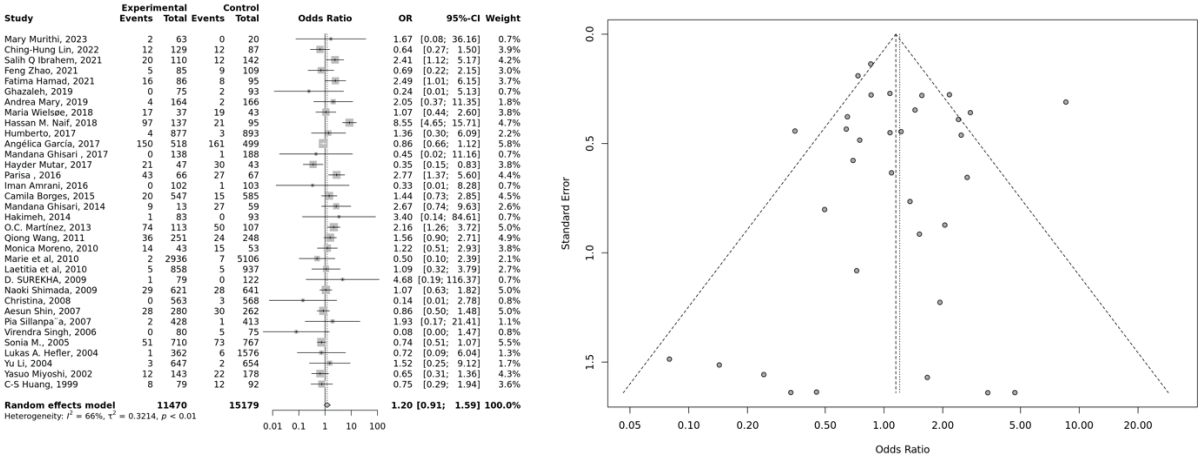

Figure 6: (A) illustrate forest plot, and (B) illustrate funnel plot for GG vs. AA genotype.

6. Heterozygote vs. Homozygote Dominant (GG vs. GA)

Overall Analysis

This comparison included 33 studies and showed no significant association (OR = 1.0514, 95% CI: 0.8530-1.2958, p = 0.639). Significant heterogeneity was observed (I^2 = 38.94%, p = 0.0129), necessitating random-effects modeling. No publication bias was detected (p = 0.3557).

Ethnicity-Specific Results

- Asian Population (19 studies): No association was found (OR = 1.0009, 95% CI: 0.7046-1.4217, p = 0.996) with moderate heterogeneity (I^2 = 59.76%, p = 0.0005). No publication bias was observed (p = 0.5844).
- Caucasian Population (7 studies): Showed no significant association (OR = 0.9791, 95% CI: 0.4833-1.9835, p = 0.953) with no heterogeneity (I^2 = 0%, p = 0.7363), allowing fixed-effects analysis. No publication bias was detected (p = 0.423).
- Mixed Population (7 studies): No significant association was observed (OR = 1.1239, 95% CI: 0.9228-1.3689, p = 0.246) with no heterogeneity (I^2 = 0%, p = 0.7121), permitting fixed-effects analysis. No publication bias was detected (p = 0.6659). (Figure:7)

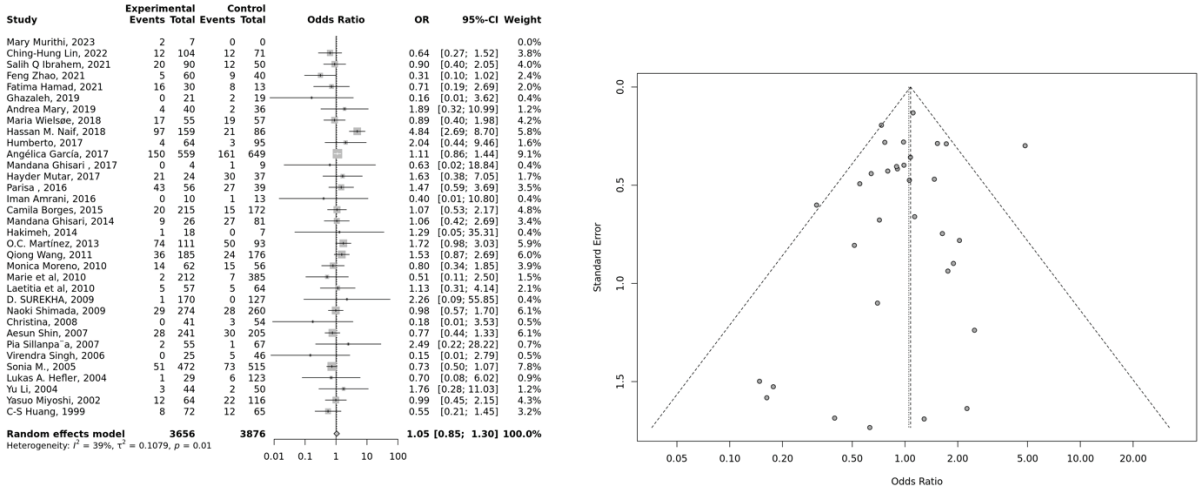

Figure 7: (A) illustrate forest plot, and (B) illustrate funnel plot for GG vs GA genotype.

7. Heterozygote vs. Homozygote Recessive (GA vs. AA)

Overall Analysis

The analysis of 34 studies showed a borderline significant association (OR = 1.1157, 95% CI: 0.9838-1.2652, p = 0.088). Moderate heterogeneity was present (I^2 = 66.53%, p < 0.001), requiring random-effects modeling. No publication bias was detected (p = 0.1125).

Ethnicity-Specific Results

- Asian Population (19 studies): Demonstrated a significant association (OR = 1.2577, 95% CI: 1.0275-1.5395, p = 0.026) with moderate heterogeneity (I^2 = 69.99%). No publication bias was observed (p = 0.3475).
- Caucasian Population (7 studies): Showed a borderline significant protective effect (OR = 0.8883, 95% CI: 0.7859-1.0041, p = 0.058) with no heterogeneity (I^2 = 0%, p = 0.514), allowing fixed-effects analysis. No publication bias was detected (p = 0.3285).
- Mixed Population (8 studies): No significant association was found (OR = 1.1372, 95% CI: 0.8869-1.4581, p = 0.311) with moderate heterogeneity (I^2 = 67.53%, p = 0.003). No publication bias was observed (p = 0.1689). (Figure:8)

A **B**

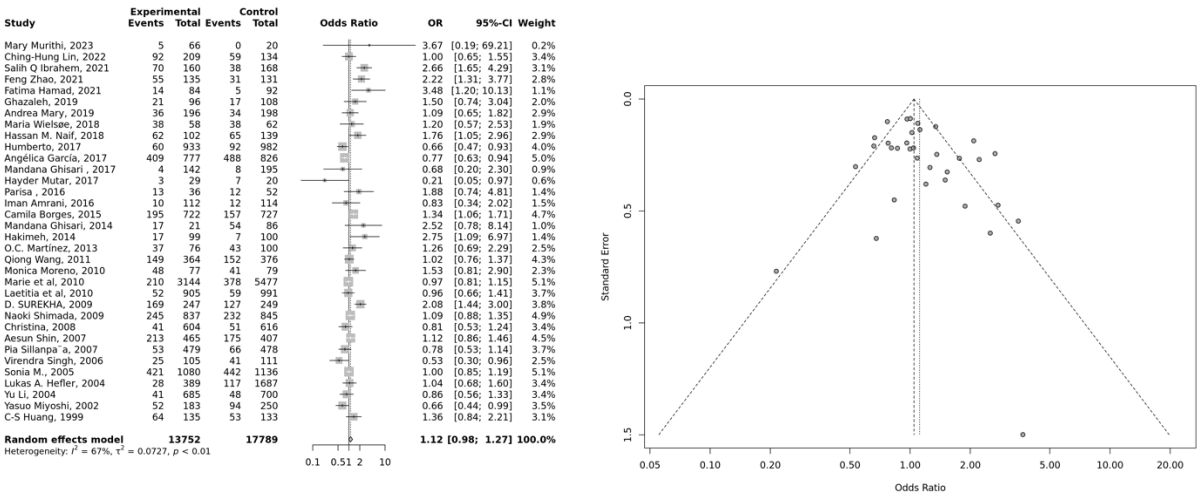

Figure 8: (A) illustrate forest plot, and (B) illustrate funnel plot for GA vs AA genotype.

Summary and Clinical Implications:

The meta-analysis reveals significant ethnic heterogeneity in genetic associations. The most robust findings include:

1. Significant associations: Dominant model overall and in Asians, allele contrast and heterozygote comparison in Caucasians showing protective effects, and heterozygote vs. homozygote recessive comparison in Asians.
2. Ethnic differences: Opposite effects observed between Asian and Caucasian populations in several models, suggesting population-specific genetic architecture.
3. Heterogeneity concerns: High I^2 values in many analyses indicate substantial between-study variation, potentially due to population stratification, linkage disequilibrium patterns, or methodological differences.

4. Publication bias: Generally low risk across analyses, supporting the reliability of findings.

These results suggest that genetic associations may vary significantly across ethnic groups, emphasizing the importance of population-specific genetic studies and personalized medicine approaches.

Table 2. Overall and Subgroup Analysis Results from Meta-Analysis.

Model	**Ethnicity**	**Number of studies**		**Test of association**			**Test of heterogeneity**		**Publication bias**
			OR	**95% CI**	**p-val**	**Model**	**p-val**	**I^2**	**p-val (Egger's test)**
Allele contrast (G vs. A)	Overall	34	1.1249	[0.9889; 1.2794]	0.0733257557	Random	0	0.8158	0.2559
	Asian	19	1.1888	[0.9614; 1.4700]	0.1103954669	Random	0	0.8611	0.5243
	Caucasian	7	0.885	[0.7874; 0.9946]	0.0402233559	Fixed	0.5754	0	0.2022
	Mixed	8	1.2412	[0.9957; 1.5472]	0.0546729972	Random	0	0.7799	0.071
Recessive model (GG vs. GA+AA)	Overall	34	1.1409	[0.8972; 1.4508]	0.2823951102	Random	0	0.5995	0.659
	Asian	19	1.0785	[0.7249; 1.6044]	0.7093546351	Random	0	0.7417	0.5924
	Caucasian	7	0.8586	[0.4309; 1.7111]	0.6648122299	Fixed	0.8035	0	0.2839
	Mixed	8	1.1695	[0.9759; 1.4015]	0.0899145955	Fixed	0.2561	0.218	0.2693
Dominant model (GG+GA vs. AA)	Overall	34	1.1533	[1.0038; 1.3250]	0.0440318334	Random	0	0.7606	0.0948

	Mixed	8	1.2346	[0.9521; 1.6008]	0.11190323 3	Random	0.0002	0.7479	0.1031
Overdominant model (GA vs. GG+AA)	Overall	34	1.0603	[0.9454; 1.1891]	0.31708895 7	Random	0	0.6213	0.2766
	Asian	19	1.1657	[0.9693; 1.4018]	0.10332333 3	Random	0	0.6667	0.5966
	Caucasian	7	0.8887	[0.7863; 1.0046]	0.059 20737	Fixed	0.51	0	0.333
	Mixed	8	1.0718	[0.8580; 1.3389]	0.54139045 6	Random	0.008	0.6326	0.2599
GG vs. AA	Overall	34	1.2036	[0.9136; 1.5856]	0.18777019 4	Random	0	0.6601	0.8707
	Asian	19	1.1731	[0.7479; 1.8401]	0.48687948 8	Random	0	0.7745	0.8795
	Caucasian	7	0.8486	[0.4258; 1.6913]	0.64086332 4	Fixed	0.8105	0	0.2736
	Mixed	8	1.3308	[0.9478; 1.8685]	0.09891731 4	Random	0.0651	0.4738	0.1142
GG vs. GA	Overall	33	1.0514	[0.8530; 1.2958]	0.63858710 9	Random	0.0129	0.3894	0.3557
	Asian	19	1.0009	[0.7046; 1.4217]	0.99606027 7	Random	0.0005	0.5976	0.5844

Sensitivity Result:

A sensitivity analysis was conducted across all genetic models using the leave-one-out method to evaluate the robustness and stability of the meta-analysis findings. In the allele contrast model (G vs. A), the sequential removal of individual studies did not significantly alter the pooled odds ratio, suggesting consistent and stable results (Figure S1). Similarly, the dominant model (GG+GA vs. AA) maintained statistical significance and demonstrated robustness throughout the analysis, confirming the reliability of the observed association (Figure S3). The recessive model (GG vs. GA+AA) and the over dominant model (GA vs. GG+AA) also exhibited stable effect estimates

with minimal variation when studies were omitted one at a time (Figures S2 and S4). Additionally, genotype-specific comparisons—homozygote comparison (GG vs. AA), heterozygote vs.

homozygote dominant (GG vs. GA), and heterozygote vs. homozygote recessive (GA vs. AA)—all displayed consistent pooled odds ratios, indicating that no single study had a disproportionate impact on the overall results (Figures S5, S6, and S7). These findings support the reliability and internal validity of meta-analysis across all genetic models. (The figures S1 to S7 are in another document).

Discussion:

Globally, breast cancer (BC) is the most frequently diagnosed cancer, occurring in 1 out of 8 women in the United States. Over the years, studies on hormonally linked risk factors have significantly helped in unraveling the etiology of BC.[52]. Breast cancer (BC) is the second most frequent malignancy in females after skin cancer, which is the most frequent cancer. [53]. Over one million new BC cases occur yearly, and over 410,000 deaths are caused by this malignancy. Although there has been a significant decline in BC mortality in many countries during the past two decades, the incidence rates continue to increase, especially in populations that traditionally have low rates. A number of polymorphisms, such as single nucleotide polymorphisms (SNPs), in genes involved in xenobiotic metabolism and the synthesis and degradation of estrogen can modulate circulating estrogen levels, increase susceptibility to environmental carcinogens, and thereby predispose to breast cancer. [54]. Cytochrome p450 (CYP) 1A1 is a phase I enzyme necessary for steroid, xenobiotic chemicals and other possible genotoxic compounds' metabolism.[55]

This meta-analysis assessed the relationship between the CYP1A1 rs1048943 (Ile462Val) polymorphism and susceptibility to breast cancer, pooling information from 34 case-control studies, including 14,166 cases and 18,912 controls. The CYP1A1 gene produces an enzyme that participates in polycyclic aromatic hydrocarbons (PAHs)phase I metabolism, which is an established carcinogen. The rs1048943 polymorphism causes an isoleucine-to-valine substitution at codon 462, possibly increasing enzymatic activity and metabolic activation of carcinogens and thus to DNA damage and carcinogenesis. In the allele contrast model (G vs. A), there was no statistically significant association (OR = 1.1249, 95% CI: 0.9889–1.2794, p = 0.073), while the direction of the effect indicated a possible increased risk with the G allele. Again, the recessive model (GG vs. GA+AA) was not significantly associated (OR = 1.1409, 95% CI: 0.8972–1.4508, p = 0.282). These results suggest that having two copies of the G allele by itself might not increase risk very much. Nonetheless, the dominant model (GG+GA vs. AA) showed a statistically significant correlation (OR = 1.1533, 95% CI: 1.0038–1.3250, p = 0.044), suggesting that a single G allele might provide higher susceptibility to breast cancer. The analyses by ethnicity, subgroup, gave more specific results. In Asian populations (19 studies), the dominant model was significant (OR = 1.2742, 95% CI: 1.0123–1.6038, p = 0.039), implying that individuals of Asian origin with the G allele could be at increased risk. The association could be due to population heterogeneity in linkage disequilibrium, environmental exposures, or gene-environment interactions. Conversely, the Caucasian subgroup (7 studies) exhibited a strong protective effect in the same model (OR = 0.8843, 95% CI: 0.7837–0.9979, p = 0.046), suggesting possible ethnic variation in genetic predisposition.

The mixed population subgroup failed to exhibit statistically significant associations across any model, but numerous estimates were borderline and merit consideration in admixed populations. Additional genotype-based comparisons reaffirmed these trends. The over dominant model (GA vs. GG+AA), which can indicate heterozygote advantage or disadvantage, was not significant overall (OR = 1.0603, 95% CI: 0.9454–1.1891, p = 0.317). Similarly, the homozygote contrast (GG vs. AA) and heterozygote-based contrasts (GG vs. GA and GA vs. AA) were not significant in the overall analysis. Nonetheless, the GA vs. AA comparison was notable in the Asian subgroup (OR = 1.2577, 95% CI: 1.0275–1.5395, p = 0.026), while highlighting the potential role of heterozygous genotypes to modulate risk in certain populations. Conversely, a borderline protective trend was observed in Caucasians (OR = 0.8883, p = 0.058). These ethnic differences might be due to underlying genetic structure, environmental exposures (such as tobacco smoke, diet), and cultural or behavioral influences that interact with variant genes. The G allele could change the enzyme activity of CYP1A1 differently in different populations because of modifier genes or co-expressed polymorphisms. This emphasizes the need for population-specific genetic studies when evaluating cancer risk.

To contextualize these findings, several previous studies offer direct support for the observed association under the dominant model in Asian populations. For instance, Naif et al., 2018 in Iraq analyzed 199 breast cancer cases and 160 healthy controls, reporting a significantly higher frequency of GG+GA genotypes in cases (79.9%) compared to controls (53.8%). The calculated odds ratio was OR = 3.38 (95% CI: 2.09–5.47), strongly suggesting increased risk among carriers of the G allele.[27]. Similarly, Bab et al., 2017 in Iran examined 79 cases and 79 controls, finding 70.9% of cases and 49.4% of controls carried the dominant genotype, yielding OR = 2.55 (95% CI: 1.29–5.05) in favor of elevated risk.[32]. In India, Surekha et al., 2009 evaluated 250 cases and 250 controls, observing 68.5% vs. 51.0% GG+GA genotype frequencies, respectively. This produced a consistent odds ratio of OR = 2.08 (95% CI: 1.45–2.98), aligning with our pooled

result.[42]. Additionally, Ghisari et al., 2014 reported dominant genotype frequencies of 86.7% in 31 breast cancer cases and 71.7% in 115 controls among Greenlandic Inuit women, corresponding to OR = 2.48 (95% CI: 0.82–7.52) — supporting the same trend despite limited sample size.[35]. Collectively, these studies reinforce our meta-analysis finding of a significant association in Asian populations under the dominant model (OR = 1.2742, p = 0.039), affirming that the CYP1A1 rs1048943 polymorphism may modestly increase breast cancer risk in this ethnic group.

To further validate the stability and reliability of our findings, a sensitivity analysis was performed across all genetic models using the leave-one-out approach. This method sequentially excluded each individual study to assess its influence on the overall pooled effect. In the allele contrast model (G vs. A), the pooled odds ratio remained stable throughout, indicating that no single study significantly impacted the overall result. Similarly, in the dominant model (GG+GA vs. AA), the observed statistical significance persisted across iterations, reinforcing the robustness of the association. The recessive model (GG vs. GA+AA) and the over dominant model (GA vs. GG+AA) also displayed minimal fluctuation in effect sizes when individual studies were omitted, suggesting consistent findings in those models as well. Moreover, genotype-specific comparisons—including the homozygote contrast (GG vs. AA), heterozygote vs. homozygote dominant (GG vs. GA), and heterozygote vs. homozygote recessive (GA vs. AA)—showed similarly stable results, with no evidence that any one study disproportionately influenced the pooled estimates. Collectively, these sensitivity analyses affirm the internal validity of this meta-analysis and underscore the consistency of the observed associations across various genetic models.

Conclusion:

The meta-analysis identified a potential association between the CYP1A1 rs1048943 (Ile462Val) polymorphism and breast cancer susceptibility, particularly under the dominant model (GG+GA vs. AA), which demonstrated a statistically significant association in the overall population. In contrast, no significant associations were found in the allele contrast, recessive, over dominant, or homozygote comparison models in the overall analysis. Subgroup analyses revealed a significant increase in breast cancer risk among Asian populations under both the dominant model and the GA vs. AA comparison, while a protective effect was observed among Caucasian populations under the dominant model. No consistent associations emerged in the mixed population subgroup. Notably, high heterogeneity was observed in most genetic models, particularly among studies involving Asian populations, whereas studies in Caucasian populations demonstrated minimal heterogeneity, suggesting more stable effect estimates within that group.

Acknowledgments:

All praises to Almighty Allah, the Most Gracious and the Most Merciful, who blessed me with the strength, patience, and knowledge to complete this work. His countless blessings have guided me through every step of this journey.

I am deeply thankful to my parents and siblings for their unconditional love, prayers, support, and sacrifices, which have been the foundation of my academic and personal growth.

I express my heartfelt thanks to my final year supervisor, Dr. Najeeb Ullah Khan, for his constant guidance, encouragement, and support throughout the course of this article.

Lastly, I want to extend special thanks to my seniors, Ms. Maryam Urooj and Mr. Waqas Khan, whose generous help and guidance were invaluable during the completion of this manuscript.

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