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# Association of interleukin 10 rs1800896 polymorphism with susceptibility to breast cancer: a meta-analysis

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LinXue Qian<sup>1</sup> 

## Abstract

**Objective:** To evaluate the correlation between interleukin 10 (IL-10) –1082A/G polymorphism (rs1800896) and breast cancers by performing a meta-analysis.

**Methods:** The Embase and Medline databases were searched through 1 September 2018 to identify qualified articles. Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were applied to evaluate associations.

**Results:** In total, 14 case-control studies, including 5320 cases and 5727 controls, were analyzed. We detected significant associations between the *IL10* –1082 G/G genotype and risk of breast cancer (AA + AG vs. GG: OR = 0.88, 95% CI = 0.80–0.97). Subgroup analyses confirmed a significant association in Caucasian populations (OR = 0.89, 95% CI = 0.80–0.99), in population-based case-control studies (OR = 0.87, 95% CI = 0.78–0.96), and in studies with ≥500 subjects (OR = 0.88, 95% CI = 0.79–0.99) under the recessive model (AA + AG vs. GG). No associations were found in Asian populations.

**Conclusions:** The *IL10* –1082A/G polymorphism is associated with an increased risk of breast cancer. The association between *IL10* –1082 G/G genotype and increased risk of breast cancer is more significant in Caucasians, in population-based studies, and in larger studies.

## Keywords

Breast cancer, genetic polymorphism, interleukin-10, meta-analysis, systematic review, IL10

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## Introduction

Breast cancer is regarded as the most common cancer among women, and about 6.6% of cases are diagnosed among women 40 years old or younger.<sup>1</sup> Breast cancer accounts for 40% of all types of cancers diagnosed in women and is the third-leading cause among all cancer deaths in Western countries,<sup>2</sup> although the death rate has decreased in most developed countries with the help of improved treatments and earlier diagnosis.

Over the last few years, several mechanisms have been postulated regarding the etiology and progression of breast cancer.<sup>3</sup> It has been shown that chronic inflammatory responses play essential roles in development of all kinds of cancers. Inflammatory cells can regulate the tumor microenvironment and are clearly implicated in tumor development by facilitating proliferation, migration, and survival.<sup>4,5</sup> Several cytokines, including interferon- $\alpha$ , interleukin (IL)-2, IL-6, IL-8, IL-10, and tumor necrosis factor- $\alpha$ , have essential and coordinated functions in breast carcinogenesis.<sup>6,7</sup> As a multifunctional anti-inflammatory cytokine, IL-10 represses the inflammatory response to tumor microenvironments. It is usually secreted by immune cells, such as monocytes, T cells, macrophages (if stimulated appropriately), certain subsets of dendritic cells, and B cells.<sup>8,9</sup>

The human *IL10* gene, containing five exons, is located on chromosome 1q32.1. The promoter region contains at least 40 polymorphic sites, and these sites may affect gene transcription.<sup>10–12</sup> An A-to-G single base pair substitution designated rs1800896 (–1082A/G) has been found in the *IL10* gene promoter region, located –1082 bp (upstream) of the transcriptional start site. The *IL10* –1082A/G polymorphism is closely connected to IL-10 expression.<sup>13–15</sup> However, there is currently no agreement on whether an association

exists between breast cancer and the –1082A/G polymorphism. This meta-analysis was designed to clarify whether rs1800896 (–1082A/G) is associated with breast cancer risk through an investigative analysis of the published literature.

## Methods

### Identification and selection of studies

Relevant studies from Medline (since 1 January 1966) and Embase (since 1 January 1974) through 1 September 2018 were systematically searched (by Z. Zhu and J.-B. Liu). Eligible studies were identified using the keywords “IL-10”, “Interleukin-10”, “–1082 A/G”, “rs1800896”, “polymorphism”, “genotype”, “mutation” “variant”, and “breast cancer”. Then, all references of retrieved studies, clinical trials, review articles, and previous meta-analyses were examined to identify relevant studies that may have been missed in the electronic database searches. The complete search strategy is shown in the supplementary data (Supplemental Document 1).

### Eligibility criteria

Eligible studies had to meet the following criteria: (1) evaluated the connection between *IL10* –1082A/G polymorphism and breast cancer risk; (2) characterized by a case-control or cohort design; (3) provided enough data for calculation of odds ratios (ORs) and their 95% confidence intervals (95% CIs). If multiple studies presented the same data, only the study with the latest data, the largest sample size, or the completed study was included. The exclusion criteria were (1) review article, case report, or an abstract only; (2) studies without a case-control population or not a cohort design; (3) lack of essential data; (4) studies without a control group of healthy individuals; and (5) duplicates of previous prior articles.

### Data collection and quality evaluation

From the eligible studies, two authors (Z. Zhu and J.-B. Liu) independently collected relevant data, if available: first author, publication year, country of origin, ethnicity of patients, total numbers of cases and controls, genotype frequencies, genotyping technique, minor allele frequency, and *P*-value for Hardy–Weinberg equilibrium (HWE). For any disagreements between the two data sets, consensus was reached through discussion or following assessment by a third author. In control groups, confirmation of HWE was applied to assess the quality of study: high-quality studies have HWE confirmation in controls whereas low-quality ones do not.

### Quality assessment of included studies

The Newcastle–Ottawa Scale (NOS) of case-control studies was used to determine the methodological quality for each included study. The NOS contains eight elements, as shown in Supplemental Table 1.

### Statistics

The correlation between the *IL10* –1082A/G polymorphism (rs1800896) and breast cancer risk was assessed by crude ORs with 95% CIs. A summary estimate of the OR was obtained by calculating the weighted average of the ORs for each study. The Z-test was carried out to assess whether the pooled OR was statistically significant. This meta-analysis was based on the allele model (A vs. G), the dominant model (AA vs. AG + GG), recessive model (AA + AG vs. GG), co-dominant heterozygote model (AA vs. AG), co-dominant homozygote model (AA vs. GG), and the over-dominant model (AA + GG vs. AG). In the meta-analysis, heterogeneity between studies was assessed using the  $I^2$  value and the Q-statistic. The  $I^2$  value describes the degree of heterogeneity between studies.

A value of 0 to 25% indicates no detected heterogeneity, 25% to 50% indicates lowly increased heterogeneity, 50% to 75% moderately increased heterogeneity, and 75% to 100% highly increased heterogeneity.<sup>16,17</sup> For the Q-statistic, a *P*-value >0.10 indicates a lack of heterogeneity between studies. An estimate of pooled OR was determined by the fixed-effects model (Mantel–Haenszel method).<sup>18</sup> In addition, the random-effects model (DerSimonian and Laird method) was used.<sup>19</sup> Subgroup analyses, HWE status, and meta-regression were performed to adjust the heterogeneity between studies. In controls, a departure from HWE was evaluated using the  $\chi^2$  test. A *P*-value <0.05 represents statistical significance. Analyses of one-way sensitivity were made to evaluate the stability of results. That is, with each calculation, one study was removed from the meta-analysis so that the effect of an individual dataset on the pooled OR could be determined. Any potential publication bias was identified by using funnel plots and Egger's linear regression test.<sup>20,21</sup> To guarantee the accuracy and reliability of the results, data were entered independently by two researchers and consensus was reached. Comprehensive Meta-Analysis software version 2.20 (Stata Corp., College Station, TX, USA) was applied to perform all data analyses. All *P*-values were two-sided and considered significant if  $P < 0.05$ .

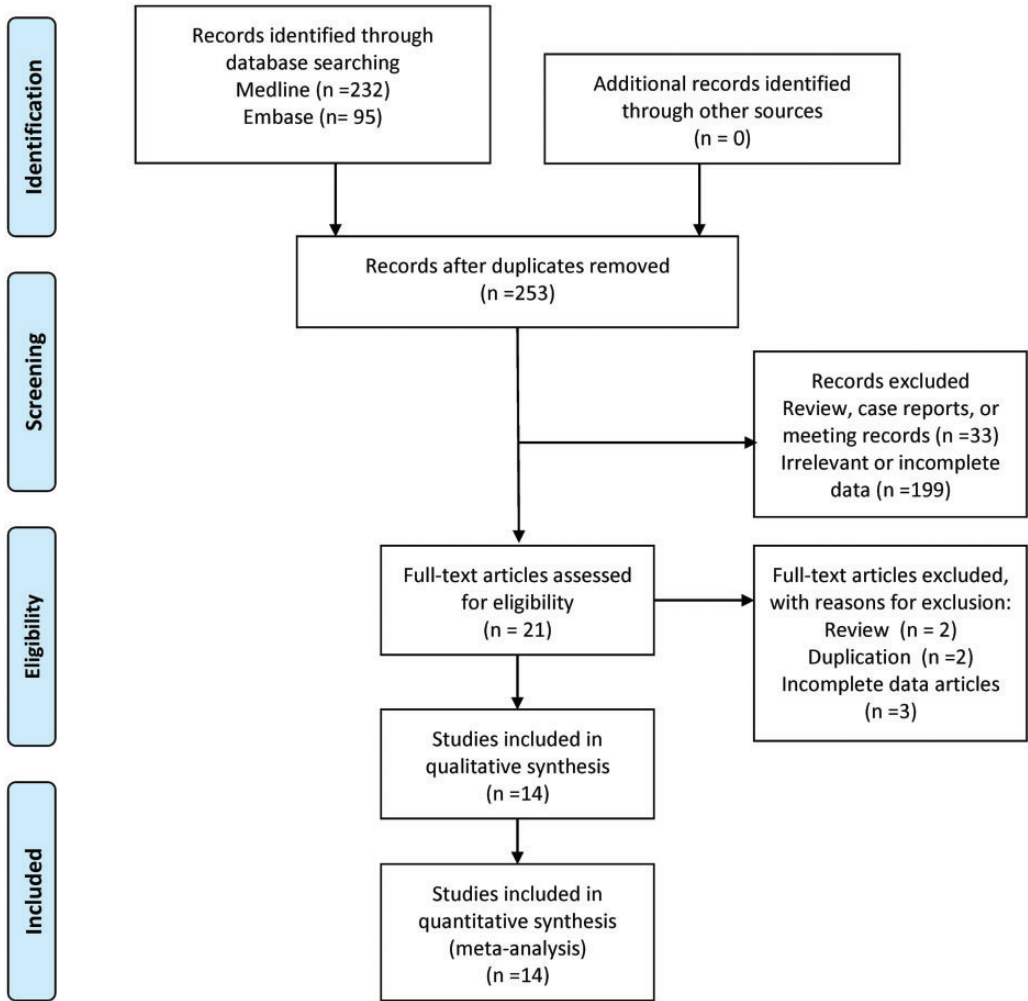
### Patient and public involvement

There was no direct patient or public involvement in current study and therefore ethical approval and patient consent were not required.

## Results

### Study characteristics

As shown in Figure 1, our search criteria returned 253 published articles. Fourteen



**Figure 1.** PRISMA flow chart depicting the procedure for the identification of studies.

studies,<sup>22–35</sup> containing 5320 breast cancer-related cases and 5727 control cases, were identified. A meta-analysis database was established based on the information extracted from the 14 selected studies: 8 (57%) focused on Caucasian populations, 4 (29%) on Asian populations, 1 (7%) on African populations, and 1 (7%) had a mixed population.

All 14 studies included cases and controls. Nine (64%) studies were population-based and 5 (36%) were hospital-based. They used

a range of gene detection methods: PCR, restriction fragment length polymorphism (RFLP)-PCR, amplification-refractory mutation system (ARMS)-PCR, allele-specific (AS)-PCR, and sequence-specific amplification (SSP)-PCR. Sample size varied greatly across studies, from a minimum of 62 to a maximum of 4483. For controls, all genotype distributions were consistent with HWE for the *IL10* –1082 A/G polymorphism. Details are shown in Table 1.

**Table 1.** Characteristics of studies (listed by first author and year) included in the meta-analysis.

Study	Country	Ethnicity	Control source	Genotyping method	No. of cases	No. of controls	HWE	Genotype frequency (case)		Genotype frequency (control)		Allele frequency (case)		Allele frequency (control)		Quality score	
								GG	AG	AA	GG	AG	AA	A	G		A
Giordani (2003)	Italy	Caucasian	HB	ARMS-PCR	125	100											
Smith (2004)	UK	Caucasian	PB	ARMS-PCR	144	263											
Guzowski (2005)	USA	Mixed	HB	PCR	50	25											
Balasubramanian (2006)	UK	Caucasian	PB	PCR	497	498											
Scola (2006)	Italy	Caucasian	HB	SSP-PCR	84	110											
Onay (2006)	Canada	Caucasian	PB	PCR	398	372											
Pharoah (2007)	UK	Caucasian	PB	PCR	2203	2280											
Gonullu (2007)	Turkey	Caucasian	HB	PCR	38	24											
Kong (2010)	China	Asian	HB	RELP-PCR	315	322											
Schonfeld (2010)	USA	Caucasian	PB	PCR	859	1083											
Pooja (2012)	India	Asian	PB	RELP-PCR	200	200											
Vinod (2015)	India	Asian	PB	AS-PCR	125	160											
AlSuhaibani (2015)	Egypt	African	PB	PCR	80	80											
Atoum (2016)	Jordan	Asian	PB	PCR	202	210											
Giordani (2003)	Blood				16	51											
Smith (2004)	Blood				57	120											
Guzowski (2005)	Blood				4	12											
Balasubramanian (2006)	Blood				117	260											
Scola (2006)	Blood				21	45											
Onay (2006)	Blood				71	194											
Pharoah (2007)	Blood				346	1096											
Gonullu (2007)	Blood				1	7											
Kong (2010)	Blood				2	35											
Schonfeld (2010)	Blood				230	530											
Pooja (2012)	Blood				55	0											
Vinod (2015)	Blood				15	78											
AlSuhaibani (2015)	Blood				16	50											
Atoum (2016)	Blood				17	42											

HB, hospital-based; PB, population-based; RELP-PCR, restriction fragment length polymorphism-PCR; ARMS, amplification-refractory mutation system-PCR; AS-PCR, allele-specific-PCR; SSP-PCR, sequence-specific amplification-PCR; HWE, Hardy-Weinberg equilibrium.

### Overall data

Fourteen separate studies, including 5320 breast cancer cases and 5727 control cases, were identified to explore associations. The key findings are demonstrated in Table 2. There was an overall significant association as determined by both the recessive model (AA + AG vs. GG: OR = 0.88, 95% CI = 0.80–0.97;  $P = 0.01$ ; Figure 2a) and the co-dominant homozygotes model (AA vs. GG: OR = 0.88, 95% CI = 0.78–0.98;  $P = 0.03$ ; Figure 2b). The results showed an association of *IL10* –1082 G/G genotype with increased breast cancer risk. However, no obvious association was found between the frequency of the *IL10* –1082 A/G polymorphism and breast cancer as determined by the allele model (A vs. G: OR = 0.97, 95% CI = 0.87–1.08), the dominant model (AA vs. AG + GG: OR = 1.02, 95% CI = 0.85–1.21), the co-dominant heterozygotes model (AA vs. GA: OR = 1.09, 95% CI = 0.9–1.33), or the over-dominant model (AA + GG vs. AG: OR = 1.13, 95% CI = 0.97–1.32).

### Subgroup analysis by ethnicity

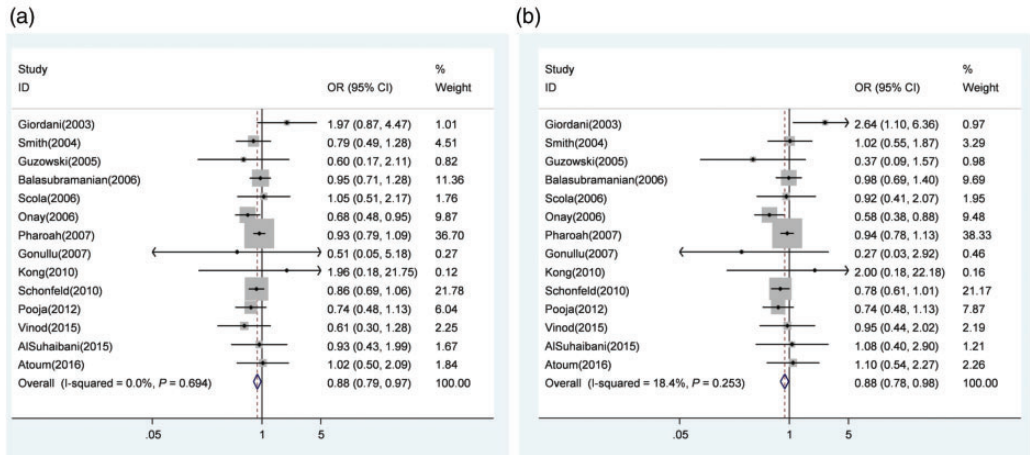
After stratifying the data for ethnicity, we observed that in Caucasian populations, based on eight studies (4348 patients and 4730 control cases), an obvious association was found between *IL10* –1082 G/G genotype and increased risk of breast cancer in the recessive model (AA + AG vs. GG: OR = 0.89, 95% CI = 0.80–0.99;  $P = 0.04$ ; Table 2 and Figure 3a) and the co-dominant homozygotes model (AA vs. GG: OR = 0.88, 95% CI = 0.78–1.00;  $P = 0.05$ ; Table 2 and Figure 3b). However, in Asian groups, there was no association between *IL10* –1082 G/G polymorphism and increased breast cancer risk in any model (Table 2, Figure 3a and 3b).

**Table 2.** The meta-analysis of *IL10* –1082A/G polymorphism and breast cancer risk.

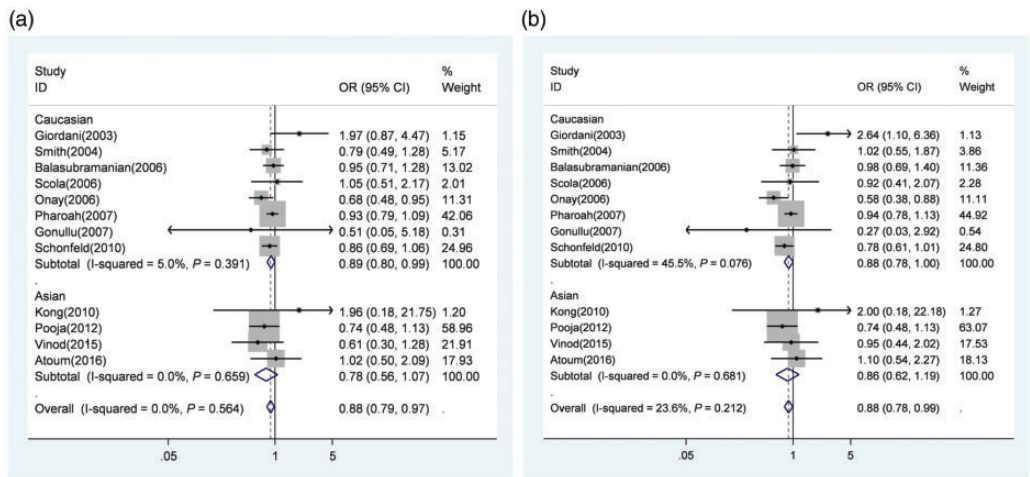
Group	A vs. G		AA vs. AG + GG (dominant model)		AA + AG vs. GG* (recessive model)		AA vs. AG (co-dominant heterozygotes model)		AA vs. GG* (co-dominant homozygotes model)		AA + GG vs. AG (over-dominant model)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Overall	0.97 (0.87, 1.08)	0.55	1.02 (0.85, 1.21)	0.85	0.88 (0.80, 0.97)	0.01	1.09 (0.90, 1.33)	0.38	0.88 (0.78, 0.98)	0.03	1.13 (0.97, 1.32)	0.12
Ethnicity												
Caucasian	0.94 (0.84, 1.06)	0.33	0.95 (0.78, 1.14)	0.56	0.89 (0.80, 0.99)	0.04	0.97 (0.81, 1.16)	0.76	0.88 (0.78, 1.00)	0.05	1.03 (0.92, 1.16)	0.59
Asian	1.10 (0.80, 1.52)	0.55	1.27 (0.81, 1.98)	0.3	0.78 (0.56, 1.07)	0.12	1.73 (1.04, 2.86)	0.03	0.86 (0.62, 1.19)	0.35	1.73 (1.03, 2.91)	0.04
Control source												
HCC	0.94 (0.62, 1.44)	0.79	0.85 (0.47, 1.53)	0.58	1.18 (0.74, 1.88)	0.48	0.84 (0.48, 1.48)	0.55	1.14 (0.69, 1.89)	0.61	0.91 (0.60, 1.38)	0.66
PCC	0.95 (0.86, 1.04)	0.27	1.02 (0.86, 1.22)	0.81	0.87 (0.78, 0.96)	0.01	1.14 (0.92, 1.42)	0.23	0.87 (0.77, 0.97)	0.02	1.18 (1.00, 1.40)	0.06
Sample size												
<500	1.00 (0.80, 1.25)	0.99	1.06 (0.74, 1.51)	0.76	0.86 (0.69, 1.07)	0.18	1.18 (0.76, 1.81)	0.46	0.94 (0.73, 1.20)	0.6	1.21 (0.83, 1.74)	0.32
≥500	0.93 (0.84, 1.02)	0.13	0.93 (0.81, 1.07)	0.3	0.88 (0.79, 0.99)	0.03	0.97 (0.88, 1.08)	0.59	0.86 (0.76, 0.98)	0.03	1.03 (0.94, 1.12)	0.54

HCC, hospital-based case-control study; PCC, population-based case-control study.

\*AA + AG vs. GG and AA vs. GG, the fixed effect model due to the heterogeneity; otherwise, the random effect model.



**Figure 2.** Forest plot of breast cancer risk in all studies (overall) associated with the *IL10* -1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 95% CI, 95% confidence interval.



**Figure 3.** Forest plot of breast cancer risk in ethnicity subgroups (Caucasian vs. Asian) associated with the *IL10* -1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 95% CI, 95% confidence interval.

### Subgroup analysis by study design

In the study design subgroups, pooled analyses of population-based case-control studies showed a close association of *IL10*

-1082 G/G genotype with an increase in breast cancer risk based on the recessive model (AA + AG vs. GG: OR = 0.87, 95% CI = 0.78–0.96;  $P = 0.01$ ; Table 2 and



Figure 4a) and the co-dominant homozygotes model (AA vs. GG: OR = 0.87, 95% CI = 0.77–0.97;  $P = 0.02$ ; Table 2 and Figure 4b). None of the ORs in hospital-based case-control studies were statistically significant (Table 2 and Figure 4a and 4b).

### Subgroup analysis by sample size

We then stratified analyses by sample size, with a cutoff of 500 subjects (i.e., sample size <500 vs.  $\geq 500$ ).<sup>36</sup> A higher risk of breast cancer was observed in studies with  $\geq 500$  subjects under the recessive model (AA + AG vs. GG: OR = 0.88, 95% CI = 0.79–0.99;  $P = 0.03$ ; Table 2 and Figure 5a) and the co-dominant homozygotes model (AA vs. GG: OR = 0.86, 95% CI = 0.76–0.98;  $P = 0.03$ ; Table 2 and Figure 5b). In the subgroup with sample size <500, there were no significant changes in ORs in any of the genetic models.

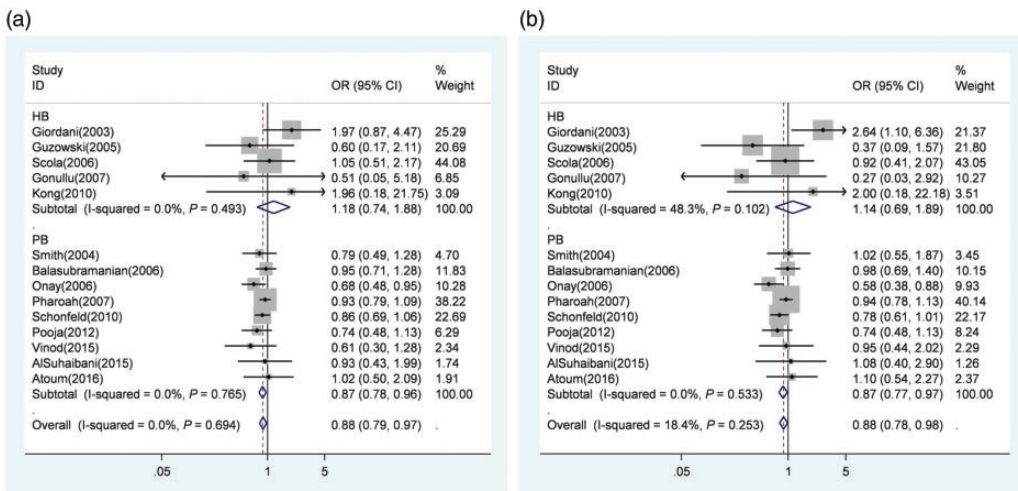
### Publication bias

To evaluate the potential publication bias of these studies, Egger's test and Begg's funnel plots were used. For the recessive (AA + AG vs. GG) and co-dominant homozygote (AA vs. GG) models, the findings from Begg's funnel plots showed no obvious asymmetry (Figure 6a and 6b). The results of Egger's tests suggested no evidence of publication bias for the recessive (AA + AG vs. GG) and co-dominant homozygote (AA vs. GG) models ( $t = 0.50$ ,  $P = 0.627$ ;  $t = 0.85$ ,  $P = 0.411$ , respectively).

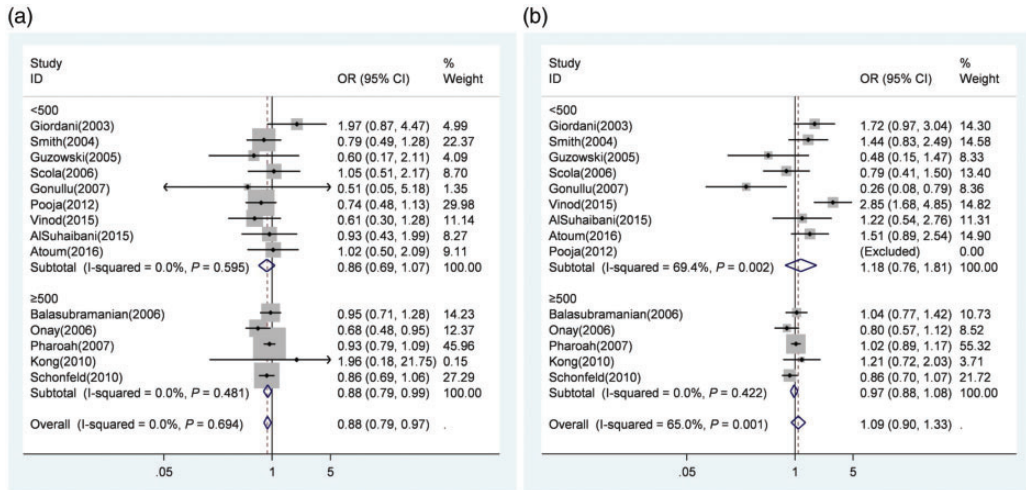
## Discussion

### Main findings

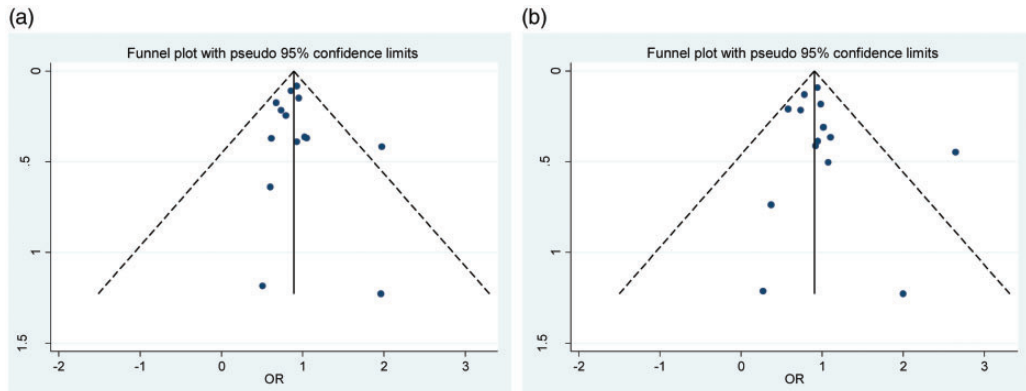
The findings from our meta-analysis of 14 studies, which involved 5320 cases and 5727 controls, indicated a significant correlation between the *IL10* –1082 G/G genotype and an increase in breast cancer risk. The significant association was confirmed in further



**Figure 4.** Forest plot of breast cancer risk in control source subgroups (hospital-based controls vs. population-based controls) associated with the *IL10* –1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 95% CI, 95% confidence interval.



**Figure 5.** Forest plot of breast cancer risk in sample size subgroups (<500 vs. ≥500 samples) associated with the *IL10* -1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 95% CI, 95% confidence interval.



**Figure 6.** Begg's funnel plot of the publication bias test under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). Each point represents a separate study for the indicated association. OR, odds ratio.

analyses among the Caucasian subgroup, the population-based case-control subgroup, and the subgroup of sample size ≥500. Tumors are closely associated with chronic inflammation.<sup>37</sup> The multifunctional cytokine IL-10 is secreted by

T helper (Th)2 cells and has both immunosuppressive and anti-angiogenic functions, suggesting that IL-10 is involved in tumor development and progression. Some *in vitro* studies have shown that IL-10 promotes the proliferation and migration of MCF-7

breast cancer cells.<sup>38</sup> Low expression of *IL10* in tumor cells increases the risk of poor prognosis in breast cancer.<sup>39</sup> Studies have also shown that *IL10* -1082A/G polymorphisms (in the promoter region of *IL10*) affect IL-10 expression,<sup>40</sup> and that the -1082 G allele is associated with poorly differentiated adenocarcinoma of breast cancer.<sup>41</sup>

Prior studies have explored the relationship between the *IL10* -1082A/G polymorphism and breast cancer risk but most failed to find a correlation. Some studies report that the AA genotype of the polymorphism is correlated with an increase in breast cancer risk,<sup>22,33</sup> which is inconsistent with the present study's findings. However, the limitations of those studies should be mentioned. Both included small sample sizes and only reported GG, GA, and AA instead of combined genotypes GG+GA and GA+AA. Our paper represents the most comprehensive meta-analysis on this issue, and it expands on prior meta-analyses by including a larger sample size as well as subgroup analyses. In particular, we believe that the present research is the most accurate meta-analysis to date because of the inclusion of a subgroup for study quality as determined by HWE status.

The incidence of gene polymorphisms can vary substantially across racial or ethnic populations with different genetic backgrounds, which influences measures of association between polymorphisms and cancer susceptibility. Subgroup analyses by ethnicity showed an obvious association between GG genotypes and an increased risk of breast cancer in Caucasian but not Asian populations. These finding suggests that genetic diversity or natural selection is occurring at different rates in different ethnicities. The sample size of the African population was too small to draw conclusions on associations.

Subgroup analyses indicate that differences in either study design or the number of

subjects affect the calculated risk associations. Significant associations between GG genotypes and an increased risk of breast cancer were identified in the population-based case-control subgroup and the large sample size ( $\geq 500$ ) subgroup, but not in the hospital-based case-control subgroup or the small sample size ( $< 500$ ) subgroup. Therefore, more rigorous and uniform studies should be conducted to accurately define these associations.

### Strengths and limitations

This study has several advantages. First, it is a comprehensive and large meta-analysis that evaluates the association of *IL10* -1082A/G polymorphism with breast cancer risk, which makes this study more powerful than prior analyses. Second, meta-analysis results showed that the GG genotype of the *IL10* -1082A/G polymorphism was associated with an increased risk of breast cancer. Finally, subgroup stratifications were designed to exclude the influence of different factors, making the statistical outcomes more precise and reliable.

There are also several study limitations. First, the raw data from the literature were limited and some relevant studies were excluded from the final analyses because of inclusion criteria, as shown in Figure 1. In three relevant articles, we could not extract the data we wanted.<sup>42-44</sup> Second, the sample sizes in some subgroups were small. Third, there were inconsistencies in the types of controls across studies. Control group samples included those from population-based healthy individuals and from hospitalized patients without cancer. Thus, samples from control groups may not represent the potential source population, especially in cases where the polymorphism affects the risk of other diseases. Finally, this study was based on unadjusted data. A more accurate study could be

performed if data from individuals were available.

Despite the above limitations, our meta-analysis suggested that the *IL10* –1082A/G polymorphism (rs1800896) is closely associated with breast cancer risk. Future investigations to estimate the effects of gene–gene and gene–environment interactions on breast cancer are necessary for a better understanding of these interactions. Stratification by ethnicity, cancer type, study design, and sample size should be standardized in future studies on the genetics of breast cancer, which should also consider correlations between the *IL10* –1082A/G polymorphism and breast cancer risk.

### Author contributions

Z. Zhu and L. Qian designed the study; Z. Zhu and J.-B. Liu collected data; Z. Zhu and X. Liu performed the statistical analysis; and all authors wrote the manuscript.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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### Supplemental material

Supplemental material for this article is available online.

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## Search Strategies

### Medline by OVID

1. "interleukin-10" [MeSH Terms]
2. "interleukin-10" [All Fields]
3. "IL 10" [All Fields]
4. 1 OR 2 OR 3
5. "breast" [All Fields]
6. "neoplasms" [MeSH Terms]
7. "neoplasms" [All Fields]
8. "cancer" [All Fields]
9. 6 OR 7 OR 8
10. 5 AND 9
11. Polymorphism
12. 4 AND 10 AND 11

**Embase by OVID**

1. "interleukin-10" [MeSH Terms]
2. "interleukin-10" [All Fields]
3. "IL 10" [All Fields]
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6. "neoplasms" [MeSH Terms]
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8. 6 OR 7
9. 5 AND 8
10. Polymorphism
11. 4 AND 8 AND 10