*Meta-Analysis and Systematic Review*

*Journal of* INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(4) 1–14

DOI: 10.1177/0300060520904863
journals.sagepub.com/home/imr
SAGE

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

**ZiYin Zhu[1], Ji-Bin Liu[2], Xi Liu[1] and LinXue Qian[1]**

## 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

Date received: 10 July 2019; accepted: 8 January 2020

[1]Department of Ultrasound, Beijing Friendship Hospital, Capital Medical University, Beijing, China
[2]Department of Radiology, Thomas Jefferson University, Philadelphia, PA, USA

**Corresponding author:**
LinXue Qian, Department of Ultrasound, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong-an Road, Beijing, 100050, China.
Email: qianlinxue2002@163.com

## 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.[1] 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,[2] 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.[3] 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.[4,5] Several cytokines, including interferon-α, interleukin (IL)-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α, have essential and coordinated functions in breast carcinogenesis.[6,7] 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.[8,9]

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.[10–12] 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.[13–15] 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.[16,17] 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).[18] In addition, the random-effects model (DerSimonian and Laird method) was used.[19] 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.[20,21] 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

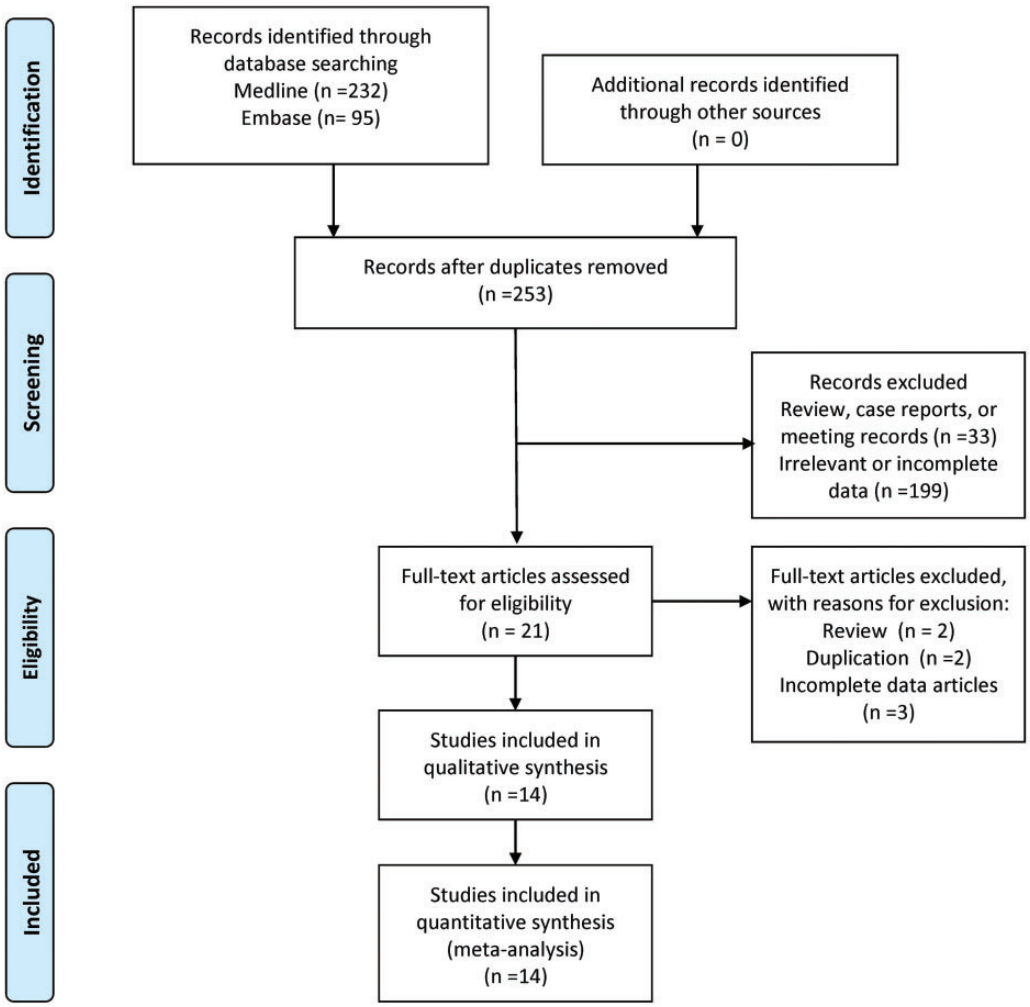


**Figure 1.** PRISMA flow chart depicting the procedure for the identification of studies.

studies,[22–35] 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 |
|---|---|---|---|---|---|---|---|
| Giordani (2003) | Italy | Caucasian | HB | ARMS-PCR | 125 | 100 | 0.61 |
| Smith (2004) | UK | Caucasian | PB | ARMS-PCR | 144 | 263 | 0.24 |
| Guzowski (2005) | USA | Mixed | HB | PCR | 50 | 25 | 1 |
| Balasubramanian (2006) | UK | Caucasian | PB | PCR | 497 | 498 | 0.32 |
| Scola (2006) | Italy | Caucasian | HB | SSP-PCR | 84 | 110 | 0.21 |
| Onay (2006) | Canada | Caucasian | PB | PCR | 398 | 372 | 0.31 |
| Pharoah (2007) | UK | Caucasian | PB | PCR | 2203 | 2280 | 0.08 |
| Gonullu (2007) | Turkey | Caucasian | HB | PCR | 38 | 24 | 0.83 |
| Kong (2010) | China | Asian | HB | RELP-PCR | 315 | 322 | 0.42 |
| Schonfeld (2010) | USA | Caucasian | PB | PCR | 859 | 1083 | 0.66 |
| Pooja (2012) | India | Asian | PB | RELP-PCR | 200 | 200 | NA |
| Vinod (2015) | India | Asian | PB | AS-PCR | 125 | 160 | 0.25 |
| AlSuhaibani (2015) | Egypt | African | PB | PCR | 80 | 80 | NA |
| Atoum (2016) | Jordan | Asian | PB | PCR | 202 | 210 | NA |

| Study | Sample type | Genotype frequency (case) | | | Genotype frequency (control) | | | Allele frequency (case) | | Allele frequency (control) | | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GG | AG | AA | GG | AG | AA | A | G | A | G | |
| Giordani (2003) | Blood | 11 | 54 | 60 | 16 | 51 | 33 | 174 | 82 | 117 | 83 | 5 |
| Smith (2004) | Blood | 39 | 58 | 32 | 57 | 120 | 46 | 122 | 136 | 212 | 234 | 4 |
| Guzowski (2005) | Blood | 12 | 28 | 10 | 4 | 12 | 9 | 48 | 52 | 30 | 20 | 6 |
| Balasubramanian (2006) | Blood | 121 | 253 | 123 | 117 | 260 | 121 | 499 | 497 | 502 | 494 | 3 |
| Scola (2006) | Blood | 16 | 40 | 28 | 21 | 45 | 40 | 96 | 72 | 125 | 87 | 5 |
| Onay (2006) | Blood | 103 | 205 | 90 | 71 | 194 | 107 | 385 | 411 | 408 | 336 | 4 |
| Pharoah (2007) | Blood | 344 | 1003 | 695 | 346 | 1096 | 743 | 2393 | 1691 | 2582 | 2480 | 4 |
| Gonullu (2007) | Blood | 3 | 22 | 13 | 1 | 7 | 16 | 48 | 28 | 39 | 9 | 5 |
| Kong (2010) | Blood | 1 | 29 | 285 | 2 | 35 | 285 | 599 | 31 | 605 | 39 | 6 |
| Schonfeld (2010) | Blood | 200 | 417 | 219 | 230 | 530 | 322 | 834 | 817 | 1176 | 990 | 3 |
| Pooja (2012) | Blood | 68 | 0 | 132 | 55 | 0 | 145 | 264 | 136 | 290 | 110 | 4 |
| Vinod (2015) | Blood | 18 | 31 | 76 | 15 | 78 | 67 | 183 | 67 | 212 | 108 | 3 |
| AlSuhaibani (2015) | Blood | 17 | 47 | 16 | 16 | 50 | 14 | 81 | 79 | 82 | 78 | 4 |
| Atoum (2016) | Blood | 16 | 29 | 157 | 17 | 42 | 151 | 343 | 61 | 344 | 76 | 3 |

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.

| | 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) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | 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.

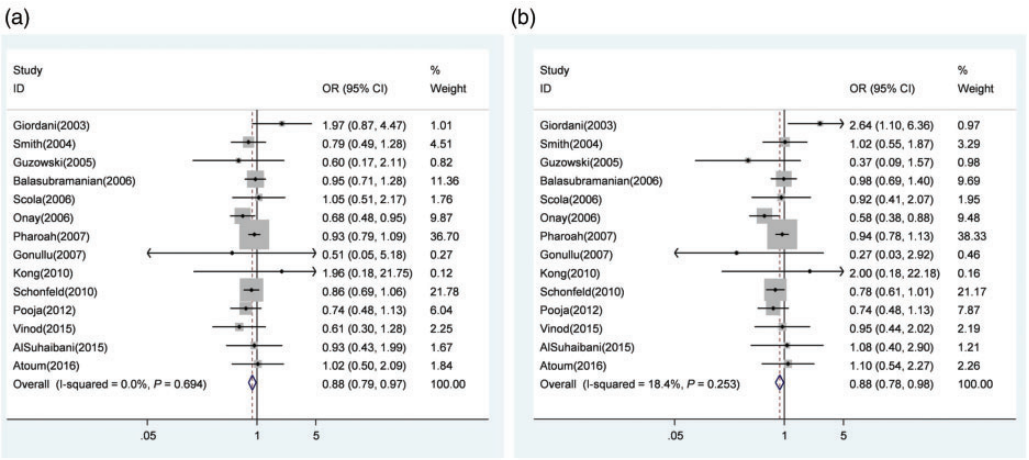


**Figure 2.** Forest plot of breast cancer risk in all studies (overall) associated with the *IL10* −1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 95% CI, 95% confidence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

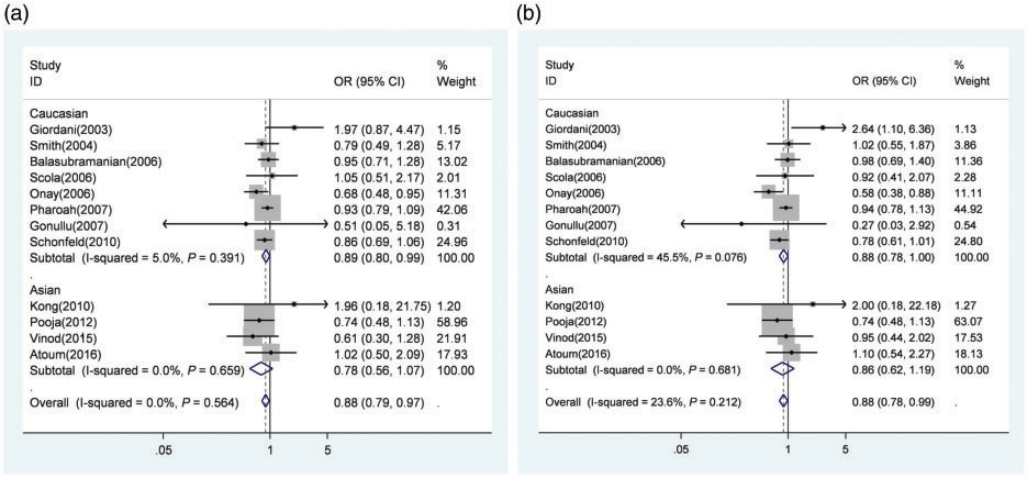


**Figure 3.** Forest plot of breast cancer risk in ethnicity subgroups (Caucasian vs. Asian) associated with the *IL10* −1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*, interleukin-10 gene, OR, odds ratio; 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. ≥500).[36] A higher risk of breast cancer was observed in studies with ≥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

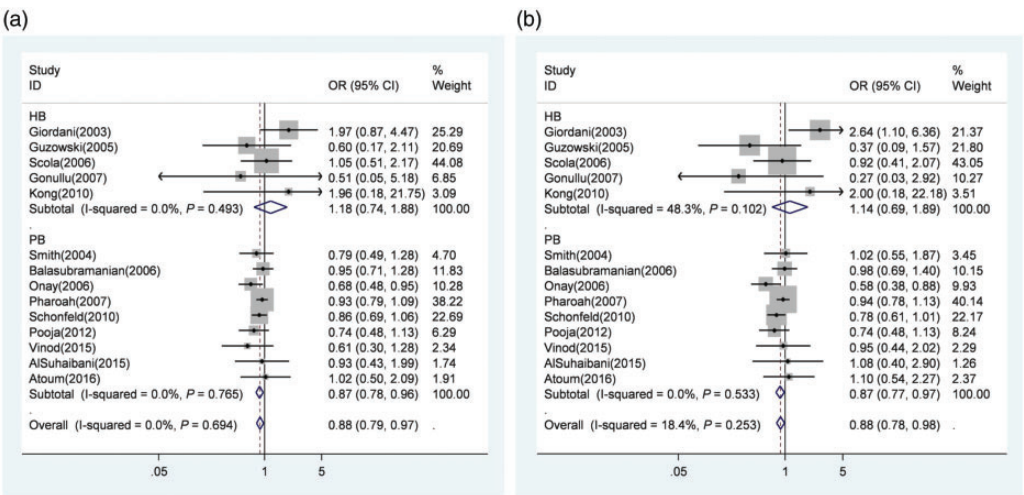


**Figure 4.** Forest plot of breast cancer risk in control source subgroups (hospital-based controls vs. population-based controls) associated with the *IL10* −1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). *IL10*,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

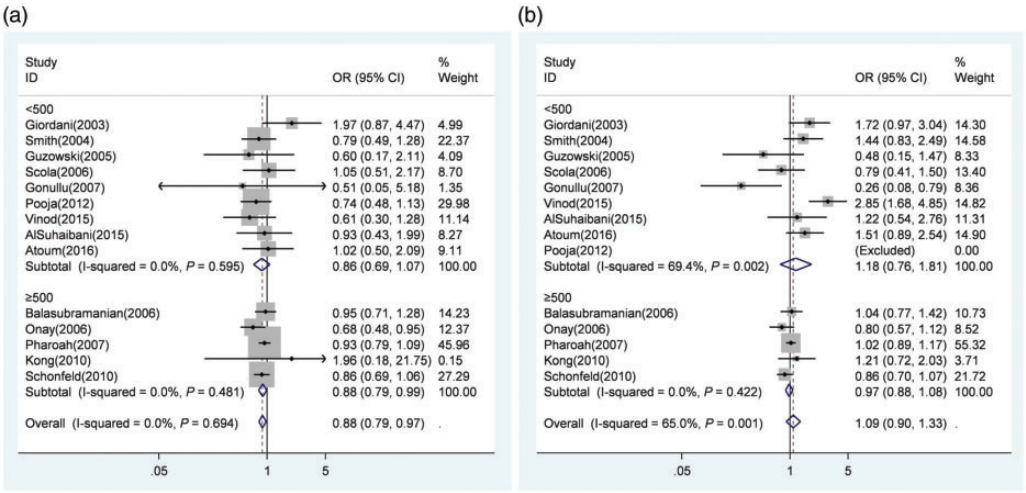


**Figure 5.** Forest plot of breast cancer risk in sample size subgroups (<500 vs. ≥500 samples) associated with the *IL10* −1082A/G (rs1800896) polymorphism under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG).
*IL10*, interleukin-10 gene, OR, odds ratio;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

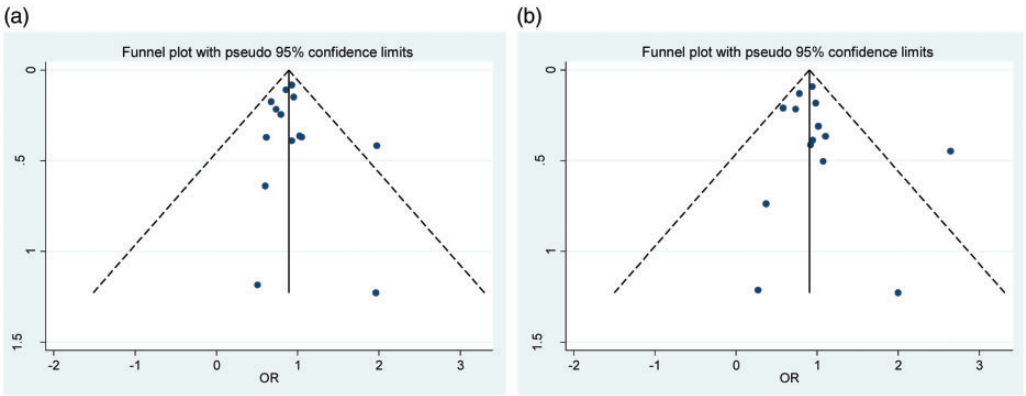


**Figure 6.** Begg's funnel plot of the publication bias test under (a) the recessive model (AA + AG vs. GG), and (b) the co-dominant homozygotes model (AA vs. GG). Each point represents a separate study for the indicated association.
OR, odds ratio.

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.[37] 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.[38] Low expression of *IL10* in tumor cells increases the risk of poor prognosis in breast cancer.[39] Studies have also shown that *IL10* −1082A/G polymorphisms (in the promotor region of *IL10*) affect IL-10 expression,[40] and that the −1082 G allele is associated with poorly differentiated adenocarcinoma of breast cancer.[41]

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,[22,33] 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.[42–44] 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.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## ORCID iD

LinXue Qian https://orcid.org/0000-0001-7116-0608

## Supplemental material

Supplemental material for this article is available online.

## References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893–2917. DOI: 10.1002/ijc.25516
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374–1403. DOI: 10.1016/j.ejca.2012.12.027
3. Cavalieri EL and Rogan EG. The etiology and prevention of breast cancer. *Drug Discov Today Dis Mech* 2012; 9: e55–e69. DOI: 10.1016/j.ddmec.2013.02.001
4. Coussens LM and Werb Z. Inflammation and cancer. *Nature* 2002; 420: 860–867. DOI: 10.1038/nature01322
5. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003; 348: 883–890. DOI: 10.1056/NEJMoa021633
6. Carpi A, Nicolini A, Antonelli A, et al. Cytokines in the management of high risk or advanced breast cancer: an update and expectation. *Curr Cancer Drug Targets* 2009; 9: 888–903.
7. Konwar R, Chaudhary P, Kumar S, et al. Breast cancer risk associated with polymorphisms of IL-1RN and IL-4 gene in Indian women. *Oncol Res* 2009; 17: 367–372.
8. Mannino MH, Zhu Z, Xiao H, et al. The paradoxical role of IL-10 in immunity and cancer. *Cancer Lett* 2015; 367: 103–107. DOI: 10.1016/j.canlet.2015.07.009
9. Ni G, Wang T, Walton S, et al. Manipulating IL-10 signalling blockade for better immunotherapy. *Cell Immunol* 2015; 293: 126–129. DOI: 10.1016/j.cellimm.2014.12.012
10. Hiroki CH, Amarante MK, Petenuci DL, et al. IL-10 gene polymorphism and influence of chemotherapy on cytokine plasma levels in childhood acute lymphoblastic leukemia patients: IL-10 polymorphism and plasma levels in leukemia patients. *Blood Cells Mol Dis* 2015; 55: 168–172. DOI: 10.1016/j.bcmd.2015.06.004
11. Korobeinikova E, Myrzaliyeva D, Ugenskiene R, et al. The prognostic value of IL10 and TNF alpha functional polymorphisms in premenopausal early-stage breast cancer patients. *BMC Genet* 2015; 16: 70. DOI: 10.1186/s12863-015-0234-8
12. de Oliveira JG, Rossi AF, Nizato DM, et al. Influence of functional polymorphisms in

TNF-alpha, IL-8, and IL-10 cytokine genes on mRNA expression levels and risk of gastric cancer. *Tumour Biol* 2015; 36: 9159–9170. DOI: 10.1007/s13277-015-3593-x
13. Li G and Li D. Relationship between IL-10 gene polymorphisms and the risk of non-Hodgkin lymphoma: a meta-analysis. *Hum Immunol* 2016; 77: 418–425. DOI: 10.1016/j.humimm.2016.03.006
14. You Y, Du X, Fan M, et al. Association between IL-10 polymorphisms (−1082A/G, −592A/C and −819T/C) and oral cancer risk. *Int J Clin Exp Med* 2015; 8: 13187–13194.
15. Chagas BS, Gurgel AP, da Cruz HL, et al. An interleukin-10 gene polymorphism associated with the development of cervical lesions in women infected with Human Papillomavirus and using oral contraceptives. *Infect Genet Evol* 2013; 19: 32–37. DOI: 10.1016/j.meegid.2013.06.016
16. Mehdinejad M, Sobhan MR, Mazaheri M, et al. Genetic association between ERCC2, NBN, RAD51 gene variants and osteosarcoma risk: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2017; 18: 1315–1321. DOI: 10.22034/APJCP.2017.18.5.1315
17. Sobhan MR, Forat Yazdi M, Mazaheri M, et al. Association between the DNA repair gene XRCC3 rs861539 polymorphism and risk of osteosarcoma: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2017; 18: 549–555. DOI: 10.22034/APJCP.2017.18.2.549
18. Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; 22: 719–748.
19. DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. *Stat Med* 1996; 15: 1237–1248; discussion 1249–1252. DOI: 10.1002/(SICI)1097-0258(19960630)15: 12<1237: : AID-SIM301>3.0.CO; 2-N
20. Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
21. Kim J, Cho YA, Choi IJ, et al. Effects of interleukin-10 polymorphisms, *Helicobacter pylori* infection, and smoking on the risk of noncardia gastric cancer. *PLoS One* 2012; 7: e29643. DOI: 10.1371/journal.pone.0029643
22. Giordani L, Bruzzi P, Lasalandra C, et al. Association of breast cancer and polymorphisms of interleukin-10 and tumor necrosis factor-alpha genes. *Clin Chem* 2003; 49: 1664–1667.
23. Smith KC, Bateman AC, Fussell HM, et al. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. *Eur J Immunogenet* 2004; 31: 167–173. DOI: 10.1111/j.1365-2370.2004.00462.x
24. Guzowski D, Chandrasekaran A, Gawel C, et al. Analysis of single nucleotide polymorphisms in the promoter region of interleukin-10 by denaturing high-performance liquid chromatography. *J Biomol Tech* 2005; 16: 154–166.
25. Scola L, Vaglica M, Crivello A, et al. Cytokine gene polymorphisms and breast cancer susceptibility. *Ann N Y Acad Sci* 2006; 1089: 104–109. DOI: 10.1196/annals.1386.017
26. Balasubramanian SP, Azmy IA, Higham SE, et al. Interleukin gene polymorphisms and breast cancer: a case control study and systematic literature review. *BMC Cancer* 2006; 6: 188. DOI: 10.1186/1471-2407-6-188
27. Onay VU, Briollais L, Knight JA, et al. SNP-SNP interactions in breast cancer susceptibility. *BMC Cancer* 2006; 6: 114. DOI: 10.1186/1471-2407-6-114
28. Pharoah PD, Tyrer J, Dunning AM, et al. Association between common variation in 120 candidate genes and breast cancer risk. *PLoS Genet* 2007; 3: e42. DOI: 10.1371/journal.pgen.0030042
29. Gonullu G, Basturk B, Evrensel T, et al. Association of breast cancer and cytokine gene polymorphism in Turkish women. *Saudi Med J* 2007; 28: 1728–1733.
30. Kong F, Liu J, Liu Y, et al. Association of interleukin-10 gene polymorphisms with breast cancer in a Chinese population. *J Exp Clin Cancer Res* 2010; 29: 72. DOI: 10.1186/1756-9966-29-72
31. Schonfeld SJ, Bhatti P, Brown EE, et al. Polymorphisms in oxidative stress and inflammation pathway genes, low-dose

ionizing radiation, and the risk of breast cancer among US radiologic technologists. *Cancer Causes Control* 2010; 21: 1857–1866. DOI: 10.1007/s10552-010-9613-7
32. Pooja S, Chaudhary P, Nayak LV, et al. Polymorphic variations in IL-1beta, IL-6 and IL-10 genes, their circulating serum levels and breast cancer risk in Indian women. *Cytokine* 2012; 60: 122–128. DOI: 10.1016/j.cyto.2012.06.241
33. Vinod C, Jyothy A, Vijay Kumar M, et al. A common SNP of IL-10 (−1082A/G) is associated with increased risk of premenopausal breast cancer in South Indian women. *Iran J Cancer Prev* 2015; 8: e3434. DOI: 10.17795/ijcp-3434
34. AlSuhaibani ES, Kizilbash NA, Malik S, et al. Polymorphisms in promoter regions of IL-6 and IL-10 genes in breast cancer: a case-control study. *Genet Mol Res* 2016; 15: gmr.150173. DOI: 10.4238/gmr.15017360
35. Atoum MF. ACC interleukin-10 gene promoter haplotype as a breast cancer risk factor predictor among Jordanian females. *Onco Targets Ther* 2016; 9: 3353–3357. DOI: 10.2147/OTT.S101628
36. Yu Z, Liu Q, Huang C, et al. The interleukin 10 −819C/T polymorphism and cancer risk: a HuGE review and meta-analysis of 73 studies including 15,942 cases and 22,336 controls. *OMICS* 2013; 17: 200–214. DOI: 10.1089/omi.2012.0089
37. Marelli G, Sica A, Vannucci L, et al. Inflammation as target in cancer therapy. *Curr Opin Pharmacol* 2017; 35: 57–65. DOI: 10.1016/j.coph.2017.05.007
38. Bishop RK, Valle Oseguera CA and Spencer JV. Human Cytomegalovirus interleukin-10 promotes proliferation and migration of MCF-7 breast cancer cells. *Cancer Cell Microenviron* 2015; 2: e678. DOI: 10.14800/ccm.678
39. Li Y, Yu H, Jiao S, et al. [Prognostic value of IL-10 expression in tumor tissues of breast cancer patients]. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2014; 30: 517–520.
40. Hussein YM, Alzahrani SS, Alharthi AA, et al. Association of serum cytokines levels, interleukin 10 −1082G/A and interferon-gamma +874T/A polymorphisms with atopic asthma children from Saudi Arabia. *Cell Immunol* 2014; 289: 21–26. DOI: 10.1016/j.cellimm.2014.03.006
41. Tuguz AR, Anokhina EN, Muzhenya DV, et al. Polymorphisms of the anti-inflammatory IL-10 gene associated with malignancy in female reproductive system. *Bull Exp Biol Med* 2015; 158: 673–675. DOI: 10.1007/s10517-015-2832-x
42. Gerger A, Renner W, Langsenlehner T, et al. Association of interleukin-10 gene variation with breast cancer prognosis. *Breast Cancer Res Treat* 2010; 119: 701–705. DOI: 10.1007/s10549-009-0417-y
43. Sabet S, El-Sayed SK, Mohamed HT, et al. Inflammatory breast cancer: high incidence of GCC haplotypes (−1082A/G, −819T/C, and −592A/C) in the interleukin-10 gene promoter correlates with over-expression of interleukin-10 in patients' carcinoma tissues. *Tumour Biol* 2017; 39: 1010428317713393. DOI: 10.1177/1010428317713393
44. Mohamed HT, El-Husseiny N, El-Ghonaimy EA, et al. IL-10 correlates with the expression of carboxypeptidase B2 and lymphovascular invasion in inflammatory breast cancer: the potential role of tumor infiltrated macrophages. *Curr Probl Cancer* 2018; 42: 215–230. DOI: 10.1016/j.currproblcancer.2018.01.009

## 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]
4. 1 OR 2 OR 3
5. “breast” [All Fields]
6. “neoplasms” [MeSH Terms]
7. “cancer” [All Fields]
8. 6 OR 7
9. 5 AND 8
10. Polymorphism
11. 4 AND 8 AND 10