REVIEW

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Association of the *CXCL12* rs1801157 Polymorphism with Breast Cancer Risk: A Meta-Analysis

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Abstract

Studies on the *CXCL12* rs1801157 polymorphism show that this polymorphism is involved in development of breast cancer, but its specific relationships or effects are not consistent. The purpose of this meta-analysis was to investigate the association between *CXCL12* rs1801157 polymorphism and susceptibility to breast cancer. PubMed, Scopus, Embase, the Cochrane Library, Web of Science, and CNKI were searched for eligible studies through February 01, 2023. A total of ten studies with 2093 cases and 2302 controls were included in this meta-analysis. Overall, there is a significant association between *CXCL12* rs1801157 polymorphism and risk of breast cancer under the homozygote genetic model (AA vs. GG, OR= 1.350, 95% CI: 1.050-1.734, p= 0.019). Stratified by ethnicity showed a significant association in Caucasian women, but not among Asian and mixed populations. This meta-analysis confirms that *CXCL12* rs1801157 polymorphism is related to breast cancer risk, especially among Caucasian women. However, well-designed large-scale studies are required to further evaluate the results.

Keywords: Breast cancer- *CXCL12*- rs1801157- polymorphism- risk- meta-analysis

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Introduction

Breast cancer is the most-commonly diagnosed malignant tumor in women in the world, as well as the first cause of death from malignant tumors [1-3]. Breast cancer patients account for as much as 36% of oncological patients. An estimated 287,850 new cases women were diagnosed with breast cancer in USA and 43,250 women will die from breast cancer in 2022 [4, 5]. The occurrence of breast cancer is associated with many risk factors, including genetic and hereditary predisposition [6, 7]. Breast cancers are highly heterogeneous [8, 9]. There is growing evidence that germline mutations in certain genes influence cancer susceptibility, tumor evolution, as well as clinical outcomes. For breast cancer, several genes such as BRCA1, BRCA2, PALB2, ATM, and CHEK2 act as high- to moderate-penetrance cancer susceptibility genes [10, 11]. Heritable predisposition genes are important risk factors for breast cancer susceptibility, accounting for 5.03% of all breast cancer cases [12].

A large number of genes associated with susceptibility to breast cancer contain single nucleotide polymorphisms (SNPs) [13-15]. The chemokine protein *CXCL12* (also known as SDF1) and its receptor *CXCR4* are involved in the proliferation, differentiation, and migration of specific cells in the body [16, 17]. SDF-1 belongs to the CXC

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subfamily of chemokines and is produced by stromal cells and mostly known for its pivotal role in the smooth muscle progenitor cells (SPCs) accumulation. The *CXCL12* gene is located on chromosome 10q11.1. A single nucleotide polymorphism (SNP) in noncoding region 801 (G/A) a G-to-A base (G>A) at position 801 in the 3'untranslated region (UTR) of the *CXCL12* gene up regulated the expression of SDF1 [18-21]. Growing evidence suggests that the SDF-1 rs1801157 polymorphism plays an important role in the pathogenesis of cancer. Razmkhah et al. reported that the SDF-1 rs1801157 polymorphism increased the risk of breast [22] and lung cancer [22, 23], but not colorectal and gastric cancers Iranian patients [24]. Kucukgergin and co-workers showed that the SDF-1 rs1801157 polymorphism was associated with bladder cancer susceptibility [25, 26]. Dommange et al. showed that *CXCL12* 801A carriers were associated with blast invasion in acute myelogenous leukemia (AML) [27, 28]. *CXCL12* is closely related to invasion and metastasis of breast cancer through the *CXCL12*/*CXCR4* axis, but it is unclear whether there is a risk associated with breast cancer [22]. Recently, studies have been conducted concerning the link between the *CXCL12* rs1801157 polymorphism and the risk of breast cancer. Thus, we have performed this meta-analysis to evaluate the association between *CXCL12* rs1801157 polymorphism and susceptibility to breast cancer.

Materials and Methods

Search Strategy

We conducted a comprehensive literature search on electronic databases including PubMed, EMBASE, Wed of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD) and Chinese National Knowledge Infrastructure (CNKI) to identify all relevant studies on the association of *CXCL12* rs1801157 polymorphism with susceptibility to breast cancer up to February 01, 2023. The combination of following keywords and terms were used: (''breast cancer'' OR "breast tumor" OR "breast neoplasm" OR "breast malignant tumor" OR "breast carcinoma'') and (''stromal cell derived factor-1'' OR ''C-X-C motif chemokine 12" "*CXCL12*" or "SDF1" OR ''*CXCL12*'' OR ''SDF-1'' OR ''rs1801157'') AND (''Polymorphism'' OR ''Mutation'' OR ''Genotype'' OR ''Allele'' OR ''Variation'' OR ''Variant''). Languages were limited to English, Portuguese, Farsi and Chinese. In addition, hand searching of the references in retrieved reviews and eligible articles were performed as sources to find potential studies. Languages were limited to English and Chinese.

Inclusion and Exclusion Criteria

We have considered the studies to the meta-analysis that met the following predetermined inclusion criteria: (1) studies investigating the between *CXCL12* rs1801157 polymorphism and breast cancer risk, (2) Studies with cohort and case-control design, (3) Studies provided sufficient data for estimating an odds ratio (OR) with a 95% confidence interval (95% CI) and (4) only conducted on the female breast cancer. The major exclusion criteria were as follow: (1) not conducted on human, (2) not breast cancer research, (3) investigated male breast cancer, (4) Only included cases, (5) duplicate of previous publications and (6) have not sufficient data for genotypes.

Data Extraction

We have extracted the following data about the eligible studies: first author name, year of publication, country of study, ethnicity of studied subjects, frequencies of genotypes in both case and control groups, and HWE. In this study the diverse ethnicity populations were categorized as Asian, Caucasian, African and Mixed. However, in the studies where the ethnicity of the case and controls was not clearly stated, we have inferred ethnicity on the basis of the largest ethnic group inhabiting the country of study. The data was extracted and confirmed by two authors; however, any disagreement was resolved by discussion among the three investigators.

Statistical Analysis

The strength of association between *CXCL12* rs1801157 polymorphism with breast cancer risk was estimated by Odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance of the pooled effect size was determined by Z-test, in which $P<0.05$ was considered statistically significant. The associations was evaluated under all five genetic models, i.e., allele (A vs. G), heterozygote (AG vs. GG), homozygote (AA vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG). Between-study heterogeneity was evaluated by the Cochran Q-test, in which $P \leq 0.10$ indicated significant heterogeneity was found. I^2 statistic was also utilized to qualify between-study heterogeneity (range of 0 to 100%: I^2=0-25%, no heterogeneity; I^2=25-50%, moderate heterogeneity; I^2= 50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity) [29-31]. Therefore, a random-effects model (DerSimonian and Laird method) or fixed-effects model (Mantel-Haenszel method) was used to calculate pooled effect estimates in the presence or absence of heterogeneity, respectively [32-34]. Moreover, Hardy-Weinberg equilibrium (HWE) assessed by chi-square test was made in control group of each study [35-38], $P>0.05$ were considered to have reliable and representative controls. Subgroup analyses were conducted by stratification of ethnicity to identifying potential source of heterogeneity [39-41]. Begg's funnel plot and Egger's test were used to test any publication bias in the results [42-44]. On the other way, the underlying effects of each single study to overall results were evaluated by sensitivity analyses, with the method of deletion one independent study each time. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided P-values < 0.05 were considered statistically significant.

Results

Characteristics of Eligible Studies

The flow chart of the literature selection process is shown in Figure 1. Initially, 328 potentially relevant

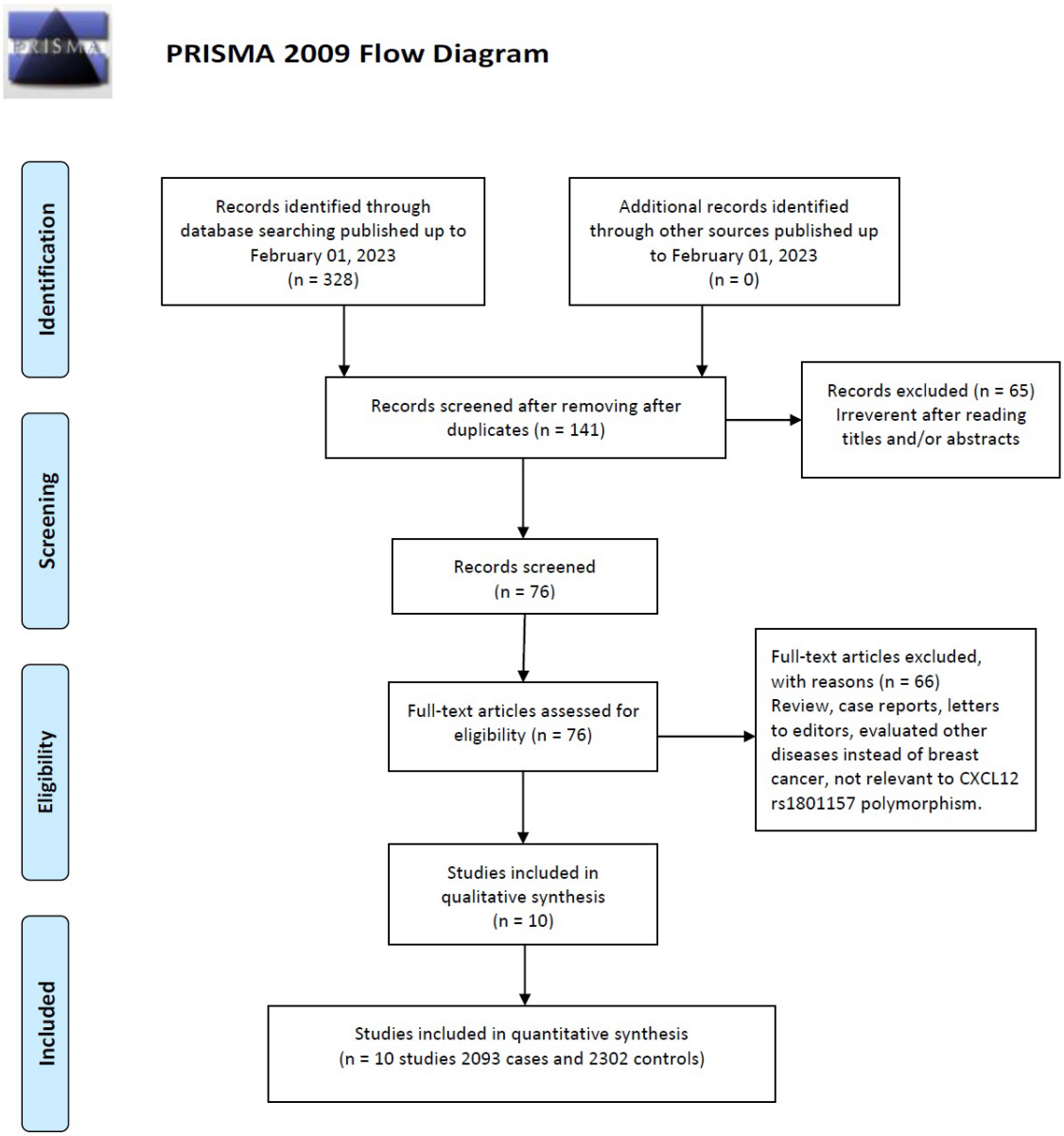

Figure 1. Flow Diagram of the Study Selection Process

published works were obtained with the initial search of databases. Of these studies, the first screening excluded 187 publications were excluded as duplicates, leaving 141 studies for further selection. Among these publications, 83 studies were excluded because they were review articles, case reports, meta-analysis, other polymorphisms of *CXCL12* and related to cancer. Finally, a total of ten case-control studies [45-54] with 2093 cases and 2302 controls published from 2004 and 2022, were included were included in this meta-analysis. The basic information of each study is presented in Table 1. The countries of these studies included Greece, Iran, China, Brazil, Poland and Pakistan. Subjects in four of the studies with 1158 cases and 1207 controls belonged to Asian ethnicity [46, 49, 50, 53], three other studies with 718 cases and 30,649 controls were conducted on Caucasians [45, 51, 52] and three with 215 cases and 695 controls among mixed (Brazilian women) [47, 48, 54] populations. Moreover, six genotypic methods altogether were performed in all these studies using PCR-RFLP and MassARRAY. The genotype in the healthy control group for a study was not consistent with HWE ($P < 0.05$).

Quantitative Syntheses

As is shown in Table 2, the main analyses performed on the *CXCL12* rs1801157 polymorphism and breast cancer included association and heterogeneity tests. Pooled data showed that there was an increased *CXCL12* rs1801157 polymorphism with breast cancer risk under the homozygote genetic model (A vs. GG, OR= 1.350, 95% CI: 1.050-1.734, p= 0.019, Figure 2). Moreover, after stratified by ethnicity, a significant association was revealed between this polymorphism and breast cancer among Caucasians under all five genetic models, i.e., allele (A vs. G, OR= 1.294, 95% CI: 1.117-1.531, p= 0.001), heterozygote (AG vs. GG, OR= 1.340, 95% CI: 1.071-1.640, p= 0.010), homozygote (AA vs. GG, OR= 1.646, 95% CI: 1.191-2.581, p= 0.004), dominant (AA+AG vs. GG, OR= 1.379, 95% CI: 1.128-1.696, p= 0.002) and recessive (AA vs. AG+GG, OR= 1.424, 95% CI: 1.038-2.179, p= 0.031), but not in Asian and mixed populations.

Table 1. Characteristics of Studies Included in the Meta-Analysis of *CXCL12* rs1801157 Polymorphism and Breast Cancer.

First author	Country (Ethnicity)	SOC	Genotyping methods	Case/ Control	Cases					Controls					HWE	MAF
					Genotype			Allele		Genotype			Allele			
					GG	AG	AA	G	A	GG	AG	AA	G	A		
Zafiropoulos 2004	Greece(Caucasian)	HB	PCR-RFLP	264/212	98	136	30	332	196	101	92	19	294	130	0.764	0.307
Razmkhah 2005	Iran(Asian)	HB	PCR-RFLP	278/181	105	139	34	349	207	101	67	13	269	93	0.681	0.257
Lin 2009	China(Asian)	HB	PCR-RFLP	220/334	106	98	16	310	130	175	136	23	486	182	0.62	0.272
de oliverira 2009	Brazil(mixed)	HB	PCR-RFLP	103/97	59	41	3	159	47	61	32	4	154	40	0.938	0.206
Kruszyna 2010	Poland(Caucasian)	PB	PCR-RFLP	193/199	123	61	9	307	79	136	58	5	330	68	0.685	0.171
de oliverira 2011	Brazil (mixed)	HB	PCR-RFLP	55/54	32	21	2	85	25	37	15	2	89	19	0.757	0.176
Kontogianni 2013	Greece (Caucasian)	HB	PCR-RFLP	261/480	114	118	29	346	176	247	198	35	692	268	0.584	0.279
Khalid 2017	Pakistan (Asian)	HB	PCR-RFLP	218/147	138	59	21	335	101	47	86	14	180	114	0.004	0.388
Guembarovski 2018	Brazil (mixed)	PB	PCR-RFLP	59/150	37	19	3	93	25	109	38	3	256	44	0.882	0.147
Lin 2022	China(Asian)	NS	Mass ARRAY	442/448	259	167	16	685	199	293	134	21	720	176	0.266	0.196

SOC, source of controls; HB, hospital based; PB, population based; NS, Not stated; PCR-RFLP, restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium; MAF: minor allele frequency

Sensitivity Analysis

Sensitivity analysis was performed to estimate the influence of some individual study on pooled results on *CXCL12* rs1801157 and breast cancer by calculating the ORs before and after exclusion of a single article from meta-analysis in turn. No outlying study was observed to significantly change the pooled ORs after it was removed which confirmed our results were stable under the all five genetic models. Moreover, the test of HWE was conducted in this study, results of which indicate that results remain unchanged.

Publication Bias

In this meta-analysis, the potential effect of publication bias in literatures was estimated by funnel plots (Figure 3) and the Egger's test. No asymmetry was found in heterozygote and dominant plots for *CXCL12* rs1801157 polymorphism association with breast cancer. Moreover, there was no statistically significant difference in the Egger's test for *CXCL12* rs1801157 polymorphism, which indicating no publication bias in the association. Thus, No significant publication bias was demonstrated in any genetic model of studied on *CXCL12* rs1801157 polymorphism and breast cancer.

Discussion

In this study, our pooled data demonstrate significant association between *CXCL12* rs1801157 polymorphism and breast cancer susceptibility under the homozygote genetic model (A vs. GG, OR= 1.350, 95% CI: 1.050-1.734, p= 0.019) from ten case-control studies. Several meta-analyses have explored the association between this polymorphism and breast cancer risk and it is difficult to judge if the analysis with small sample size would be more valid or not. An overall meta-analysis by, Xia et al., showed that the *CXCL12* rs1801157 polymorphism was associated with breast cancer was in an allelic genetic model (OR: 1.214, 95%CI: 1.085- 1.358, p=0.001), a homozygote model (OR: 1.663, 95%CI: 1.240-2.232, p=0.001), a heterozygote model (OR: 1.392, 95%CI: 1.190-1.629, p≤0.001), a recessive genetic model (OR:

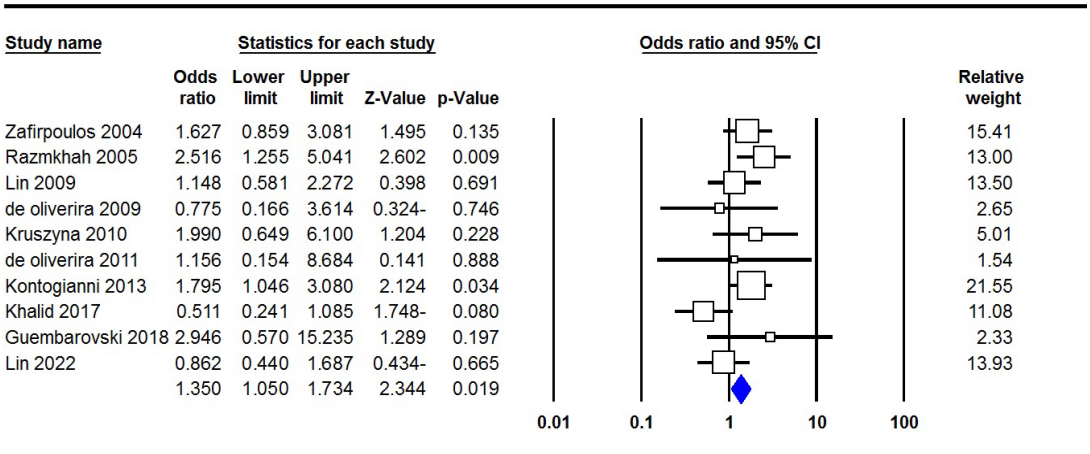

Figure 2. Forest Plots for the Association of *CXCL12* rs1801157 Polymorphism with Breast Cancer Risk under the Homozygote Genetic Model (AA vs. GG).

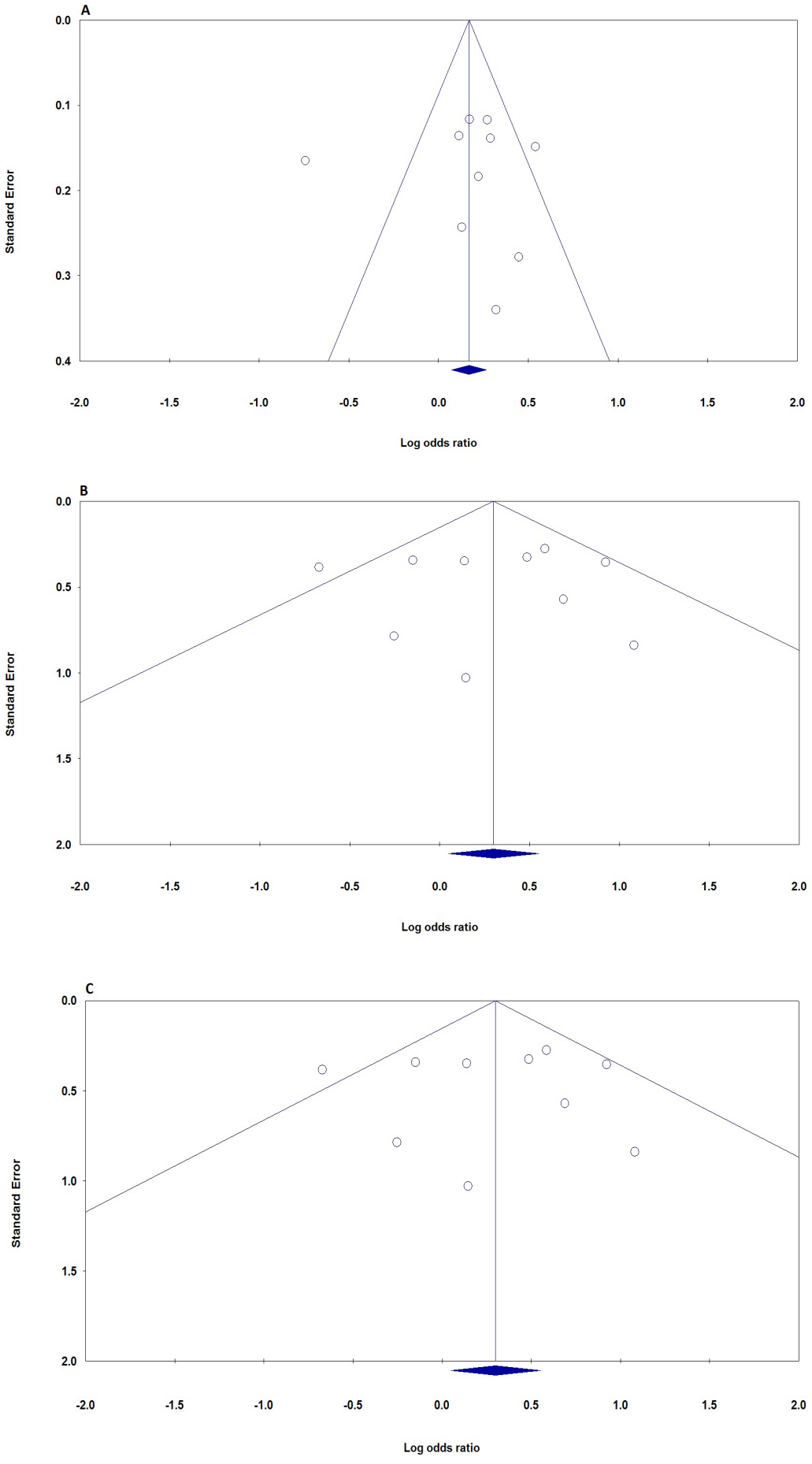

Figure 3. Begg's Funnel Plots (Publication Bias) for the association of *CXCL12* rs1801157 Polymorphism with Breast Cancer Risk. A, allele (A vs. G); B, heterozygote (AG vs. GG); C, homozygote (AA vs. GG)

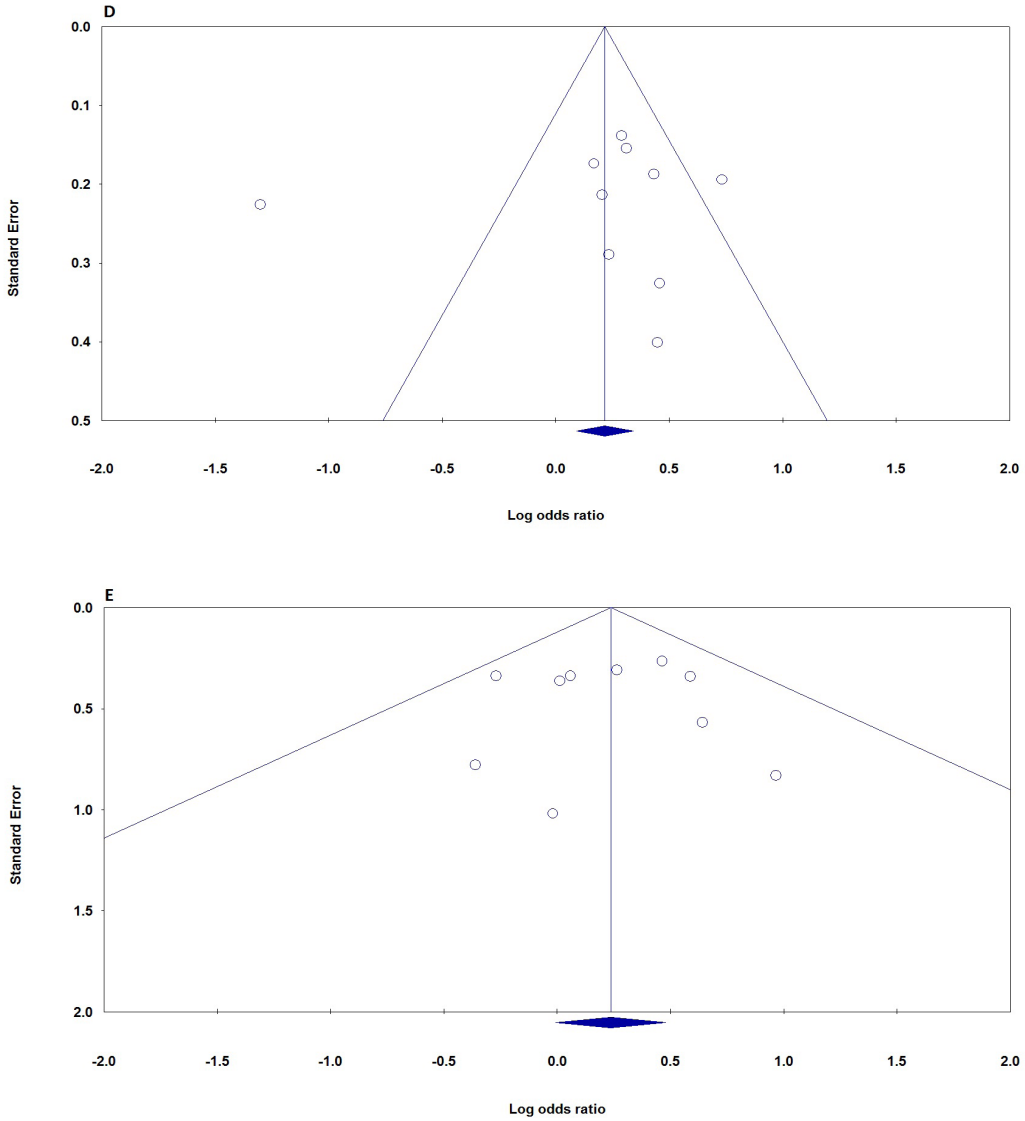

Figure 3. Begg's Funnel Plots (Publication Bias) for the association of *CXCL12* rs1801157 Polymorphism with Breast Cancer Risk. D, dominant (AA+AG vs. GG); E, recessive (AA vs. AG+GG).

1.407, 95%CI: 1.060-1.868, p=0.018) and a dominant genetic model (OR: 1.427, 95%CI: 1.228-1.659, p=0.000). Moreover, their subgroup analysis based on ethnicity, significance was observed between the Caucasian women and the mixed group [55]. Zhu et al. [56] in a study based pooled data showed that *CXCL12* rs1801157 was associated with risk of breast cancer, lung cancer, and other cancers. Moreover, their subgroup analysis revealed that this polymorphism was associated with cancer risk in the Asians under all genetic models. However, in the Caucasian subgroup, a significant association was only found under an additive genetic model and a dominant genetic model [56]. In 2012, Shen et al. [57] in a meta-analysis based on 5 case-control studies with 1,058 breast cancer cases and 1,023 controls evaluated the association of *CXCL12* rs1801157 polymorphism with breast cancer. Their pooled data showed that the *CXCL12* rs1801157 polymorphism was significantly associated with risk of breast cancer under three genetic models (AA vs. GG, OR = 1.64, 95% CI = 1.16-2.33; GA vs. GG, OR = 1.42, 95% CI = 1.18-1.71; and AA/GA vs. GG, OR = 1.44, 95% CI = 1.21-1.72) [57]. Ma et al. [58] in a meta-analysis of 16 publications with 2,888 cases and 3,611 controls examined the association of *CXCL12* rs1801157 polymorphism with multiple kinds of malignant cancer. Their pooled data revealed that this polymorphism was associated with the increased risk of overall cancer under the homozygote model (AA vs. GG, OR=1.43, 95%CI=1.07-1.91), the recessive model (AA vs. GG+GA, OR=1.26, 95%CI=1.03-1.54), and the dominant model (GA+AA vs. GG, OR=1.35, 95%CI=1.15-1.58). Their stratified analysis showed that *CXCL12* rs1801157 polymorphism was associated in breast cancer, Asians and hospital-based controls groups [58]. In 2012, Gong et al., in a meta-analysis based on meta-analysis of 17 studies with 3048 cancer patients and 4522 controls assessed the association between the *CXCL12* rs1801157 polymorphism and cancer risk. The meta-analysis showed that this variant polymorphism was associated with a significantly increased risk of all cancer types (OR=1.38, 95%CI=1.18-1.61 for GA vs. GG, and OR=1.36, 95%CI=1.17-1.59 for GA+AA vs. GG),

Table 2. Meta-Analysis of the Association of *CXCL12* rs1801157 Polymorphism and Breast Cancer

	Genetic Model	Type of Model	Heterogeneity		Odds ratio			Publication Bias	
			I^2(%)	PH	OR	95% CI	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs. G	Random	77.34	≤0.001	1.18	0.951-1.464	0.134	0.858	0.961
	AG vs. GG	Random	84.21	≤0.001	1.183	0.843-1.655	0.331	0.858	0.709
	AA vs. GG	Fixed	38.6	0.101	1.35	1.050-1.734	0.019	0.858	0.909
	AA+AG vs. GG	Random	83.66	≤0.001	1.212	0.881-1.668	0.237	0.72	0.941
	AA vs. AG+GG	Fixed	0	0.676	1.266	0.994-1.613	0.056	0.72	0.941
Caucasians	A vs. G	Fixed	0	0.957	1.308	1.117-1.531	0.001	1	0.45
	AG vs. GG	Fixed	0	0.644	1.325	1.071-1.640	0.01	1	0.89
	AA vs. GG	Fixed	0	0.947	1.753	1.191-2.581	0.004	1	0.653
	AA+AG vs. GG	Fixed	0	0.724	1.383	1.128-1.696	0.002	1	0.819
	AA vs. AG+GG	Fixed	0	0.807	1.504	1.038-2.179	0.031	1	0.685
Asians	A vs. G	Random	91.44	≤0.001	1.027	0.643-1.641	0.911	0.734	0.514
	AG vs. GG	Random	94.41	≤0.001	0.952	0.438-2.070	0.902	0.734	0.378
	AA vs. GG	Random	69.83	0.019	1.071	0.566-2.024	0.833	1	0.52
	AA+AG vs. GG	Random	94.12	≤0.001	0.984	0.477-2.028	0.964	0.734	0.44
	AA vs. AG+GG	Fixed	9.38	0.346	1.104	0.787-1.547	0.568	1	0.947
Mixed	A vs. G	Fixed	0	0.684	1.322	0.964-1.813	0.083	1	0.629
	AG vs. GG	Fixed	0	0.922	1.436	0.976-2.114	0.066	0.296	0.137
	AA vs. GG	Fixed	0	0.5	1.372	0.514-3.661	0.528	1	0.948
	AA+AG vs. GG	Fixed	0	0.849	1.432	0.986-2.079	0.06	1	0.47
	AA vs. AG+GG	Fixed	0	0.494	1.212	0.458-3.204	0.698	1	0.967

especially in breast cancer (OR=1.64, 95% CI=1.16-2.33 for AA vs. GG, OR=1.42, 95%CI=1.18-1.71 for GA vs. GG, and OR=1.44, 95%CI=1.21-1.72 for GA+AA vs. GG) and lung cancer (OR=2.86, 95% CI=1.75-4.69 for AA vs. GG, OR=1.62, 95% CI=1.20-2.18 for GA vs. GG, OR=1.80, 95% CI=1.36-2.39 for GA+AA vs. GG, and OR=2.24, 95%CI=1.41-3.57 for AA vs. GA+GG) [59].

Heterogeneity in meta-analysis refers to the variation in study outcomes between studies. Thus, assessing heterogeneity in meta-analysis is critical for model selection and decision making [60-62]. High heterogeneity was found in this meta-analysis under three genetic models in overall population [63]. First, we used random models when significant heterogeneity. Second, we performed stratified analyses to explore sources of heterogeneity. In the subgroup analysis based on ethnicity, heterogeneity increased in Asians but decreased in Caucasian and mixed populations which suggest that ethnicity may be a factor in heterogeneity.

Although our study pooled a number of 2093 breast cancer cases and 2302 controls, limitations which might affect the objectivity of the results still exist. First, the moderate sample size in the meta-analysis of *CXCL12* rs1801157 polymorphism might be still unable to draw a conclusion of the association between *CXCL12* rs1801157 polymorphism and breast cancer. Second, our studies included data from only Asian, Caucasian, Brazilian population and none from the African women. Moreover, the amount of case-control studies in the stratified analysis was relatively small, which might cause the potential false associations. Third, there is significant heterogeneity for several studies in our meta-analysis which may distort the current meta-analysis. Fourth, limited data hampered our attempts to examine association of *CXCL12* rs1801157 polymorphism and the clinical manifestation of breast cancer. As a multifactorial disease, breast cancer is influenced by genetic combined with environmental factors. Focusing on single gene region, this meta-analysis ignored the complex interaction between various factors such as age, gender, lifestyle, family history, and nutrient intake. Thus, gene-gene and gene-environment interactions should have been taken into consideration, if the relevant information was available.

In conclusion, this study showed that the *CXCL12* rs1801157 polymorphism was significantly associated with breast cancer, with an increased breast cancer susceptibility among Asians, but not among Caucasian and mixed populations. Future work which takes into account gene-gene and gene-environment interactions is warranted for more precise evidence and to understand the mechanism of association between the *CXCL12* rs1801157 polymorphism and breast cancer.

Author Contribution Statement

Conceptualization: Abolhasan Alijanpour, Ahmadreza Golshan, Nazanin Hajizadeh; Data curation: Mojgan Karimi-Zarchi, Nazanin Hajizadeh; Formal analysis: Abolhasan Alijanpour, Hossein Neamatzadeh; Investigation: Kazem Aghili, Maedeh Barahman; Sepideh Azizi Methodology: Maryam Aghasipour, Maryam Aghasipour; Supervision: Mohammad Vakili-Ojarood, Ahmad Shirinzadeh-Dastgiri; Validation: Mohammad Vakili-Ojarood, Ahmad Shirinzadeh-Dastgiri, Sepideh

Azizi; Writing – original draft: Sahel Khajehnoori, Maedeh Barahman; Writing – review & editing: Amirhosein Naseri, Hossein Neamatzadeh.

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Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors. An ethical approval was not necessary as this study was a meta-analysis based on previous studies.

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