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# Association of Vascular Endothelial Growth Factor (*VEGF*) Gene Polymorphisms With Gastric Cancer and Its Development, Prognosis, and Survival

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**Abstract**

The relationship between vascular endothelial growth factor gene polymorphism and gastric cancer risk and its development, prognosis, and survival are still being debated. This meta-analysis was performed to assess these relationships. The association reports were identified from PubMed, Embase, Cochrane Library, and CBM-disc (China Biological Medicine Database), and eligible studies were included and calculated using the meta-analysis method. *VEGF*+936C/T, *VEGF*+405 G>C, *VEGF*-460 T>C, *VEGF*-1498 T>C, and *VEGF*-2578 C>A gene polymorphisms were found to be unassociated with gastric cancer risk for the overall population in this meta-analysis, whereas the *VEGF*-634 G>C GG genotype was associated with gastric cancer risk in the overall population. Furthermore, *VEGF*-634 G>C C allele and the GG genotype were associated with gastric cancer risk in Caucasians, and *VEGF*+1612G/A gene polymorphism was associated with gastric cancer risk for the Asian population. *VEGF*+936C/T gene polymorphism was not associated with the stage of cancer, lymph node metastasis, Lauren classification, or survival of gastric cancer. However, *VEGF*+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer. In conclusion, the *VEGF*-634 G>C GG genotype was associated with gastric cancer risk in the overall population with the *VEGF*-634 G>C C allele and GG genotype being associated with risk in Caucasians and *VEGF*+1612G/A in the Asian population.

**Keywords**

gastric cancer, vascular endothelial growth factor (VEGF), gene polymorphism, meta-analysis

**Abbreviations**

CI, confidence interval; OR, odds ratio; VEGF, vascular endothelial growth factor.

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## Introduction

Gastric cancer is one of the most common diagnosed cancers and cause of cancer-related deaths worldwide.[1-3] It is a heterogeneous disease with diverse histological and molecular subtypes.[2] Although there have been vital improvements in diagnostic and therapeutic techniques for gastric cancer, prognosis for patients remains poor.[3] Developing a suitable indicator for early diagnosis of gastric cancer and to predict the development, prognosis, and survival of the disease are urgently needed.

Vascular endothelial growth factor (VEGF), a potent endothelial cell mitogen, regulates vasculogenesis and postnatal vascular remodeling, and its expression is upregulated under a variety of pathophysiological conditions.[4] Vascular endothelial growth factor is known as a lymphangiogenic growth factor and plays an important role in tumor lymphangiogenesis via activation of the VEGF receptor.[5] Present data indicate that VEGF gene polymorphisms were associated with

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**Table 1.** General Characteristics of the Included Studies in This Meta-Analysis for Vascular Endothelial Growth Factor (VEGF) +936C/T Gene Polymorphism With Gastric Cancer Risk.

| | | | | GC | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| First Author, Year | Country/District | Ethnicity | Control Source | TT | CT | CC | Total | TT | CT | CC | Total |
| Chae[12] | Korea | Asian | Population based | 8 | 122 | 283 | 413 | 12 | 149 | 252 | 413 |
| Tzanakis[13] | Greece | Caucasian | Population based | 26 | 33 | 41 | 100 | 22 | 27 | 51 | 100 |
| Bae[14] | Korea | Asian | Population based | 7 | 58 | 89 | 154 | 3 | 57 | 169 | 229 |
| Ke[15] | China | Asian | Population based | 15 | 152 | 373 | 540 | 11 | 164 | 386 | 561 |
| Guan[16] | USA | Caucasian | Population based | 3 | 41 | 127 | 171 | 2 | 20 | 78 | 100 |
| Tahara[17] | Japan | Asian | Hospital based | 11 | 118 | 256 | 385 | 19 | 140 | 300 | 459 |
| Al-Moundhri[18] | Oman | Asian | Population based | 2 | 19 | 109 | 130 | 0 | 20 | 110 | 130 |
| Zhou[19] | China | Asian | Population based | 8 | 45 | 97 | 150 | 7 | 49 | 94 | 150 |

the risk of cancers, such as bladder cancer,[6] papillary thyroid carcinoma,[7] lung cancer,[8] hepatocellular carcinoma,[9] and renal cell carcinoma.[10] The VEGF pathway also plays a prominent role in the growth and progression of human cancer, including gastric cancer.[11]

Current evidence shows that VEGF plays a role in the pathogenesis of gastric cancer. This meta-analysis was performed to assess the relationship between *VEGF* gene polymorphism and gastric cancer risk and its development, prognosis, and survival.

## Materials and Methods

### Search Strategy

The relevant studies were searched and included from the databases of PubMed, Embase, Cochrane Library, and CBM-disc (China Biological Medicine Database) on June 1, 2016. The retrieval strategy of "(vascular endothelial growth factor OR VEGF) AND (polymorphism OR polymorphisms OR genotype OR genotypes OR allele OR alleles) AND (gastric cancer OR gastric carcinoma)" was entered into the above-mentioned databases.

### Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) the outcome must be gastric cancer; (2) the study included 2 comparison groups (gastric cancer group vs control group); and (3) the report should present the data of *VEGF* genotype distribution.

Exclusion criteria were as follows: (1) case reports, review articles, and editorials; (2) preliminary results were not on *VEGF* gene polymorphism or gastric cancer; (3) investigating the role *VEGF* gene expression as to gastric cancer; and (4) If multiple publications from the same study group were published, we only included the study with the largest sample size in our final analysis.

### Data Extraction

The following information from each eligible investigation was extracted by 2 investigators independently: first author's surname, year of publication, ethnicity, control source of the control group, and the number of cases and controls for *VEGF* genotypes. Frequencies of allele for VEGF were calculated for the case and control group. If disagreements occurred, the results were to be resolved by discussion.

### Statistical Analysis

Cochrane Review Manager version 5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used in this meta-analysis to calculate the extracted data from each report. The pooled statistic was counted using the fixed-effects model. However, a random-effects model was conducted when the $P$ value of heterogeneity test was less than .1. Results were expressed using odds ratios (ORs) for dichotomous data, and 95% confidence intervals (CIs) were also calculated. $P < .05$ was required for the pooled OR to be statistically significant, and $I^2$ was used to test the heterogeneity among the included studies. Sensitivity analysis was also performed according to the source of the controls (population vs hospital).

## Results

### Association of VEGF+936C/T Gene Polymorphism With Gastric Cancer Risk

Eight studies[12-19] were evaluated for the relationship between *VEGF*+936C/T gene polymorphism and gastric cancer risk and included in this meta-analysis. We found that *VEGF*+936C/T gene polymorphism was not associated with gastric cancer risk in the overall population (T allele: OR = 1.08, 95% CI: 0.88-1.32, $P = .45$; TT genotype: OR = 1.12, 95% CI: 0.80-1.55, $P = .51$; CC genotype: OR = 0.93, 95% CI: 0.74-1.17, $P = .52$; Figure 1 and Table 2).

In the subgroup analysis organized by ethnicity, the meta-analysis indicated that *VEGF*+936C/T gene polymorphism was not associated with gastric cancer risk in the Asian and Caucasian population (Table 2).

Sensitivity analysis was also performed according to the source of the controls (population based vs hospital based). The results from this sensitivity analysis for health were similar with

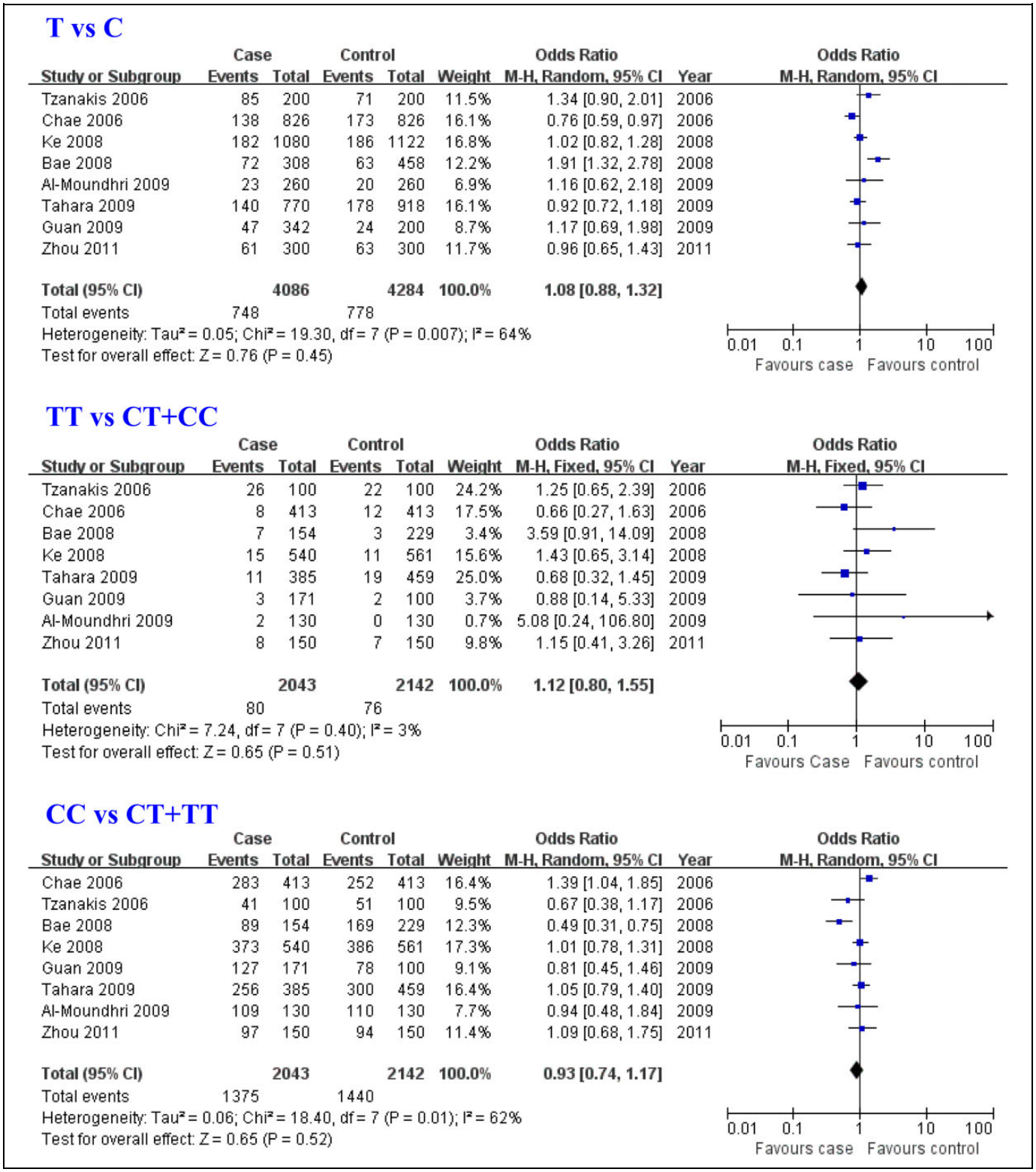


**Figure 1.** Association between *VEGF*+936C/T gene polymorphism and gastric cancer risk (overall populations). VEGF indicates vascular endothelial growth factor.

**Table 2.** Meta-Analysis of the Association of Vascular Endothelial Growth Factor (VEGF) Gene Polymorphism With Gastric Cancer Risk.

| Genetic Contrasts | Group and Subgroups | Studies Number | Q Test *P* Value | Model Selected | OR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| VEGF+936C/T | | | | | | |
| T vs C | Overall | 8 | .007 | Random | 1.08(0.88-1.32) | .45 |
| | Asian | 6 | .004 | Random | 1.04(0.82,1.32) | .73 |
| | Caucasian | 2 | .68 | Fixed | 1.27(0.93,1.76) | .14 |
| TT vs CT+CC | Overall | 8 | .40 | Fixed | 1.12(0.80,1.55) | .51 |
| | Asian | 6 | .22 | Fixed | 1.08(0.73,1.60) | .68 |
| | Caucasian | 2 | .72 | Fixed | 1.20(0.65,2.21) | .57 |
| CC vs CT+TT | Overall | 8 | .01 | Random | 0.93(0.74,1.17) | .52 |
| | Asian | 6 | .007 | Random | 0.98(0.75,1.27) | .85 |
| | Caucasian | 2 | .63 | Fixed | 0.73(0.49,1.10) | .13 |
| Sensitivity analysis according to the controls source from population based | | | | | | |
| T vs C | Overall | 7 | .005 | Random | 1.12(0.88,1.43) | .35 |
| TT vs CT+CC | Overall | 7 | .51 | Random | 1.26(0.87,1.82) | .22 |
| CC vs CT+TT | Overall | 7 | .006 | Random | 0.90(0.68,1.19) | .45 |
| Sensitivity analysis according the controls source from hospital based | | | | | | |
| T vs C | Overall | 1 | – | Fixed | 0.92(0.72,1.18) | .53 |
| TT vs CT+CC | Overall | 1 | – | Fixed | 0.68(0.32,1.45) | .32 |
| CC vs CT+TT | Overall | 1 | – | Fixed | 1.05(0.79,1.40) | .73 |
| VEGF-634 G>C | | | | | | |
| C vs G | Overall | 4 | .31 | Fixed | 1.12(0.98,1. 27) | .11 |
| | Asian | 2 | .80 | Fixed | 1.05(0.91,1.23) | .49 |
| | Caucasian | 2 | .26 | Fixed | 1.34(1.02,1.76) | .04 |
| CC vs CG+GG | Overall | 4 | .21 | Fixed | 1.02(0.81,1.30) | .84 |
| | Asian | 2 | .94 | Fixed | 0.98(0.74,1.29) | .87 |
| | Caucasian | 2 | .04 | Random | 1.32(0.46,3.83) | .60 |
| GG vs CG+CC | Overall | 4 | .56 | Fixed | 0.81(0.67,0.98) | .03 |
| | Asian | 2 | .70 | Fixed | 0.88(0.70,1.10) | .25 |
| | Caucasian | 2 | .97 | Fixed | 0.65(0.45,0.94) | .02 |
| Sensitivity analysis according to the controls source from population based | | | | | | |
| C vs G | Overall | 4 | .31 | Fixed | 1.12(0.98,1. 27) | .11 |
| CC vs CG+GG | Overall | 4 | .21 | Fixed | 1.02(0.81,1.30) | .84 |
| GG vs CG+CC | Overall | 4 | .56 | Fixed | 0.81(0.67,0.98) | .03 |
| VEGF+405 G>C | | | | | | |
| C vs G | Asian | 2 | .0005 | Random | 0.97(0.48,1.99) | .94 |
| CC vs CG+GG | Asian | 2 | .0001 | Random | 0.71(0.14,3.66) | .69 |
| GG vs CG+CC | Asian | 2 | .91 | Fixed | 0.96(0.49,1.88) | .91 |
| VEGF-460 T>C | | | | | | |
| C vs T | Asian | 2 | .80 | Fixed | 0.95(0.79,1.14) | .57 |
| CC vs CT+TT | Asian | 2 | .05 | Random | 0.54(0.20,1.41) | .21 |
| TT vs CT+CC | Asian | 2 | 1.00 | Fixed | 0.93(0.73,1.19) | .58 |
| VEGF-1498 T>C | | | | | | |
| C vs T | Overall | 2 | .95 | Fixed | 1.00(0.86,1.17) | .99 |
| CC vs CT+TT | Overall | 2 | .71 | Fixed | 0.95(0.69,1.31) | .76 |
| TT vs CT+CC | Overall | 2 | .76 | Fixed | 0.98(0.80,1.20) | .83 |
| VEGF+1612G/A | | | | | | |
| A vs G | Asian | 2 | .83 | Fixed | 1.61(1.27,2.04) | <.0001 |
| AA vs AG+GG | Asian | 2 | .98 | Fixed | 6.22(1.96,19.77) | .002 |
| GG vs AG+AA | Asian | 2 | .40 | Fixed | 0.64(0.49,0.83) | .0008 |
| VEGF-2578 C>A | | | | | | |
| A vs C | Overall | 2 | .22 | Fixed | 0.96(0.81,1.14) | .65 |
| AA vs CA+CC | Overall | 2 | .44 | Fixed | 1.09(0.73,1.62) | .68 |
| CC vs CA+AA | Overall | 2 | .12 | Fixed | 1.10(0.88,1.37) | .42 |

Abbreviations: CI, confidence interval; OR, odds ratio; GC, gastric cancer .

those from the nonsensitivity analysis, and *VEGF*+936C/T gene polymorphism was once again not associated with gastric cancer risk for the overall population (Table 2).

### Association of VEGF-634 G>C Gene Polymorphism With Gastric Cancer Risk

Four studies[13,15,16,19] were investigated for the relationship between *VEGF*-634 G>C gene polymorphism and gastric cancer risk and included in this meta-analysis. We found that the *VEGF*-634 G>C C allele and CC genotype were not associated with gastric cancer risk, but the GG genotype was associated with gastric cancer risk in the overall population (C allele: OR = 1.12, 95% CI: 0.98-1.27, $P = .11$; CC genotype: OR = 1.02, 95% CI: 0.81-1.30, $P = .84$; GG genotype: OR = 0.81, 95% CI: 0.67-0.98, $P = .03$; Figure 2 and Table 2).

In the subgroup analysis organized by ethnicity, the meta-analysis indicated that *VEGF*+936C/T gene polymorphism was not associated with gastric cancer risk in the Asian population (Table 2). Additionally, the *VEGF*+936C/T C allele and GG genotype were associated with gastric cancer risk in Caucasians; however, the CC genotype was not associated with gastric cancer risk (Table 2).

### Association of VEGF+405 G>C Gene Polymorphism With Gastric Cancer Risk

Two studies[12,18] were explored for the relationship between *VEGF*+405 G>C gene polymorphism and gastric cancer risk and included in this meta-analysis, and all of these studies focused on Asian populations. We found that *VEGF*+405 G>C gene polymorphism was not associated with gastric cancer risk in the Asian population (C allele: OR = 0.97, 95% CI: 0.48-1.99, $P = .94$; CC genotype: OR = 0.71, 95% CI: 0.14-3.66, $P = .69$; GG genotype: OR = 0.96, 95% CI: 0.49-1.88, $P = .91$; Table 2).

### Association of VEGF-460 T>C Gene Polymorphism With Gastric Cancer Risk

Two studies[12,18] were researched for the relationship between *VEGF*-460 T>C gene polymorphism and gastric cancer risk and included in this meta-analysis and all of these reports were also on Asian populations. We found that *VEGF*-460 T>C gene polymorphism was not associated with gastric cancer risk in the Asian population (Table 2).

### Association of VEGF-1498 T>C Gene Polymorphism With Gastric Cancer Risk

Two studies[15,16] were probed for the relationship between *VEGF*-1498 T>C gene polymorphism and gastric cancer risk and included in this meta-analysis. We found that *VEGF*-1498 T>C gene polymorphism was not associated with gastric cancer risk (Table 2).

### Association of VEGF+1612G/A Gene Polymorphism With Gastric Cancer Risk

Two studies[17,19] were looked at for the relationship between *VEGF*+1612G/A gene polymorphism and gastric cancer risk and included in this meta-analysis, and all of these reports fixated on Asian populations. We found that *VEGF*+1612G/A gene polymorphism was associated with gastric cancer risk in the Asian population (A allele: OR = 1.61, 95% CI: 1.27-2.04, $P < .0001$; AA genotype: OR = 6.22, 95% CI: 1.96-19.77, $P = .002$; GG genotype: OR = 0.64, 95% CI: 0.49-0.83, $P = .0008$; Table 2).

### Association of VEGF-2578 C>A Gene Polymorphism With Gastric Cancer Risk

Two studies[13,15] were examined for the relationship between *VEGF*-2578 C>A gene polymorphism and gastric cancer risk and included in this meta-analysis. We found that *VEGF*-2578 C>A gene polymorphism was not associated with gastric cancer risk (Table 2).

### Association of VEGF+936C/T Gene Polymorphism With Gastric Cancer Development, Prognosis, and Survival

We identified an association of *VEGF*+936C/T gene polymorphism with gastric cancer development, prognosis, and survival. Five studies[12,13,17-19] were included for the overall stage of gastric cancer, 2 studies[13,18] for tumor size of gastric cancer, 4 studies[12,13,17,18] for lymph node metastasis of gastric cancer, 5 studies[13,14,17-19] for Lauren classification of gastric cancer, and 2 studies[13,18] for survival of gastric cancer. We found that *VEGF*+936C/T gene polymorphism was not associated with the overall stage, lymph node metastasis, Lauren classification, or survival of gastric cancer (Table 3). However, the *VEGF*+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer; however, the CC genotype was not (T allele: OR = 0.47, 95% CI: 0.29-0.77, $P = .002$; TT genotype: OR = 0.13, 95% CI: 0.04-0.38, $P = .0002$; CC genotype: OR = 1.37, 95% CI: 0.73-2.58, $P = .33$; Table 3).

## Discussion

For this meta-analysis, we tried to find a beneficial indicator for early diagnosis of gastric cancer and to predict the development, prognosis, and survival of the cancer. It was found that *VEGF*+936C/T, *VEGF*+405 G>C, *VEGF*-460 T>C, *VEGF*-1498 T>C, and *VEGF*-2578 C>A gene polymorphisms were not associated with gastric cancer risk for the overall populations in this meta-analysis. Interestingly, the *VEGF*-634 G>C GG genotype was associated with gastric cancer risk in the overall population. The *VEGF*-634 G>C C allele and GG genotype were also associated with gastric cancer risk in Caucasians, whereas *VEGF*+1612G/A gene polymorphism was associated with gastric cancer risk for the Asian population.

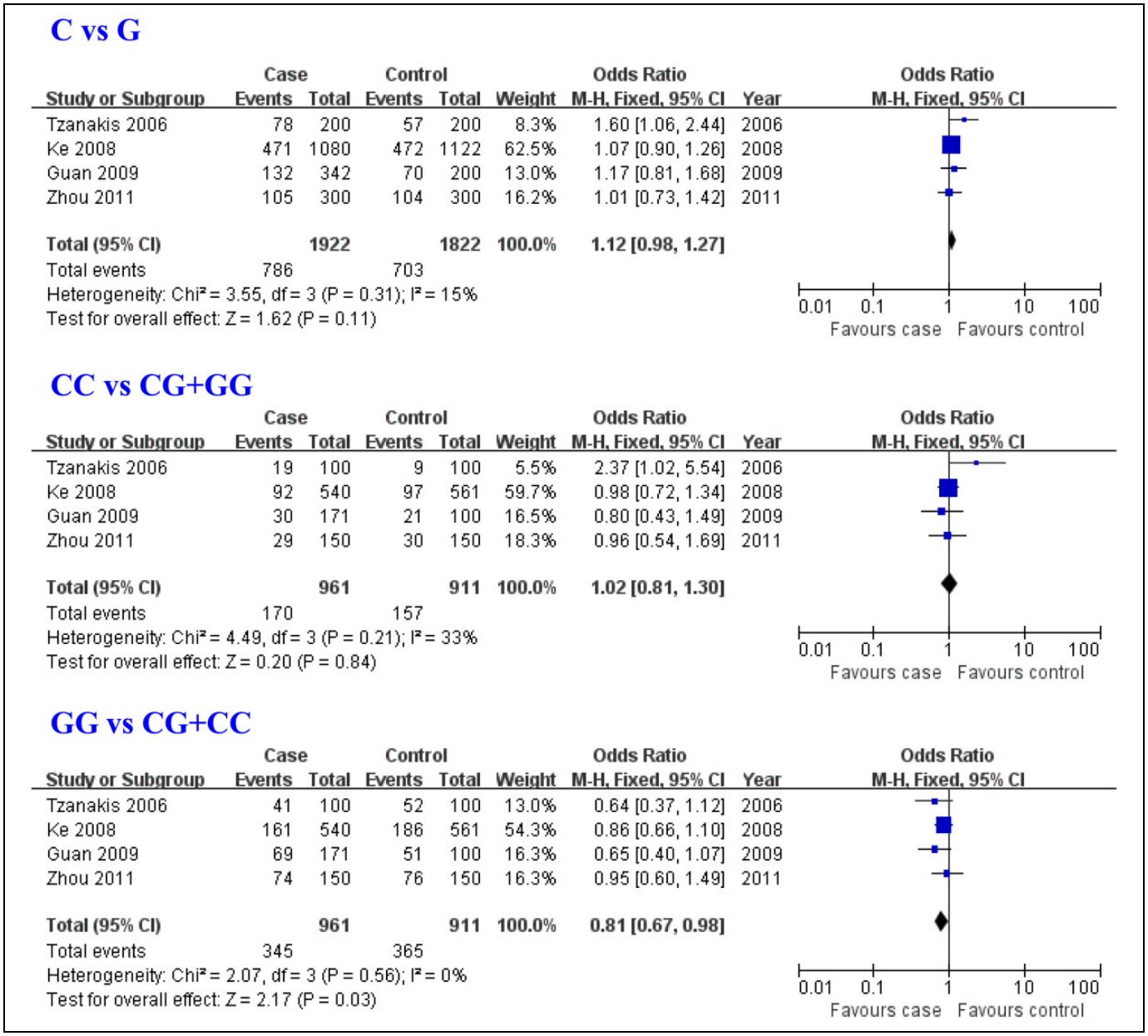


**Figure 2.** Association between *VEGF*-634 G>C gene polymorphism and gastric cancer risk (overall populations). VEGF indicates vascular endothelial growth factor.

Furthermore, *VEGF*+936C/T gene polymorphism was not associated with the overall stage, lymph node metastasis, Lauren classification, or survival of gastric cancer. However, *VEGF*+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer.

Sensitivity analysis according to the source of the controls (population based vs hospital based) was performed, and the results for *VEGF*+936C/T and *VEGF*-634 G>C from the sensitivity analysis using the studies including the population based as the control group were consistent with the nonsensitivity analysis. Furthermore, the results for *VEGF*+936C/T from the sensitivity analysis including the studies using the hospital based as the control group were consistent with the nonsensitivity analysis. We speculate that the relationship between *VEGF*+936C/T, *VEGF*-634G>C gene polymorphism, and gastric cancer risk is robust. However, additional studies should be performed to explore this speculation.

Gastric cancer cells can produce a variety of proangiogenic growth factors, and VEGF is a powerful potential tumor angiogenic growth factor. Vascular endothelial growth factor plays a major role in the multistep process of angiogenesis stimulation and is closely related to the development of gastric cancer.[20,21] Some gene polymorphisms of *VEGF* might be associated with the activity of VEGF and take part in the risk of gastric cancer.

In previous research, Zhou *et al*[22] included 7 studies in their meta-analysis, and their meta-analysis suggested that no

**Table 3.** Meta-Analysis of the Association of Vascular Endothelial Growth Factor (VEGF)+936C/T Gene Polymorphism With Gastric Cancer Development, Prognosis, and Survival.

| Variables | Genetic Contrasts | Studies Number | Q Test *P* Value | Model Selected | OR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Overall stage (Advanced stage vs Early stage) | | | | | | |
| | T vs C | 5 | .62 | Fixed | 0.92(0.73-1.16) | .48 |
| | TT vs CT+CC | 5 | .70 | Fixed | 0.68(0.37-1.28) | .23 |
| | CC vs CT+TT | 5 | .33 | Fixed | 1.05(0.79-1.38) | .75 |
| Tumor size (>5 cm vs ≤5 cm) | | | | | | |
| | T vs C | 2 | .12 | Fixed | 0.47(0.29-0.77) | .002 |
| | TT vs CT+CC | 2 | .91 | Fixed | 0.13(0.04-0.38) | .0002 |
| | CC vs CT+TT | 2 | .35 | Fixed | 1.37(0.73-2.58) | .33 |
| Lymph node metastasis (positive vs negative) | | | | | | |
| | T vs C | 4 | .61 | Fixed | 0.92(0.71-1.21) | .57 |
| | TT vs CT+CC | 4 | .88 | Fixed | 0.71(0.34-1.48) | .37 |
| | CC vs CT+TT | 4 | .68 | Fixed | 1.05(0.76-1.44) | .78 |
| Lauren classification (diffuse type vs intestinal type) | | | | | | |
| | T vs C | 5 | .004 | Random | 1.37(0.83-2. 27) | .22 |
| | TT vs CT+CC | 5 | .11 | Fixed | 1.80(1.00-3.22) | .05 |
| | CC vs CT+TT | 5 | .02 | Random | 0.74(0.43-1.27) | .27 |
| Survival (death vs alive) | | | | | | |
| | T vs C | 2 | .82 | Fixed | 0.98(0.59-1.63) | .94 |
| | TT vs CT+CC | 2 | .18 | Fixed | 0.85(0.36-1.99) | .70 |
| | CC vs CT+TT | 2 | .67 | Fixed | 0.93(0.47-1.84) | .84 |

Abbreviations: CI, confidence interval; OR, odds ratio.

association between *VEGF*+936 C/T gene polymorphism and gastric cancer risk was found. Zhou *et al*[23] also performed a meta-analysis to assess whether *VEGF*+936C/T gene polymorphism conferred susceptibility to gastric cancer and reported that *VEGF*+936 C/T gene polymorphism was not associated with gastric cancer risk. Likewise, Liu *et al*[24] performed a meta-analysis to estimate the association of *VEGF*+936C/T gene polymorphism and gastric cancer risk and reported that no association were observed between gastric cancer risk and the variant genotypes of *VEGF*+936C/T in different genetic models. Results from our meta-analysis were similar to those above-mentioned meta-analyses.

In this meta-analysis, we firstly explored the relationship between *VEGF*+405 G>C, *VEGF*-460 T>C, *VEGF*-1498 T>C, *VEGF*+1612G/A, *VEGF*-2578 C>A, and gastric cancer risk. We found that *VEGF*+405 G>C, *VEGF*-460 T>C, *VEGF*-1498 T>C, and *VEGF*-2578 C>A gene polymorphisms were not associated with gastric cancer risk for the overall population in this meta-analysis. Interestingly, *VEGF*+1612G/A gene polymorphism was associated with gastric cancer risk for Asian population.

In this meta-analysis, we also explored the association between *VEGF*+936C/T gene polymorphism with gastric cancer development, prognosis, and survival and reported that the relationship between *VEGF*+936C/T gene polymorphism was not associated with the overall stage, lymph node metastasis, Lauren classification, or survival of gastric cancer. However, the *VEGF*+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer.

*VEGF*+936C/T gene polymorphism was not associated with the onset of gastric cancer. However, *VEGF*+936C/T T allele and TT genotype were associated with the tumor size of gastric cancer. It seemed that the *VEGF*+936C/T T allele and TT genotype play a role in gastric cancer development.

There were some limitations in this studies. Multitest correction data were not showed from the included studies, and we could not perform the multitest correction test.

## Conclusions

The *VEGF*-634 G>C GG genotype was found to be associated with gastric cancer risk in the overall population. Furthermore, *VEGF*-634 G>C C allele and GG genotype were associated with gastric cancer risk in Caucasians, and *VEGF*+1612G/A gene polymorphism was associated with gastric cancer susceptibility for Asian population. However, additional associated investigations are required to further clarify these associations.

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