

ORIGINAL ARTICLE

Lack of association between +405G/C polymorphism in VEGF and breast cancer risk: A meta-analysis

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Summary

Purpose: To explore whether the vascular endothelial growth factor (VEGF) +405G/C polymorphism confers susceptibility to breast cancer (BC) by conducting a meta-analysis.

Methods: Publications addressing the association between the VEGF +405G/C polymorphism and BC risk were selected from the PubMed, Embase and Google Scholar databases. Data were extracted from studies by three independent reviewers. The meta-analysis was performed by STATA 12.0 software, and odds ratio (OR) with 95% confidence interval (CI) were calculated.

Results: Finally, 10 case-control studies were retrieved with a total of 8,855 BC patients and 9,393 controls. No signif-

icant association was identified between VEGF +405G/C polymorphism and BC risk in overall populations under 5 models (C vs G: OR=1.001, 95% CI=0.896-1.119, $p=0.987$; CC vs GG: OR=1.006, 95% CI=0.853-1.186, $p=0.997$; CG vs GG: OR= 0.985, 95% CI= 0.823-1.178, $p=0.779$; CC vs CG/GG: OR=1.019, 95% CI=0.921-1.127, $p=0.722$; CC/CG vs GG: OR=0.985, 95 % CI=0.835-1.162, $p=0.862$), and also in the subgroup analysis by ethnicity.

Conclusion: Our study confirms that there is a lack of association between the VEGF +405 G/C polymorphism and BC risk.

Key words: breast cancer, meta-analysis, polymorphism, rs2010963, VEGF +405G/C

Introduction

BC is the malignancy most common diagnosed and the primary cause of cancer-related death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths [1], with an estimated 1.67 million new cancers diagnosed in 2012 [2]. Angiogenesis is an important step in the progression of cancer and is essential for primary tumor growth [3]. VEGF is a dominant angiogenic factor in solid tumors, which can increase vascular permeability and induce endothelial cell proliferation, migration, and differentia-

tion and capillary formation [4]. In BC, VEGF is believed to be cardinal for the process of initiation of angiogenesis and a primary mediator of cancer angiogenesis [5].

VEGF gene is located in chromosome 6p12 and consists of a 14 kb coding region with 8 exons and 7 introns [6]. Several single nucleotide polymorphisms (SNPs) have been described in the 5'-untranslated region (UTR), as well as in the promoter region, associated with BC susceptibility [7]. One of them, +405G/C polymorphism

(rs2010936), which is at position -634 before transcription initiation site in the 5'-UTR, and a significant correlation was uncovered between this polymorphism and lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells (PBMC) VEGF protein production [8]. Several studies have uncovered the association between VEGF +405G/C polymorphisms and susceptibility to malignancy, including gastric cancer [9-12], colorectal cancer [13-16], esophageal adenocarcinoma [17], and oral squamous cell cancer [18]. Recently, Sanguanraksa et al. [19] investigated the association between VEGF -634G/C polymorphisms and BC risk in a middle-sized case-control study in a Thailand population, and suggested that the -634CC variant genotype was associated with an increased risk of BC with a marginal significance. However, lack of association between the polymorphism and BC risk was reported by Rani et al. [20]. Based on the significant role of VEGF in breast carcinogenesis and the genotype-phenotype correlation, we hypothesized that genetic variants of VEGF might be associated with BC susceptibility. Paradoxically the data reported are conflicting and inconclusive. The lack of concordant conclusions can be partly explained by the relatively small sample sizes, differences in ethnic compositions, and research methodologies among studies.

Thus, we carried out a meta-analysis on all eligible studies to derive a more robust estimation of the association between VEGF +405G/C polymorphism and BC susceptibility.

Methods

Search strategy

We performed an in silico search of the PubMed, Embase, and CBM (Chinese Biomedical Literature Database) to retrieve articles linking VEGF +405G/C gene polymorphism and susceptibility to BC available up to December 2014 with keywords "breast cancer," "breast neoplasm", "breast tumor", "vascular endothelial growth factor", "VEGF", "Vascular Endothelial Growth Factors", "polymorphism," "variant", "Genomic Structural Variation", and "Polymorphism, Genetic". Additionally, a search of the references of original studies was also performed, and review articles were also examined. The authors of articles that had unclear data were directly contacted by us. Publications in English and Chinese were included for all the aforementioned methodologies.

Quality control

Eligible studies had to meet the following criteria: (i) case-control studies; (ii) the parameters about the

VEGF +405G/C polymorphism and BC risk should be evaluated; (iii) detailed information on genotype frequency in cases and controls should be reported; (iv) sufficient statistical data for estimating an OR with 95% CI should be included. The exclusion criteria were as follows: (i) not a case-control study that has evaluated the association between the VEGF +405G/C polymorphism and BC risk; (ii) no usable data reported; or (iii) contained duplicate data; (iv) abstract, comment, review, and editorial; (v) family-based experiment. When multiple publications reported on the same or overlapping data, the publication with the latest data or the largest population was selected.

Data extraction

Three investigators (Meng Zhang, Xun Wu and Xiang Wang) independently extracted data in a standardized form and reached a consensus of all studies. The following information was extracted from each study: name of the first author, year of publication, ethnicity, source of cases and controls, cancer type, the total number of cases and controls, genotype frequencies for each case and control, and HWE (Hardy-Weinberg equilibrium) of controls.

Statistics

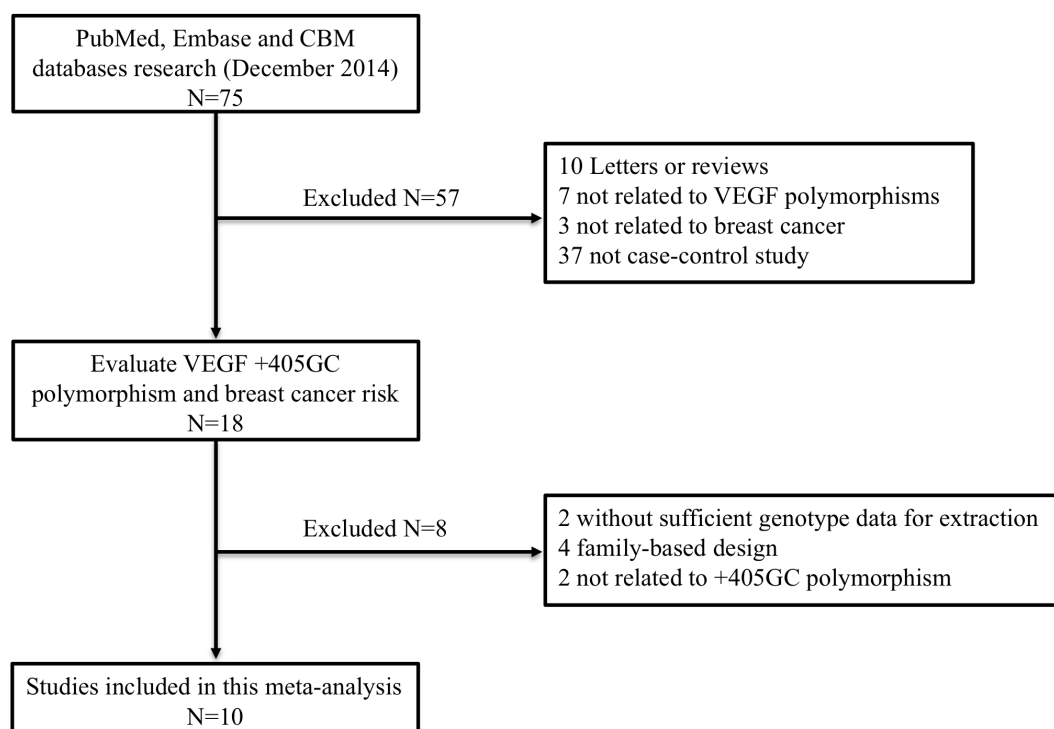
The OR and 95% CI were used to evaluate the strength of associations between the VEGF +405G/C polymorphism and the risk of BC according to 5 genetic models: allele contrast (C vs G), homozygote (CC vs GG), heterozygote (CG vs GG), recessive (CC vs CG/GG), and dominant (CC/CG vs GG) models. The heterogeneity was tested by a chi-square based Q statistic test. The effect of heterogeneity was quantified by using I^2 values, as well as p values [21]. If I^2 value <50% and $p > 0.10$, indicating that no significant heterogeneity existed, ORs were pooled by a fixed-effects model. Otherwise, we chose a random-effects model (DerSimonian and Laird method) [22].

A professional web-based program (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>) was used to test the HWE of controls [23], if $p > 0.05$, indicating that the controls followed the HWE balance. Sensitivity analysis was conducted to assess the stability of these results. One single study obtained in the meta-analysis was eliminated each time to reveal the impression of the individual data set on the pooled ORs [24]. When HWE disequilibrium existed ($p < 0.05$ was considered statistically significant), the sensitivity analysis was also conducted. In the meta-analysis, the possibility of publication bias was tested by Egger's test and Begg's test ($p < 0.05$ was considered representative of statistically significant publication bias) [25] and visual observation of a funnel plot [26]. STATA Software (version 12.0, Stata Corp) was used in all statistical tests, and $p < 0.05$ for any test or model was considered to be statistically significant.

Table 1. Characteristics of eligible case-control studies included in the meta-analysis

First author	Year	Ethnicity	Genotyping method	Control of source	Cancer type	Case			Control			HWE
						GG	GC	CC	GG	GC	CC	
James et al.	2014	Asian	PCR-RFLP	H-B	BC	89	88	23	85	89	26	0.722
Kapahi et al.	2014	Asian	PCR-RFLP	P-B	BC	104	77	11	74	94	24	0.485
Luo et al.	2013	Asian	PCR-RFLP	H-B	BC	338	205	137	341	204	135	8.773
Sanguanraksa et al.	2013	Asian	<u>ARMS</u>	H-B	BC	223	199	61	234	81	40	4.632
Oliveira et al.	2011	Mixed	PCR-RFLP	P-B	BC	95	102	38	82	129	24	0.01
Balasubramanian et al.	2007	Caucasian	TaqMan	P-B	BC	226	207	57	209	225	64	0.777
Pharoah et al.	2007	Caucasian	TaqMan	P-B	BC	962	872	210	988	936	245	0.301
Kataoka et al.	2006	Asian	TaqMan	P-B	BC	395	508	192	418	598	182	0.181
Jacobs et al.	2006	Mixed	TaqMan	P-B	BC	221	222	52	232	221	47	0.588
Jin et al.	2005	Caucasian	TaqMan	P-B	BC	488	363	85	492	367	82	0.254

HWE: Hardy-Weinberg equilibrium; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; ARMS: refractory mutation system; H-B: hospital based; P-B: population based

**Figure 1.** Flow chart showing the study selection procedure.

Results

Characteristics of eligible studies

After careful examination according to the inclusion criteria, a total of 10 case-control studies comprising 8,855 cases and 9,393 healthy controls were included [19,20,27-34]. The flow chart of the study selection is summarized in Figure 1.

All the included studies were case-control studies that had evaluated the association between VEGF +405G/C gene polymorphisms and susceptibility to BC. The selected study characteristics are summarized in Table 1. All 10 eligible studies presented data on VEGF +405G/C polymorphisms with BC risk. In one study, the distribution of the genotypes in the control groups were not in HWE [30].

Table 2. Results of meta-analysis for VEGF +405G/T polymorphism and breast cancer risk

Comparison	Population	Number	Test of association		p value	Model	Test of heterogeneity	
			OR	95%CI			p value	I-square (%)
C vs. G	Overall	10	1.001	0.896-1.119	0.987	R	0	75.8
	Asian	5	1.009	0.785-1.298	0.941		0	87.7
	Caucasians	3	0.952	0.887-1.022	0.174		0.518	0
	Mix	2	1.048	0.899-1.221	0.552		0.733	0
CC vs. GG	Overall	10	1.006	0.853-1.186	0.997	R	0.041	48.6
	Asian	5	0.977	0.702-1.361	0.892		0.011	69.3
	Caucasians	3	0.907	0.773-1.064	0.231		0.601	0
	Mix	2	1.230	0.866-1.746	0.247		0.664	0
CG vs. GG	Overall	10	0.985	0.823-1.178	0.779	R	0	81
	Asian	5	1.062	0.698-1.616	0.328		0	90.3
	Caucasians	3	0.952	0.862-1.051	0.521		0.633	0
	Mix	2	0.870	0.570-1.329	0.865		0.071	69.3
CC vs. CG/ GG	Overall	10	1.019	0.921-1.127	0.722	F	0.150	32.3
	Asian	5	1.055	0.909-1.224	0.485		0.116	46
	Caucasians	3	0.930	0.799-1.083	0.350		0.709	0
	Mix	2	1.315	0.945-1.828	0.104		0.248	25.1
CC/CG vs. GG	Overall	10	0.985	0.835-1.162	0.862	R	0	80.4
	Asian	5	1.028	0.703-1.504	0.887		0	90.2
	Caucasians	3	0.944	0.859-1.036	0.224		0.542	0
	Mix	2	0.952	0.709-1.276	0.74		0.181	44.1

OR: odds ratio, CI: confidence interval, F: fixed-effects models, R: random-effects models

Meta-analysis results

The main results of this meta-analysis and the heterogeneity test are shown in Table 2. No significant association was found between VEGF +405G/C polymorphism and the risk of BC in the overall populations under 5 genetic models (C vs G: OR=1.001, 95% CI=0.896-1.119, p=0.987; CC vs GG: OR=1.006, 95% CI=0.853-1.186, p=0.997; CG vs GG: OR= 0.985, 95% CI= 0.823-1.178, p=0.779; CC vs CG/GG: OR=1.019, 95% CI=0.921-1.127, p = 0.722; CC/CG vs GG: OR=0.985, 95% CI=0.835-1.162, p = 0.862). In the subgroup analysis by ethnicity, there was also lack of association between VEGF +405G/C polymorphisms and BC risk in Asians (C vs G: OR=1.009, 95% CI=0.785-1.298, p =0.941; CC vs GG: OR=0.977, 95 % CI=0.702-1.361, p=0.892; CG vs GG: OR=1.062, 95% CI=0.698-1.616, p=0.328; CC vs CG/GG: OR=1.055, 95% CI=0.909-1.224, p=0.485; CC/CG vs GG: OR=1.028, 95% CI=0.703-1.504, p=0.887) and Caucasians (C vs G: OR=0.952, 95% CI=0.887-1.022, p=0.174; CC vs

GG: OR=0.907, 95% CI=0.773-1.064, p=0.231; CG vs GG: OR=0.952, 95% CI=0.862-1.051, p=0.521; CC vs CG/GG: OR=0.930, 95% CI=0.799-1.083, p =0.350; CC/CG vs GG: OR=0.944, 95% CI=0.859-1.036, p=0.224) (Table 2).

Publication bias and sensitivity analysis

We performed a sensitivity analysis to explore the influence of individual studies on the collected results by deleting a single study from the pooled analysis once at a time. The results showed that no individual study significantly affected the pooled OR (Figure 2). Publication bias was assessed by Begg's funnel plot and Egger's test. No apparent publication bias was assessed in VEGF +405G/C polymorphisms (VEGF +405G/T C vs G: Begg's test: p= 0.787; Figure 3).

Discussion

Angiogenesis is vital for the growth of micro-

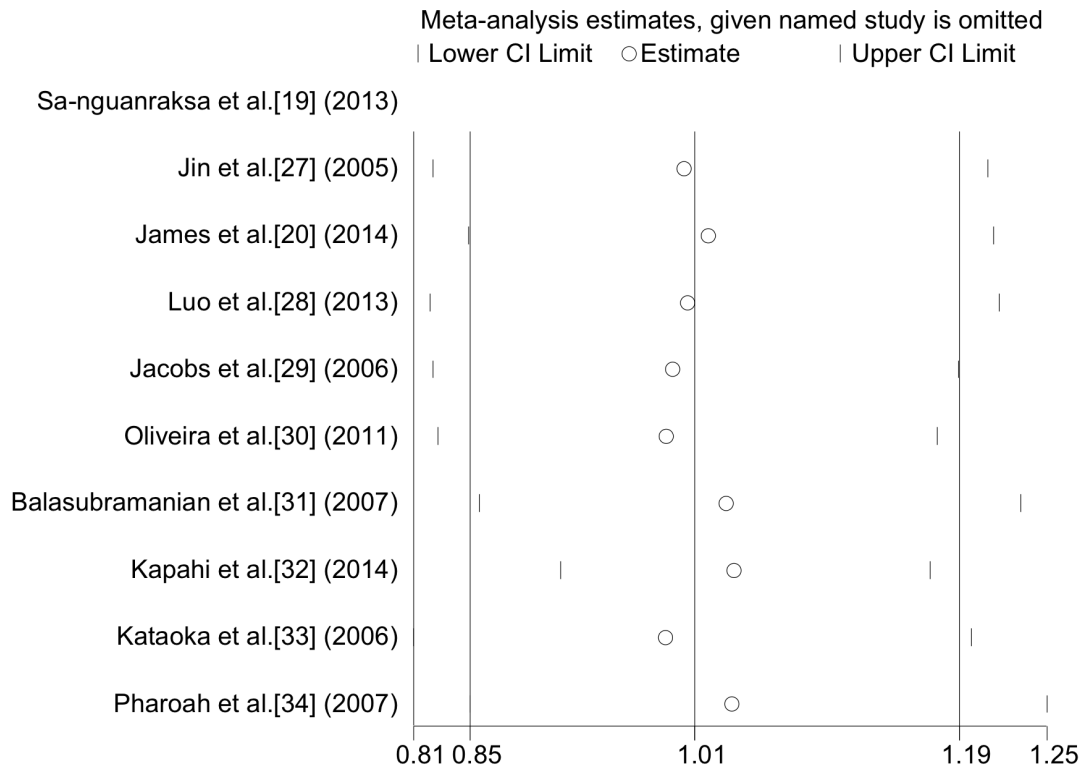


Figure 2. Sensitivity analysis of overall odds ratio coefficients for VEGF +405G/T (CC vs GG). Results were calculated by omitting each study in turn. The two ends of the dotted lines represent the 95%CI.

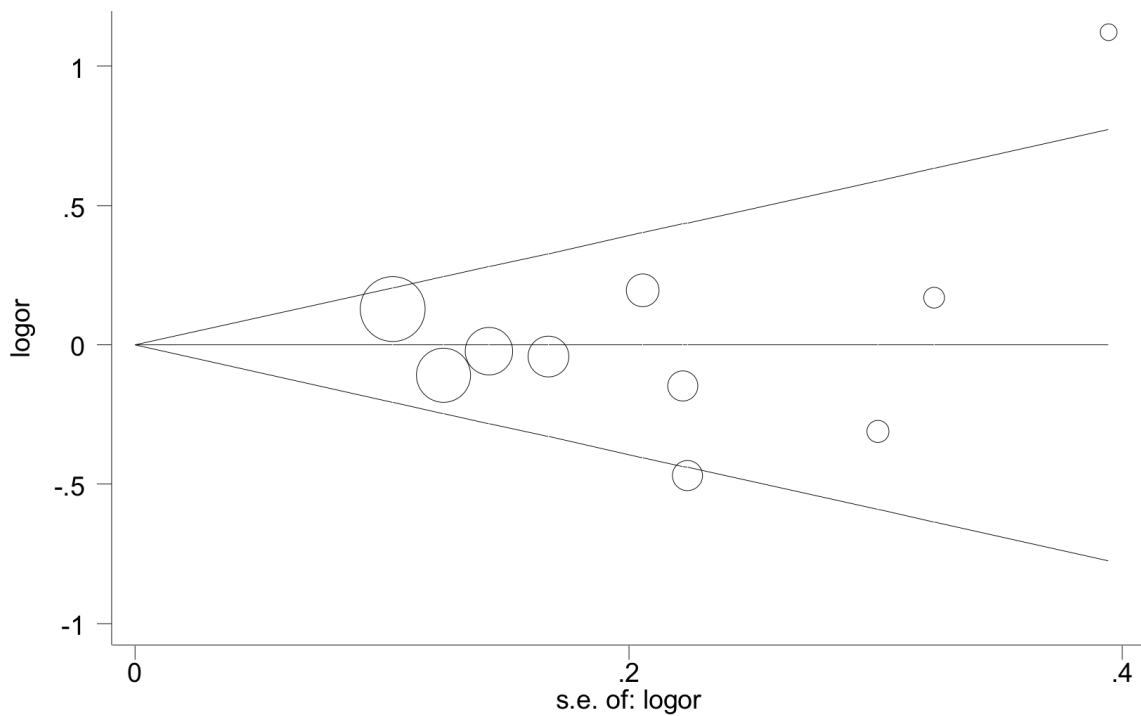


Figure 3. Begg's funnel plot for publication bias test (VEGF +405G/T C vs G). Each point represents a separate study for the indicated association. The circles represent the weight of individual study.

scopic cancers into larger tumors, which is largely controlled via VEGF by various mechanisms, such as effects on the process of endothelial cell proliferation, survival, and cell migration [35,36]. Up-regulation of VEGF is associated with the occurrence and development of malignant neoplasms as *in vitro* and *in vivo* experiments have shown; furthermore, a few of potentially functional SNPs which are located in VEGF have revealed to be related to VEGF gene expression [37]. One of them, the +405G/C polymorphism, which is located in the potential binding site for MZF1 transcription factor in the 5'UTR of VEGF, has been identified as remarkably associated with VEGF protein production [8]. It has been illustrated that this polymorphism can alter the activity of the internal ribosome entry site (IRES)-B domain which is crucial for the expression of the VEGF A isoform, influencing the expression at the post-transcriptional level [38,39].

To date, although many efforts have been made to illustrate the association between VEGF +405G/C polymorphisms and BC risk, the results remain controversial. In this study, we employed a meta-analysis to assess of the association between VEGF +405G/C polymorphisms and BC risk by critically reviewing 10 studies (8,855 cases and 9,393 controls). Heterogeneity and sensitivity analyses were also performed to ensure the eligibility of the analysis. However, no significant association was obtained by the meta-analysis on the relationship between the polymorphisms +405G/C in VEGF and BC risk in the overall populations under 5 genetic models. Furthermore, in the subgroup analysis by ethnicity, there was also a lack of association between the polymorphism and BC risk in Asians, Caucasians and mixed groups.

Although we performed a comprehensive *in silico* search for all available eligible studies and provided an overview of the association between VEGF +405G/C polymorphisms and BC susceptibility, there are still some limitations in our meta-analysis which should be noted. First, the number of studies and the sample size were con-

siderably small, resulting in insufficient strength which is unable to uncover slight effects on BC. Second, most of the included studies are from Asians and the considerably small sample size in Caucasians might cause inconspicuousness. Third, data was largely unavailable for Africans. Furthermore, these samples were not uniformly defined. Several studies used controls that were population-based, while others were hospital-based, which may not represent the general population. Lastly, the original data of the eligible studies was unavailable, which makes it difficult to evaluate the roles of some special environmental factors and different lifestyles, such as diet, alcohol consumption, and smoking, and particularly, the status of estrogen receptor (ER), progesterone receptor (PR) and HER2, which are closely related to the prognosis of patients after surgery and can help guide therapy options [40].

In summary, our meta-analysis has successfully indicated absence of association between VEGF +405G/C polymorphism and BC risk in all ethnic groups; no persuasive evidence of association between the polymorphism and BC was detected in the pooled analyses. However, more studies with larger sample size, especially Africans, are required to further assess the associations of VEGF +405G/C polymorphisms with the BC susceptibility in order to refine the investigation on this interesting issue.

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Author contributions

Z.C., S.W. and Y.W. accessed information from literature for this article. M.Z., X.W., D.Z., Y.C., W.L. and X.W. contributed in the writing, discussing, and editing the manuscript.

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