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# Vascular endothelial growth factor +405G/C and -2578C/A polymorphisms and breast cancer risk: a meta-analysis

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**ABSTRACT.** This study aimed to analyze the association between the 405G/C and -2578C/A polymorphisms of the vascular endothelial growth factor (*VEGF*) gene and breast cancer risk by meta-analysis. A systematic computerized search of PubMed, Google Scholar, and Web of Science databases was performed to identify relevant publications. After rigorous searching and screening, 9 eligible case-control studies were included in this meta-analysis. The associations between the *VEGF* gene 405G/C and -2578C/A polymorphisms and breast cancer risk were estimated by pooled ORs and 95%CIs using fixed- or random-effect models. Meta-analysis results showed no significant association between the 405G/C polymorphism and breast cancer risk (CC *vs* GG: OR = 1.04, 95%CI = 0.92-1.17; CC *vs* GC: OR = 1.04, 95%CI = 0.93-1.17; dominant model: OR = 0.95, 95%CI = 0.85-1.06; recessive model: OR = 0.92, 95%CI = 0.70-1.20). The results also did not show significant association for the -2578C/A polymorphism: (AA *vs* CC: OR = 1.03, 95%CI = 0.91-1.15; AA *vs* GA: OR = 0.99, 95%CI = 0.89-1.10; dominant model: OR = 1.00, 95%CI = 0.90-1.10; recessive

 

model: OR = 1.03, 95%CI = 0.94-1.13). Similar results were observed in the subgroup analyses on ethnicity, sample size, and Hardy-Weinberg equilibrium. These findings suggested a lack of association between the *VEGF* gene 405G/C and -2578C/A polymorphisms and breast cancer susceptibility.

**Key words:** *VEGF*; 405G/C; -2578C/A; Breast cancer; Meta-analysis; Genetic polymorphism

## INTRODUCTION

Breast cancer is currently one of the most common cancers among females worldwide and is the leading cause of cancer-related mortality accounting for almost 14% of all cancer deaths (Jemal et al., 2011). The global breast cancer incidence has been increasing by more than one million new cases every year, and the incidence is significantly higher in developed countries than in developing countries (Sturgeon et al., 2004; Liang et al., 2013). The primary risk factors for breast cancer are female gender and older age. Other risk factors that might potentially influence the development of breast cancer include lack of childbearing or lack of breastfeeding, higher levels of certain hormones, certain dietary patterns, and obesity (Guo et al., 2014b). In addition, genetic epidemiological studies provide direct evidence supporting the concept that genetic factors are important in the pathogenesis of breast cancer, indicating that approximately 27% of breast cancer risk is due to inherited susceptibility (Lichtenstein et al., 2000).

Vascular endothelial growth factor (VEGF) plays a key role in a number of pathological processes including angiogenesis, tumor growth, and metastasis. Evidence from *in vitro* and *in vivo* experiments has shown that increased VEGF expression is associated with tumor growth and metastasis. Furthermore, the inhibition of VEGF signaling results in suppression of both tumor-induced angiogenesis and tumor growth (Ferrara, 2002). In tumor angiogenesis, VEGF supports the development of tumor vessels through the promotion of endothelial cell growth and migration (Kaumaya and Foy, 2012).

The *VEGF* gene is located on chromosome 6p12-p21, and consists of eight exons separated by seven introns that exhibit alternative splicing to form a family of proteins (Vincenti et al., 1996). At least 15 single nucleotide polymorphisms in the *VEGF* gene have been described in the literature (Ruggiero et al., 2011). Among these, the +405G/C (rs2010963) polymorphism in the 5'-untranslated region of the *VEGF* gene and the -2578C/A (rs699947) polymorphism in its promoter region are associated with altered VEGF secretion (Almawi et al., 2013). Accordingly, these polymorphisms have been suspected to correlate with the progression and prognosis of cancer.

Previous studies have shown that the *VEGF* +405G/C and -2578C/A polymorphisms were associated with increased risk of digestive system cancer (Zhao et al., 2012; Guo et al., 2014a). Subsequently, many studies have assessed the associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and the risk of breast cancer. However, the results have been inconsistent, suggesting that the association between the *VEGF* +405G/C and -2578C/A polymorphisms and cancer requires further investigation. In this paper, a meta-analysis was performed on previous reports to investigate the associations of the *VEGF* +405G/C

 

and -2578C/A polymorphisms with breast cancer.

## MATERIAL AND METHODS

### Selection of studies

We searched the PubMed, Google Scholar, and Web of Science databases for all studies on the associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and breast cancer risk before October 2014. The following key words were used: "vascular endothelial growth factor", "VEGF", "breast cancer", "polymorphism", "mutation", and "variant". The reference lists of major textbooks, reviews, and included articles were screened through manual searches to find other potentially eligible studies. Studies that were reported by the same authors were checked for possible overlapping participant groups.

### Inclusion and exclusion criteria

Eligible studies were required to meet the following criteria: a) case-control studies that addressed patients with breast cancer and healthy controls; b) studies that evaluated the associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and breast cancer risk; and c) studies that included sufficient genotype data for extraction. Studies were excluded when they were: a) not case-control studies; b) case reports, letters, reviews, meta-analysis, and editorial articles; and c) based on incomplete data or with no usable data reported.

### Data extraction

Two investigators independently extracted and evaluated the data. The opinion of a third investigator was sought for any controversy on the baseline information. The following characteristics were collected from the eligible studies: first author, year of publication, country, ethnicity, number of patients and controls, gene polymorphisms, and evidence of Hardy-Weinberg equilibrium (HWE).

### Statistical analysis

HWE was tested by the $\chi^2$ test and $P < 0.05$ was considered as departure from HWE. The OR corresponding to the 95%CI was used to assess the intensity of the associations between *VEGF* gene polymorphisms (+405G/C and -2578C/A) and breast cancer under homozygote comparison (AA *vs* aa), heterozygote comparison (AA *vs* Aa), and dominant and recessive models between groups. In this study, the dominant model was defined as Aa+aa *vs* AA, where "A" and "a" were the major and minor alleles, respectively, and the recessive model was aa *vs* AA+Aa. Between-study heterogeneities were estimated using the $I^2$ test. $I^2$ values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively (Wu et al., 2002). When $I^2 > 50\%$ indicated heterogeneity across studies, the random-effect model was used for meta-analysis; else the fixed-effect model was used. Subgroup analyses were performed by ethnicity and sample size (studies with more than 1000 participants were defined as ''large'', and studies with less 1000 participants were defined as ''small''). Sensitivity analysis was performed by omission of a non-HWE study or by altering the statistical

models to ensure the stability of the results. Both the funnel plot and the Begg test were used to assess the publication bias ($P < 0.05$ showed statistical significance). All analyses were done with STATA Version 12.0 software (Stata Corp., College Station, TX, USA).

## RESULTS

### Characteristics of the studies included

We identified 72 papers relevant to the search words. Through screening the titles and reading the abstracts and the entire articles, 9 eligible articles were selected for this meta-analysis (Jin et al., 2005; Jacobs et al., 2006; Kataoka et al., 2006; Balasubramanian et al., 2007; Pharoah et al., 2007; Oliveira et al., 2011; Sa-Nguanraksa et al., 2013; James et al., 2014; Rahoui et al., 2014). The flow chart for study selection is summarized in Figure 1. For the +405G/C polymorphism, 9 studies were available, including a total of 6054 patients and 6170 controls. There were 4 studies with cohorts of Caucasian descent (Jin et al., 2005; Jacobs et al., 2006; Balasubramanian et al., 2007; Pharoah et al., 2007), 3 studies of Asian descent (Kataoka et al., 2006; Sa-Nguanraksa et al., 2013; James et al., 2014), 1 study of African descent (Rahoui et al., 2014), and 1 study of mixed descent (Oliveira et al., 2011). The HWE test was performed on the genotype distributions of the controls, and all studies were in agreement with HWE except Oliveira et al. (2011) and Sa-Nguanraksa et al. (2013). For the -2578C/A polymorphism, 7 studies from 5 articles were included, including a total of 4572 patients and 4652 controls. There were 5 studies in 3 articles with cohorts of Caucasian descent (Jin et al., 2005; Jacobs et al., 2006; Pharoah et al., 2007), 1 study of Asian descent (Sa-Nguanraksa et al., 2013), and 1 study of African descent (James et al., 2014). The distribution of genotypes in the controls was consistent with HWE in all studies. The main characteristics of the eligible studies are summarized in Table 1.

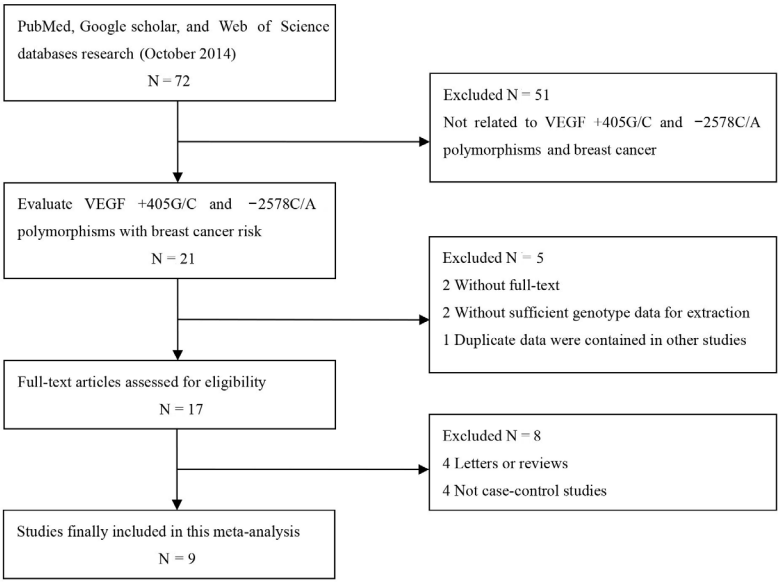


**Figure 1.** Detailed process of identifying eligible studies.

**Table 1.** Characteristics of the studies included for meta-analysis.

| Study included | Area | Race | Cases/Controls | Genotypes for cases | | | Genotypes for controls | | | HWE test |
|---|---|---|---|---|---|---|---|---|---|---|
| +405G/C | | | | GG | GC | CC | GG | GC | CC | |
| Jin et al. (2005) | Swedish | Caucasian | 936/941 | 488 | 363 | 85 | 492 | 367 | 82 | 0.25 |
| Jacobs et al. (2006) | USA | Caucasian | 501/504 | 221 | 222 | 52 | 232 | 221 | 47 | 0.59 |
| Kataoka et al. (2006) | China | Asian | 1095/1198 | 395 | 508 | 192 | 418 | 598 | 182 | 0.18 |
| Balasubramanian et al. (2007) | England | Caucasian | 490/498 | 226 | 207 | 57 | 209 | 225 | 64 | 0.78 |
| Pharoah et al. (2007) | England | Caucasian | 2044/2169 | 962 | 872 | 210 | 988 | 936 | 245 | 0.30 |
| Oliveira et al. (2011) | Brazil | mixed | 235/235 | 95 | 102 | 38 | 82 | 129 | 24 | 0.01 |
| Sa-Nguanraksa et al. (2013) | Thailand | Asian | 483/355 | 223 | 199 | 61 | 234 | 81 | 40 | 0.00 |
| James et al. (2014) | india | Asian | 200/200 | 89 | 88 | 23 | 85 | 89 | 26 | 0.72 |
| Rahoui et al. (2014) | Morocco | African | 70/70 | 26 | 33 | 11 | 36 | 30 | 4 | 0.48 |
| -2578C/A | | | | CC | CA | AA | CC | CA | AA | |
| Jin et al. (2005) | Polish | Caucasian | 411/423 | 104 | 195 | 112 | 106 | 207 | 110 | 0.66 |
| Jin et al. (2005) | German | Caucasian | 153/162 | 44 | 75 | 34 | 50 | 72 | 40 | 0.17 |
| Jin et al. (2005) | Swedish | Caucasian | 939/940 | 258 | 449 | 232 | 257 | 451 | 232 | 0.22 |
| Jacobs et al. (2006) | USA | Caucasian | 501/504 | 114 | 245 | 139 | 130 | 236 | 129 | 0.30 |
| Pharoah et al. (2007) | England | Caucasian | 2015/2139 | 498 | 1012 | 505 | 544 | 1054 | 541 | 0.50 |
| Sa-Nguanraksa et al. (2013) | Thailand | Asian | 483/414 | 240 | 213 | 30 | 214 | 173 | 27 | 0.30 |
| Rahoui et al. (2014) | Morocco | African | 70/70 | 32 | 28 | 10 | 19 | 40 | 11 | 0.19 |

HWE = Hardy-Weinberg equilibrium in controls.

## Meta-analysis

The evaluation of the association between the +405G/C polymorphism in the *VEGF* gene and the risk of breast cancer is displayed in Figure 2 and Table 2. Meta-analysis results showed that there was no association between the +405G/C polymorphism and breast cancer risk (CC *vs* GG: OR = 1.04, 95%CI = 0.92-1.17; CC *vs* GC: OR = 1.04, 95%CI = 0.93-1.17; dominant model: OR = 0.95, 95%CI = 0.85-1.06; recessive model: OR = 0.92, 95%CI = 0.70-1.20). In the analysis stratified by ethnicity, the results also did not show significant association between the +405G/C polymorphism and the susceptibility to breast cancer in either Caucasians or Asians. According to the sample size, no significant association was observed in any genetic model in small (<1000) or large (≥1000) sample studies. Sensitivity analysis was performed by omission of the two non-HWE studies (Oliveira et al., 2011; Sa-Nguanraksa et al., 2013) and the results were not altered, indicating that the result of the meta-analysis was statistically significant (Table 2).

The combined results for the -2578C/A polymorphism in the *VEGF* gene and breast cancer risk are summarized in Figure 3 and Table 3. Meta-analysis results identified no significant association between the -2578C/A polymorphism and susceptibility to breast cancer (AA *vs* CC: OR = 1.03, 95%CI = 0.91-1.15; AA *vs* GA: OR = 0.99, 95%CI = 0.89-1.10; dominant model: OR = 1.00, 95%CI = 0.90-1.10; recessive model: OR = 1.03, 95%CI = 0.94-1.13). In the subgroup analysis by ethnicity, we detected no significant association between the -2578C/A polymorphism and breast cancer risk in either Caucasians or Asians. According to the sample size, no significant association was observed in any genetic model in small (<1000) or large (≥1000) sample studies. Sensitivity analyses were conducted by altering the statistical models. No material alteration was detected, indicating that our results were statistically robust.

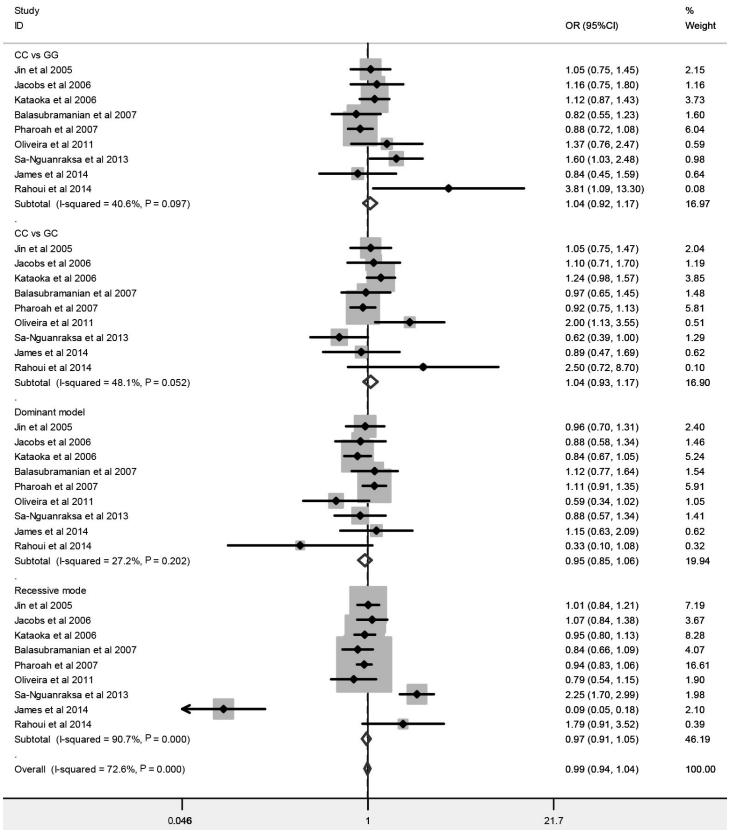


**Figure 2.** Meta-analysis of the relationship between +405G/C polymorphism in the VEGF gene and breast cancer risk.

**Table 2.** Meta-analysis for the association of VEGF+405G/C polymorphism with breast cancer.

| Variables | N | Cases/controls | CC *vs* GG | CC *vs* GC | Dominant model | Recessive mode |
|---|---|---|---|---|---|---|
| | | | OR (95%CI) P $I^2$ | OR (95%CI) P $I^2$ | OR (95%CI) P $I^2$ | OR (95%CI) P $I^2$ |
| Total | 9 | 6054/6170 | 1.04 (0.92-1.17) 0.10 40.6% | 1.04 (0.93-1.17) 0.05 48.1% | 0.95 (0.85-1.06) 0.20 27.2% | 0.92 (0.70-1.20) 0.00 90.7% |
| Ethnicity | | | | | | |
| Caucasian | 4 | 3971/4112 | 0.93 (0.80-1.08) 0.55 0.0% | 0.97 (0.84-1.13) 0.85 0.0% | 1.05 (0.91-1.21) 0.70 0.0% | 0.96 (0.88-1.05) 0.55 0.0% |
| Asian | 3 | 1778/1753 | 1.17 (0.96-1.44) 0.21 35.6% | 0.92 (0.58-1.46) 0.03 71.0% | 0.88 (0.73-1.06) 0.63 0.0% | 0.62 (0.20-1.89) 0.00 97.5% |
| African mixed | 1 | 70/70 | 3.81 (1.09-13.30) / | 2.50 (0.72-8.70) / | 0.33 (0.10-1.08) / | 1.79 (0.91-3.52) / |
| | 1 | 235/235 | 1.37 (0.76-2.47) / | 2.00 (1.13-3.55) / | 0.59 (0.34-1.02) / | 0.79 (0.54-1.15) / |
| HWE | | | | | | |
| Yes | 7 | 5336/5580 | 0.99 (0.87-1.12) 0.22 27.8% | 1.05 (0.93-1.19) 0.44 0.0% | 0.98 (0.87-1.10) 0.26 21.8% | 0.84 (0.65-1.08) 0.00 88.1% |
| No | 2 | 718/590 | 1.51 (1.06-2.15) 0.67 0.0% | 1.10 (0.35-3.47) 0.00 89.5% | 0.76 (0.54-1.06) 0.26 21.5% | 1.34 (0.48-3.76) 0.00 94.8% |
| Sample size | | | | | | |
| ≥1000 | 4 | 4576/4812 | 1.00 (0.87-1.14) 0.43 0.0% | 1.05 (0.92-1.20) 0.31 16.3% | 0.97 (0.86-1.10) 0.30 17.6% | 0.97 (0.89-1.05) 0.78 0.0% |
| <1000 | 5 | 1478/1358 | 1.23 (0.82-1.84) 0.05 58.2% | 1.09 (0.70-1.72) 0.02 65.9% | 0.89 (0.71-1.11) 0.14 42.9% | 0.78 (0.35-1.72) 0.00 95.3% |

N = number; $I^2$ = inconsistency index; CI = confidence interval; OR = odds ratio.

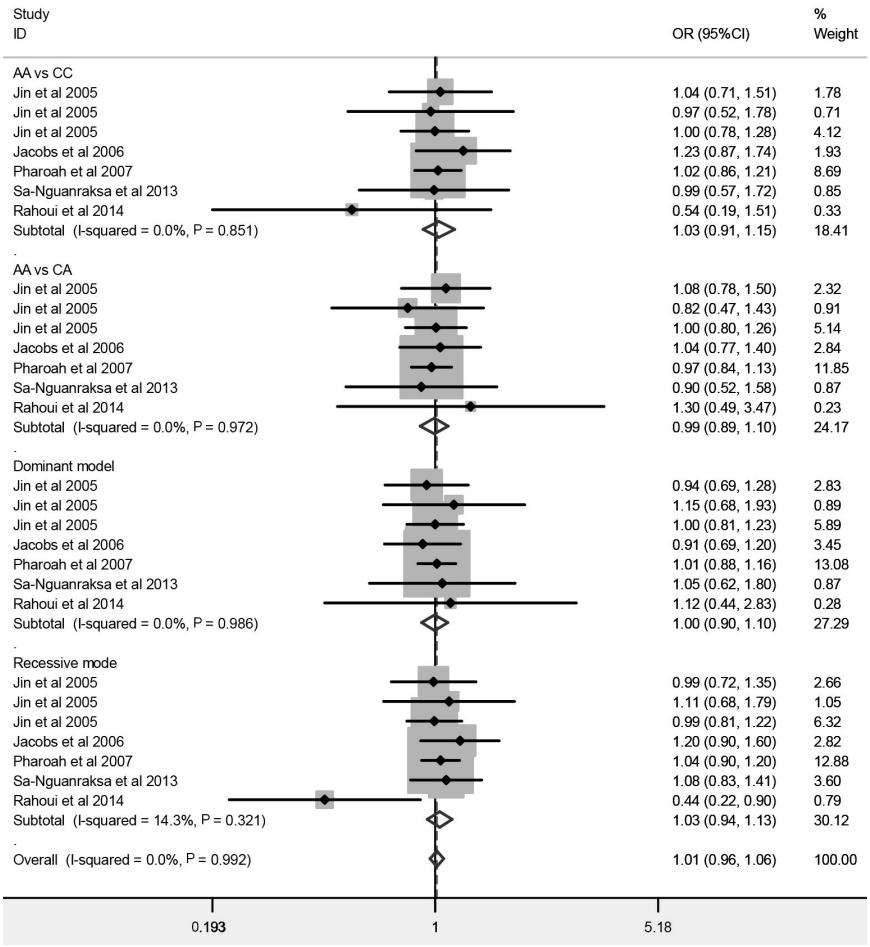


**Figure 3.** Meta-analysis of the relationship between -2578C/A polymorphism in the VEGF gene and breast cancer risk.

**Table 3.** Meta-analysis of the relationship between -2578C/A polymorphism in the VEGF gene and breast cancer risk.

| Variables | N | Cases/controls | AA *vs* CC | | | AA *vs* CA | | | Dominant model | | | Recessive model | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR (95%CI) | P | $I^2$ | OR (95%CI) | P | $I^2$ | OR (95%CI) | P | $I^2$ | OR (95%CI) | P | $I^2$ |
| Total | 7 | 4572/4652 | 1.03 (0.91-1.15) | 0.85 | 0.0% | 0.99 (0.89-1.10) | 0.97 | 0.0% | 1.00 (0.90-1.10) | 0.99 | 0.0% | 1.03 (0.94-1.13) | 0.32 | 14.3% |
| Ethnicity | | | | | | | | | | | | | | |
| Caucasian | 5 | 4019/4168 | 1.04 (0.92-1.17) | 0.89 | 0.0% | 0.99 (0.89-1.17) | 0.92 | 0.0% | 0.99 (0.90-1.10) | 0.93 | 0.0% | 1.04 (0.94-1.15) | 0.86 | 0.0% |
| Asian | 1 | 483/414 | 0.99 (0.57-1.72) | / | / | 0.90 (0.52-1.58) | / | / | 1.05 (0.62-1.80) | / | / | 1.08 (0.83-1.41) | / | / |
| African | 1 | 70/70 | 0.54 (0.19-1.51) | / | / | 1.30 (0.49-3.47) | / | / | 1.12 (0.44-2.83) | / | / | 0.44 (0.22-0.90) | / | / |
| Sample size | | | | | | | | | | | | | | |
| ≥1000 | 3 | 3455/3583 | 1.04 (0.91-1.19) | 0.59 | 0.0% | 0.99 (0.88-1.11) | 0.92 | 0.0% | 0.99 (0.89-1.11) | 0.80 | 0.0% | 1.05 (0.94-1.16) | 0.57 | 0.0% |
| <1000 | 4 | 1117/1069 | 0.97 (0.74-1.27) | 0.71 | 0.0% | 1.00 (0.78-1.28) | 0.77 | 0.0% | 1.01 (0.80-1.27) | 0.91 | 0.0% | 0.99 (0.83-1.19) | 0.13 | 46.9% |

N = number; $I^2$ = inconsistency index; CI = confidence interval; OR = odds ratio.

## Publication bias

A funnel plot and the Begg test was used to assess the publication bias. The results suggested that there was no publication bias in this meta-analysis (all $P > 0.05$).

## DISCUSSION

Breast cancer is a multifactorial disease and its pathogenesis is not yet fully understood. It has been shown that the underlying mechanisms of breast cancer comprise both genetic and environmental factors, and that certain SNPs within inherited susceptibility genes might exert their effects on breast cancer development. Angiogenesis, the development of new blood vessels, is required for the growth of microscopic cancers into clinically relevant tumors (Velazquez, 2007), and has been proven to be a key step for breast cancer occurrence, progression, and prognosis. VEGF is believed to serve as an important factor for angiogenesis through various mechanisms (Yoshiji et al., 1996). Recently, the associations between *VEGF* polymorphisms and the risk of breast cancer have been extensively studied; however, the reported results have been inconsistent. The lack of concordance across many of these studies reflects their limitations including small sample sizes, ethnic differences, and research methodologies. In the current study, a meta-analysis technique was used to collect comparable published or unpublished data, and statistical methods were applied to synthesize the independent results of the studies with the same research target in order to obtain a combined quantitative conclusion. Overall, the aim of meta-analysis is to combine the same kind of studies to increase the sample size and statistical power, and thereby get a more authentic result.

In the current meta-analysis, we examined the associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and the risk of breast cancer by critically including all published studies. Ultimately, however, the results of our meta-analysis did not show any significant associations between the *VEGF* +405G/C and -2578C/A polymorphisms and breast cancer risk. Because of the differences in genetic backgrounds and the environments in which the subjects lived, we performed an ethnicity-specific subgroup analysis, but did not find any significant associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and breast cancer risk in either Caucasians or Asians. As only one study was performed in Africa, further investigation might be needed in Africans. The present meta-analysis also involved several studies with small sample sizes; accordingly, there might have been a selective bias underlying the associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and breast cancer development, and therefore, large-sample studies should be used to re-evaluate this association. Upon further stratification by sample size ($<1000$ or $\geq 1000$), this meta-analysis did not detect significant associations between the +405G/C and -2578C/A polymorphisms in the *VEGF* gene and breast cancer, indicating that there was no evidence of a small-study bias in the meta-analysis. Further sensitivity analysis confirmed that this meta-analysis was realistic and believable. As the eligible study number was limited in the meta-analysis, however, these results still need further investigation.

There were some limitations in our meta-analysis. The linkage disequilibrium of the +405G/C and -2578C/A loci of the *VEGF* gene might synergistically increase the risk of breast cancer (James et al., 2014). However, as there was not sufficient individual information on the genotypes of both the +405G/C and -2578C/A polymorphisms, we could not perform the combined analysis of linkage disequilibrium. Therefore, more studies with larger sample

sizes and providing more detailed information are needed to address this issue. We also were not able to address all the sources of heterogeneity that existed among the studies for most polymorphisms, although we could have performed stratification analyses by subgroup for the limited number of published studies. Finally, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis.

In conclusion, our meta-analysis indicated that the +405G/C and -2578C/A polymorphisms of the *VEGF* gene were not associated with the risk of breast cancer. Owing to the above-mentioned limitations, the findings should be verified by further research in the near future.

## Conflict of interest

The authors declare no conflict of interest.

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