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ORIGINAL ARTICLE

Vascular endothelial growth factor gene polymorphisms and gastric cancer risk: a meta-analysis

Meng Zhuang[1], Zhi Peng[2], Jian Wang[1], Xiangqian Su[1]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital and Institute, Beijing 100142, China; [2]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, 100142, China

Summary

Purpose: *Vascular endothelial growth factor (VEGF) plays important roles in the process of tumor growth and metastasis. Although the association between VEGF polymorphisms and gastric cancer risk has been extensively studied, available results remain controversial. To derive a convincing estimation of the relationship, a meta-analysis containing 6 VEGF (+936C/T, -634G/C, -460T/C, +1612G/A, -2578C/A and -1154G/A) gene polymorphisms was performed.*

Methods: *We conducted a systematic search of PubMed and Chinese National Knowledge Infrastructure (CNKI) to select relevant articles. Nine available case-control studies with 2,281 gastric cancer cases and 2,820 healthy controls met the inclusion criteria. The odds ratio (OR) and 95% confidence interval (95%CI) were used to evaluate the strength of the association.*

Results: *This meta-analysis indicated that the VEGF-634 G allele carrier represented a risk factor for gastric cancer (GG+GC vs CC: OR=1.23, 95%CI=1.02-1.49, p=0.03). The VEGF +1612G/A polymorphism was associated with risk of gastric cancer (G allele vs A allele: OR=0.62, 95%CI=0.49-0.79, p<0.0001; GG+GA vs AA: OR=0.16, 95%CI=0.05-0.51, p=0.002 and GA+AA vs GG : OR=1.57, 95%CI=1.21-2.04, p=0.008). For polymorphisms of VEGF +936C/T, -460C/T, -2578C/A , -1154G/A, no association was found with gastric cancer risk.*

Conclusion: *Our meta-analysis suggests that VEGF-634 G allele carrier may increase gastric cancer risk, whereas the VEGF +1612 G/A G allele and G allele carrier may decrease the risk. No association between+936C/T, -460C/T, -2578C/A, -1154G/A polymorphisms and susceptibility to gastric cancer was found.*

Key words: *gastric cancer, gene polymorphisms, meta-analysis, risk, vascular endothelial growth factor*

Introduction

Although the incidence and mortality of gastric cancer has gradually decreased over the past several decades, gastric cancer, the second most common cause of cancer mortality [1,2], remains a major health problem worldwide due to its poor prognosis. Gastric cancer is a result of a multifactorial process including many biological changes [3].

Published articles revealed that VEGF gene plays an important role in angiogenesis which is essential for the development, growth and progression of malignant tumors [4-7]. Although more than 30 single nucleotide polymorphisms (SNPs) have been described in VEGF gene [8], the association between VEGF polymorphisms and the risk of gastric cancer remains controversial. Some of these polymorphisms (+936C/T rs3025039,-634G/C rs2010963, - 460T/C rs833061, and -2578C/A rs699947) have been found to be associated with the susceptibility, development,

Correspondence to: Xiangqian Su, MD. Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital & Institute,0 52 Fucheng Road, Haidian District, Beijing 100142, China.
Tel: + 86 10 88196579, Fax: +86 10 88122437, E-mail: suxiangqian@bjmu.edu.cn
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prognosis and metastasis of gastric cancer [9,10]. Bae et al. found that +936 T was a susceptibility factor for gastric cancer, at least in Korean population [11], while other case-control studies in Korea showed +936T allele was associated with a decreased susceptibility to gastric cancer [12]. Moreover, Tzanakis et al. revealed a marginally significant association of the -634CC genotype with increased risk for gastric cancer development [13]. Furthermore, Zhou et al. suggested that the VEGF +1612G/A gene polymorphism was associated with gastric cancer in Chinese Han patients [14]. Tahara et al. showed that the +1612G/A gene polymorphism was associated with susceptibility to gastric cancer in Japanese population [15]. However, many studies indicated that VEGF polymorphisms have no associations with susceptibility for gastric cancer. Al-Moundhri et al. [16], Ke et al. [17] and Lin et al. [18] suggested that + 936C/T gene polymorphisms play no significant roles in gastric cancer risk. Some other studies indicated that the -634G/C gene polymorphism was not associated with risk of gastric cancer and its progression [14,17].

In this study, we aimed to carry out a meta-analysis in order to investigate the association between VEGF gene polymorphisms and gastric cancer risk.

Methods

Literature search

We performed a systematic search of PubMed and Chinese National Knowledge Infrastructure (CNKI) by using the following key words: "vascular endothelial growth factor" or "VEGF", "polymorphism", "single nucleotide polymorphism" and "gastric" or "stomach cancer". Only published studies with full-text articles were included without language restriction; all non-English articles were translated if necessary. Of all the studies with overlapping data published by the same investigators, only the most detailed article was included. When necessary, we contacted the authors of related articles to require additional information.

Inclusion criteria

The criteria of all included studies were as follows: (1) case-control studies that contained gastric cancer cases and healthy controls; (2) VEGF gene polymorphisms and its related gastric cancer risk; (3) sufficient genotype frequency data were provided with the original literature. According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, we made a flowchart showing the selection procedure (Figure 1).

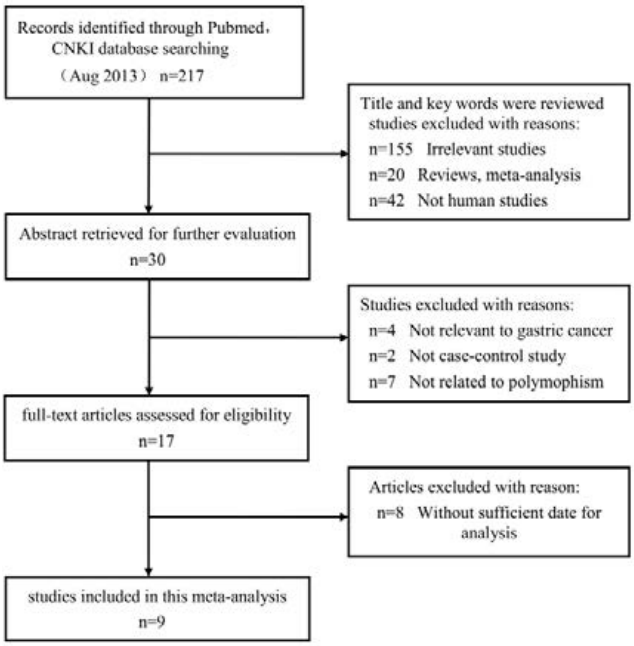

Figure 1. Flowchart of the selection procedure of the studies and reasons for exclusion.

Data extraction

Necessary data was extracted from eligible publications including surname of first author, year of publication, numbers of genotyped cases and controls, genotypes frequencies, country, ethnicity, polymorphisms, and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

Statistics

The consistency of genotype frequencies in controls, compared with HWE, was tested by x^2 test. OR with 95% CI were calculated to appraise the strength of the association between VEGF polymorphism and gastric cancer risk. Q-statistic with I^2 was used to assess the degree of heterogeneity between the trials. When heterogeneity existed ($p<0.10$ or $I^2>50\%$), we used the random-effects model to calculate OR; otherwise, the fixed-effect method was applied [19]. All statistical analyses were performed with the RevMan statistical software (version.5.0.25, provided by The Cochrane Collaboration). The Egger's test was used to assess the potential publication bias by using Stata software (version 9.0). All p values were two-sided and $p<0.05$ was considered as statistically significant publication bias [20].

Results

Study characteristics

Nine eligible case-control studies were selected to evaluate the association of VEGF polymorphisms with the risk of gastric cancer, which included 2,281 gastric cancer cases and 2,820 controls [11,12,14-

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

References	*Country*	*VEGF gene polymorphisms*	*No. of cases*	*No. of controls*
Al-Moundhri et al, 2009	Oman	+405G/C, -460T/C, +936C/T	130	130
Bae et al, 2008	Korea	+ 936C /T	154	229
Chae et al, 2006	Korea	+405G/C-460T/C, +936C/T	413	413
Guan et al, 2009	USA	-634G/C +936C/T -1498T/C	171	353
Ke et al, 2008	China	-2578C/A,-1498T/C,-634G/C,+936C/T	540	561
Nikiteas et al, 2007	Greece	-2578C/A,-1154G/A,–634G/C,+936C/T	100	100
Tahara et al, 2009	Japan	+936C/T,+1612G/A	385	459
Xia et al, 2010	China	+936C/T	238	425
Zhou et al, 2011	China	-634 G/C,+936 C/T,+1612 G/A	150	150

Table 2. The genotype distribution and frequency of included studies

Reference	*Cases*				*Controls*				*HWE test of controls*	
+936C/T polymorphism	**Total**	**CC**	**CT**	**TT**	**Total**	**CC**	**CT**	**TT**	**x^2**	**p value**
Al-Moundhri et al.2009	130	109	19	2	130	110	20	0	0.903	0.342
Bae et al. 2008	154	89	58	7	229	169	57	3	0.551	0.458
Chae et al. 2006	413	283	122	8	413	252	149	12	3.304	0.069
Guan et al. 2009	171	127	41	3	353	276	70	7	1.034	0.309
Ke et al. 2008	540	373	152	15	561	386	164	11	1.818	0.177
Nikiteas et al. 2007	100	41	33	26	100	51	27	22	16.84	<0.001
Tahara et al. 2009	385	256	118	11	459	300	140	19	0.271	0.603
Xia et al. 2010	228	155	63	10	413	276	131	6	4.807	0.028
Zhou et al. 2011	150	97	45	8	150	94	49	7	0.036	0.85
-634G/C polymorphism	**Total**	**GG**	**GC**	**CC**	**Total**	**GG**	**GC**	**CC**	**x^2**	**p value**
Al-Moundhri et al.2009	130	49	59	22	130	62	54	14	0.189	0.664
Chae et al. 2006	413	129	253	31	413	106	223	84	2.844	0.092
Guan et al. 2009	171	69	72	30	353	180	99	74	51.92	<0.001
Ke et al. 2008	540	161	287	92	561	186	278	97	0.156	0.693
Nikiteas et al. 2007	100	41	40	19	100	52	39	9	0.185	0.667
Zhou et al. 2011	150	74	47	29	150	76	44	30	18.63	<0.001
-460C/T polymorphism	**Total**	**CC**	**CT**	**TT**	**Total**	**CC**	**CT**	**TT**	**x^2**	**p value**
Al-Moundhri et al. 2009	130	22	66	42	130	25	61	44	0.219	0.64
Chae et al. 2006	413	9	186	218	413	27	161	225	0.063	0.802
Ke et al. 2008	540	38	207	295	561	39	215	307	0.026	0.871
+1612G/Apolymorphism	**Total**	**GG**	**GA**	**AA**	**Total**	**GG**	**GA**	**AA**	**x^2**	**p value**
Tahara et al. 2009	385	262	121	2	459	359	100	0	6.86	0.009
Zhou et al. 2011	150	104	29	17	150	112	35	3	0.019	0.891
-2578C/A polymorphism	**Total**	**CC**	**CA**	**AA**	**Total**	**CC**	**CA**	**AA**	**x^2**	**p value**
Ke et al. 2008	540	293	216	31	561	301	234	26	5.397	0.02
Nikiteas et al. 2007	100	32	39	29	100	21	48	31	0.092	0.762
-1154G/A polymorphism	**Total**	**GG**	**GA**	**AA**	**Total**	**GG**	**GA**	**AA**	**x^2**	**p value**
Nikiteas et al. 2007	100	45	36	19	100	42	43	15	0.524	0.469

17,21-23]. Study characteristics are summarized in Table 1. The publication year of the 9 studies ranged from 2006 to 2011. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay was adopted in most articles. The distribution of genotypes in the controls were consistent with HWE (p>0.05) in all except 4 of the studies [14,15,21,22]. The characteristics of genotype distribution are summarized in Table 2.

VEGF +936C/T polymorphism was not associated with gastric cancer risk

The meta-analysis about the associations between VEGF +936C/T polymorphism and gastric cancer risk is presented in Figure 2. The results revealed that there was no significant association between +936C>T polymorphism and susceptibility to gastric cancer in the comparisons of C allele vs T allele (OR=0.93, 95%CI=0.77-1.13, p=0.48), CC+CT vs TT (OR=0.80, 95%CI=0.59-1.10, p=0.18), or CT+TT vs CC (OR=0.99, 95%CI=0.88-1.13, p=0.92).

VEGF -634 G allele carrier increased the risk of gastric cancer

The meta-analysis involved 4 studies that revealed a significant association between the -634G/C polymorphism and susceptibility to gastric cancer (Figure 3) in comparison with G allele carrier GG+GC vs CC (OR=1.23, 95%CI=1.02-1.49, p= 0.03).

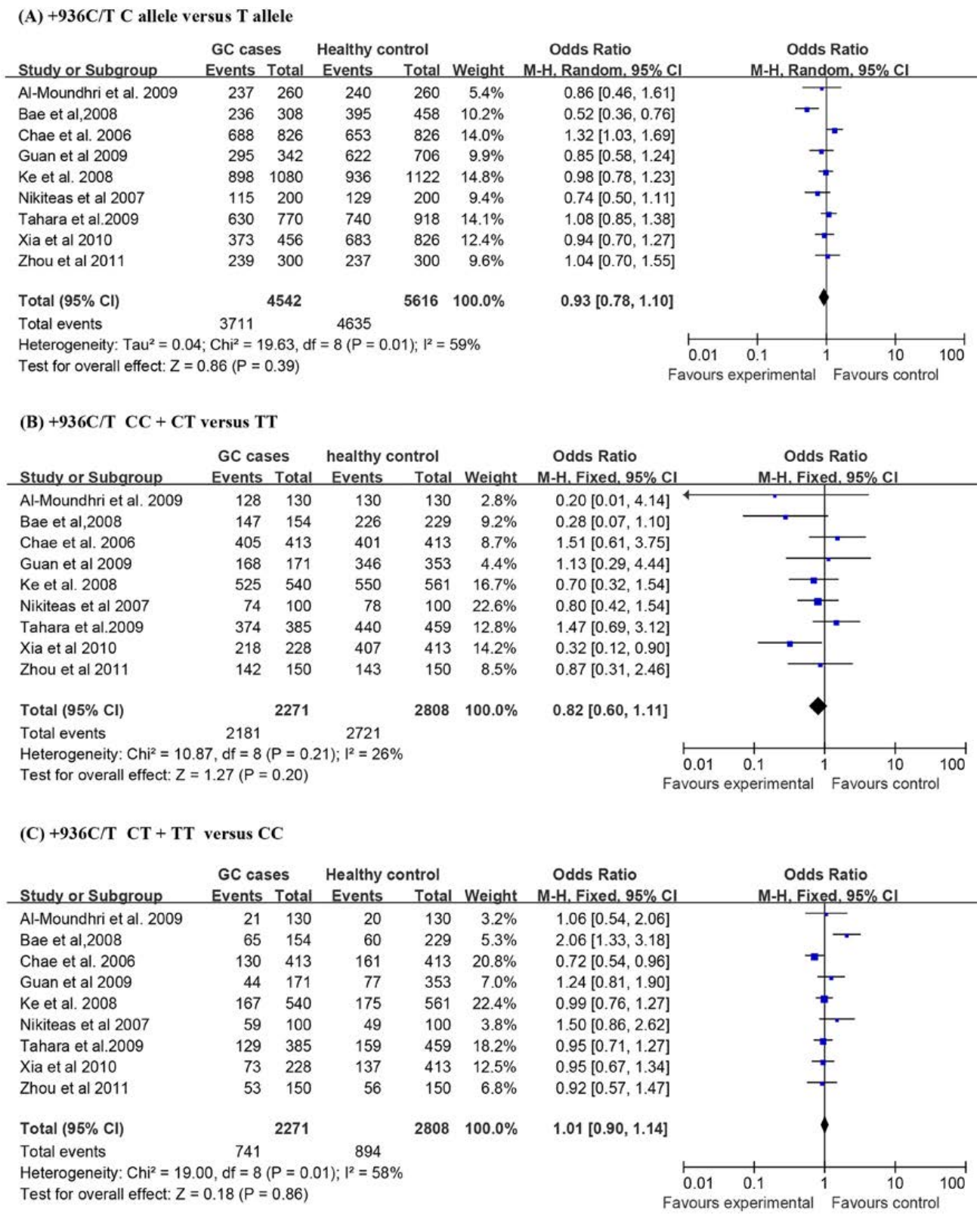

Figure 2. Forest plot showing the association between +936C>T polymorphism and gastric cancer risk. **(A)** +936C/T C allele versus T allele; **(B)** +936C/T CC + CT versus TT; **(C)** +936C/T CT + TT versus CC

However, VEGF -634 G allele and C allele carrier had no influence on gastric cancer risk for G allele vs C allele (OR=0.83, 95%CI=0.60-1.15, p=0.26) and GC+CC vs GG (OR=1.14, 95%CI=0.98-1.32, p=0.09).

No association was found between -460C/T polymorphism and susceptibility to gastric cancer

The evaluation of the association between VEGF -460C/T polymorphism and gastric cancer

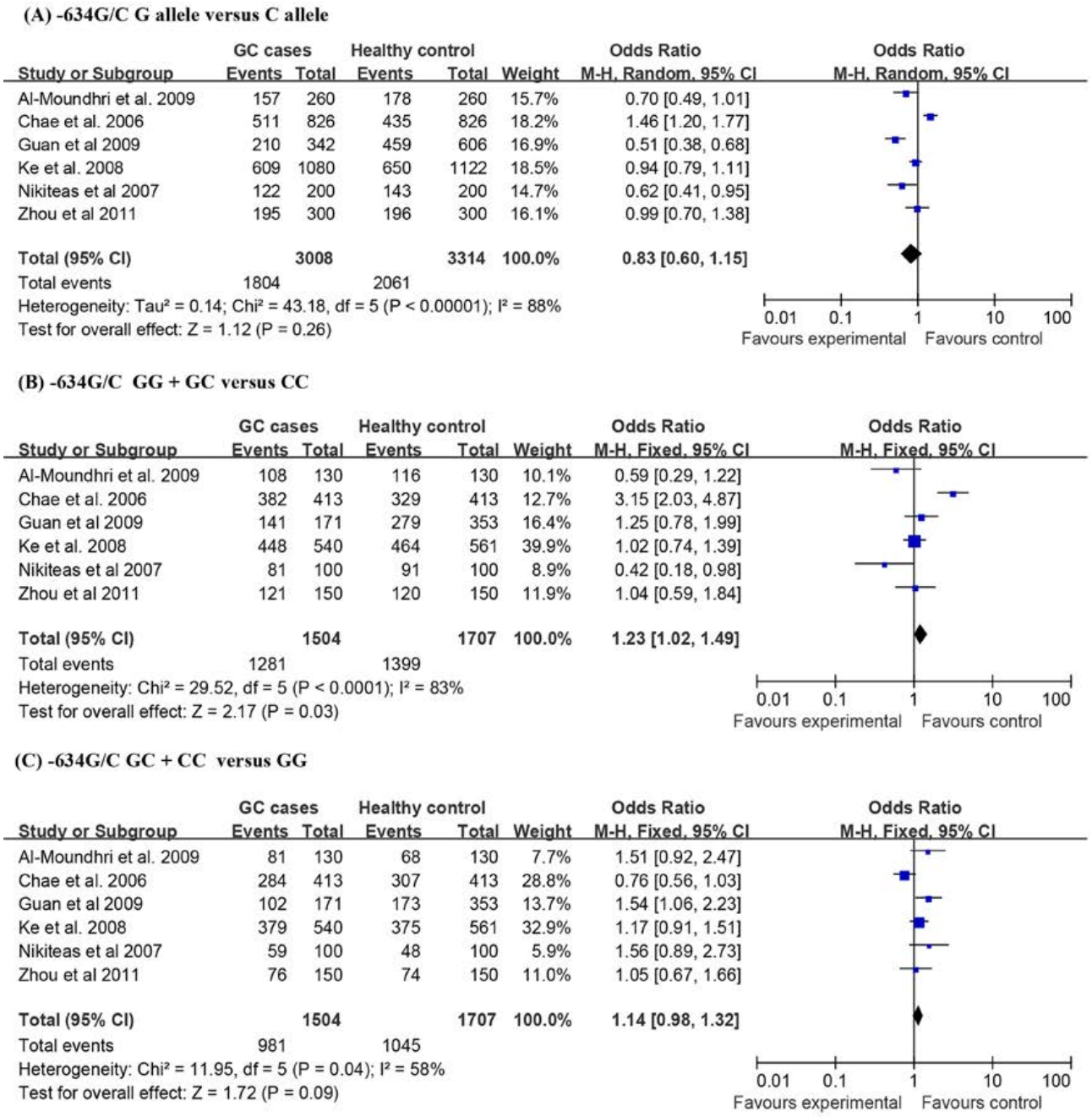

Figure 3. Forest plot showing the association between -634G/C polymorphism and gastric cancer risk. **(A)** -634G/C G allele versus C allele; **(B)** -634G/C GG + GC versus CC; **(C)** -634G/C GC + CC versus GG

risk is presented in Figure 4. We found that VEGF -460C/T polymorphism had no impact on the susceptibility to gastric cancer, when referring to the comparisons of C allele vs T allele (OR=0.98, 95%CI = 0.86-1.12, p=0.73), CC+CT vs TT (OR=1.04, 95%CI=0.87-1.23, p=0.68), and CT+TT vs CC (OR=1.33, 95%CI=0.96-1.85, p= 0.09) .

VEGF +1612 G allele and G allele carrier decreased the risk of gastric cancer

According to the analysis of 2 included studies (Figure 5), significant association was found between +1612 G/A polymorphism and susceptibility to gastric cancer in the comparisons of G allele vs A allele (OR=0.62, 95%CI=0.49-0.79, p<0.0001), GG+GA vs AA (OR=0.16, 95%CI=0.05-0.51, p=0.002), and GA+AA vs GG (OR=1.57, 95%CI=1.21-2.04, p=0.008). The results suggested that the G allele and G allele carrier (GG+GA) of +1612 G/A might be protective factors for gastric cancer.

Susceptibility to gastric cancer was not due to VEGF -2578C/A polymorphism

There was no significant association between -2578C/A polymorphism and susceptibility to gas-

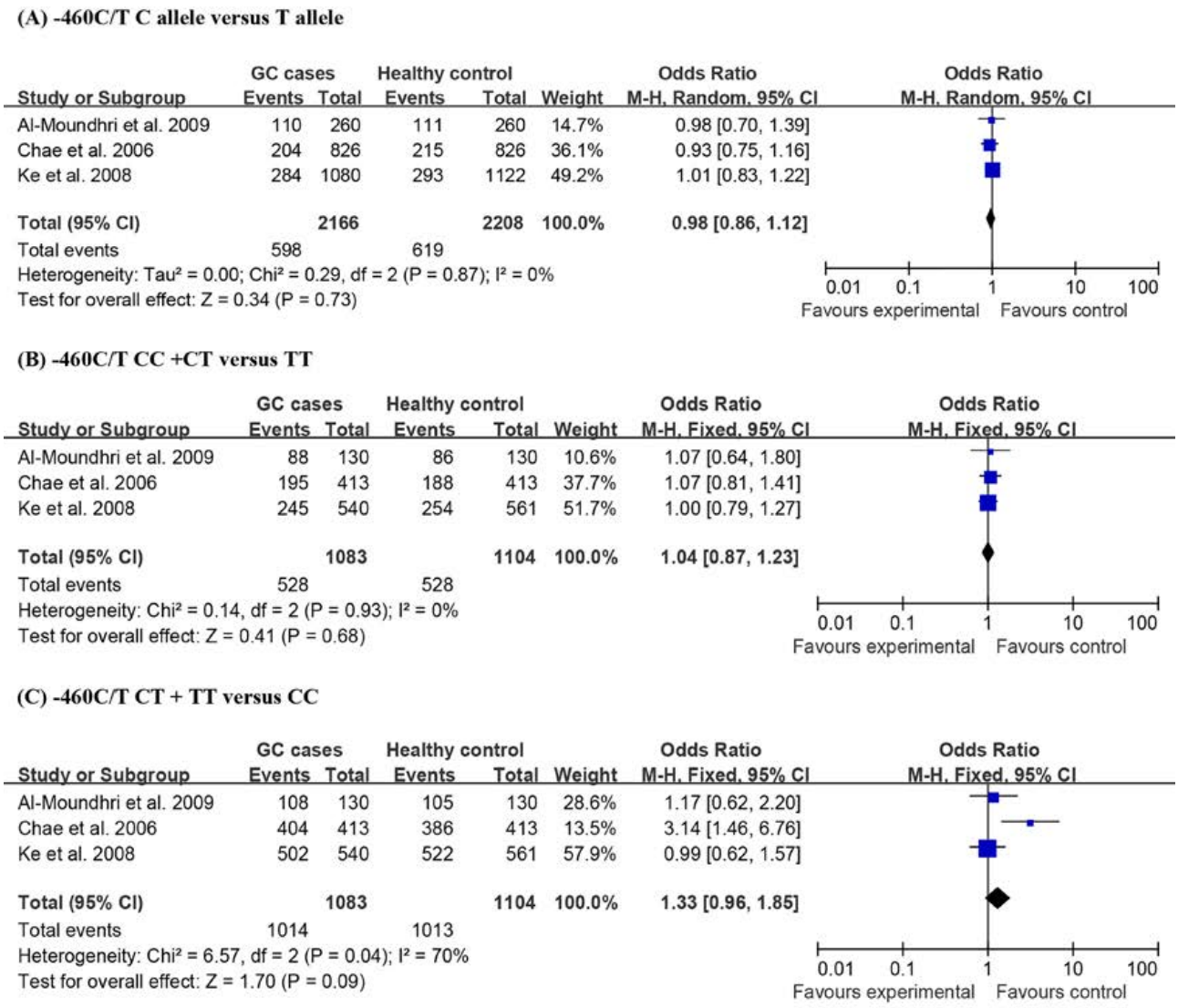

Figure 4. Forest plot showing the association between -460C/T polymorphism and gastric cancer risk. **(A)** -460C/T C allele versus T allele; **(B)** -460C/T CC +CT versus TT; **(C)** -460C/T CT + TT versus CC.

tric cancer (Figure 6) , when it comes to C allele vs A allele (OR = 1.07, 95%CI = 0.84-1.37, p=0.59), CC +CA vs AA (OR=0.92, 95%CI=0.62-1.37,p=0.68), and CA+AA vs CC (OR=0.91, 95%CI=0.73-1.14, p=0.42).

VEGF -1154G/A polymorphism could not influence the susceptibility to gastric cancer

The meta-analysis included only one relevant study about the associations between VEGF -1154G/A polymorphism and gastric cancer risk, as presented in Figure 7. VEGF -1154G/A polymorphism was not correlated with susceptibility to gastric cancer in the comparisons of G allele vs A allele (OR=0.98, 95%CI=0.65-1.47, p=0.92), GG+-GA vs AA (OR=1.42, 95%CI=0.72-2.79, p=0.31), and GA+AA vs GG (OR=0.89, 95%CI =0.51-1.55, p=0.67).

Table S1. Supporting information. Evaluation of publication bias by Egger's linear regression test

Polymorphisms	*t*	*p value*
+936C/T		
C allele vs T allele	1.55	0.164
CC + CT vs TT	1.64	0.145
CT + TT vs CC	1.51	0.175
-634G/C		
G allele vs C allele	-1.24	0.282
GG + GC vs CC	-0.4	0.707
GC + CC vs GG	1.19	0.299

Publication bias

Egger's test to assess the publication bias for +936C/T and -634G/C polymorphisms did not show statistically evidence of publication bias, all p values were >0.05 (Table S1).

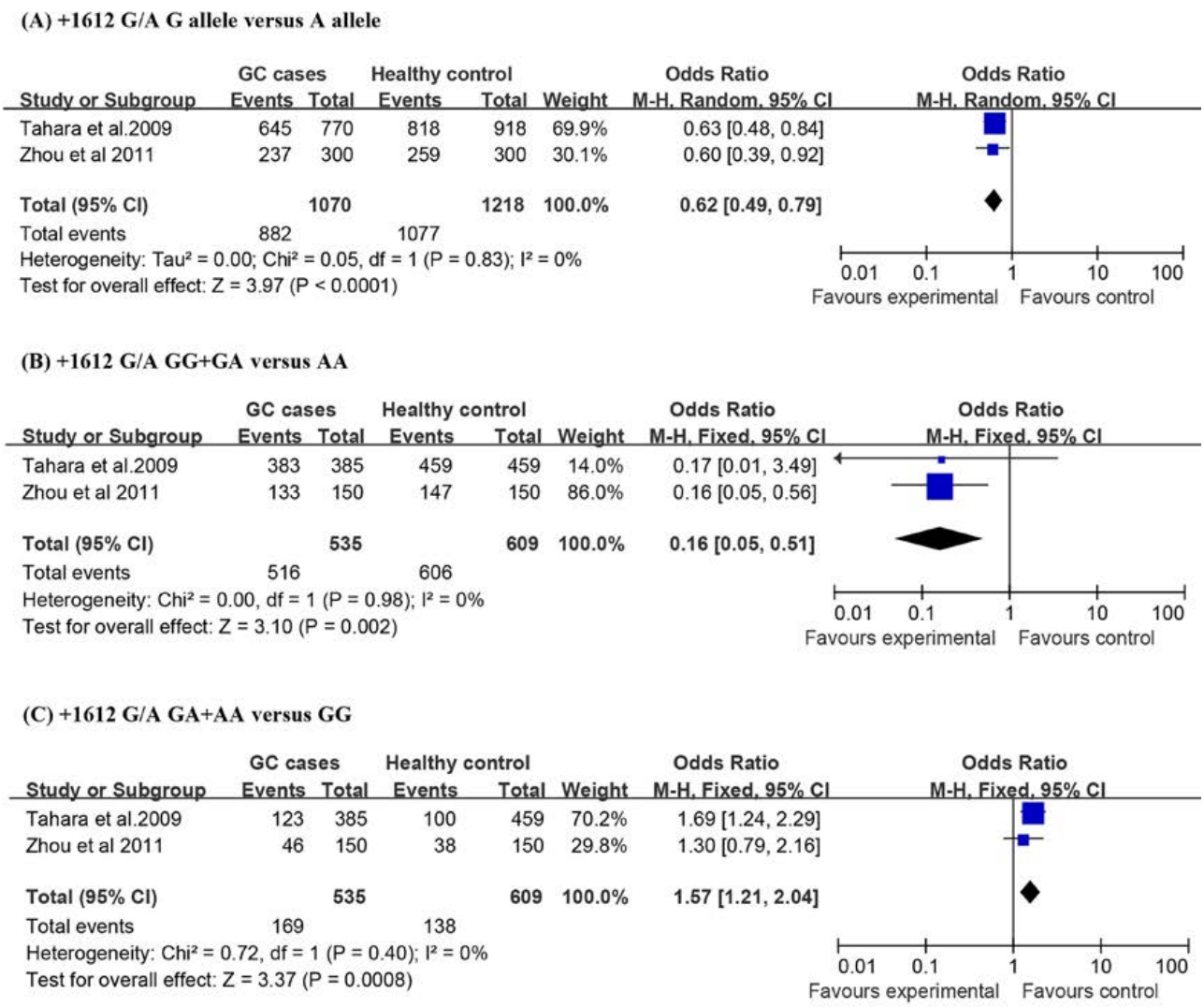

Figure 5. Forest plot showing the association between +1612G/A polymorphism and gastric cancer risk. **(A)** +1612 G/A G allele versus A allele; **(B)** +1612 G/A GG + GA versus AA; **(C)** +1612 G/A GA + AA versus GG.

Discussion

VEGF is associated with tumor angiogenesis, and it is essential to tumor growth, invasion and metastasis [4-7]. Genetic polymorphisms are identified to associate with the translation and expression of VEGF, and have a contribution on cancer susceptibility [24]. Among several functional VEGF polymorphisms , only a small portion may have effects on the risk of malignant tumor, such as VEGF +936C/T, -634G/C, -460G/C, +1612 G/A ,-2578C/A and -1154 G/A [25-28]. A case–control study indicated that VEGF +936 C/T is likely an important genetic marker of susceptibility to breast cancer [29]. Lin et al. provided strong evidence that VEGF -2578C/A polymorphism is capable of increasing lung cancer susceptibility [18]. A meta-analysis suggested that the VEGF -460T/C, -634G/C, and -2578C/A gene polymorphisms were associated with colorectal cancer risk [30]. In gastric cancer, several case–control studies have assessed whether any relationships existed between the VEGF polymorphisms and the risk of disease. Also, some previous meta-analyses examined the association between the VEGF +936C/T or 634G/C polymorphisms and gastric cancer risk. For instance, a meta-analysis conducted by Zhou et al. showed that there was no significant association between VEGF +936C/T gene polymorphism and gastric cancer risk [31]. Similarly, another meta-analysis involving 31 case-controls studies also suggested that the VEGF +936C/T or -634G/C polymorphisms were not correlated with cancer risk in all examined patients [32]. In contrast, Liu et al. recently conducted a meta-analysis to estimate potential associations between the VEGF+936C/T , -634G/C polymorphisms and susceptibility to gastric cancer [33]. Their results showed that the VEGF -634G/C polymorphism did contribute to gastric cancer susceptibility.

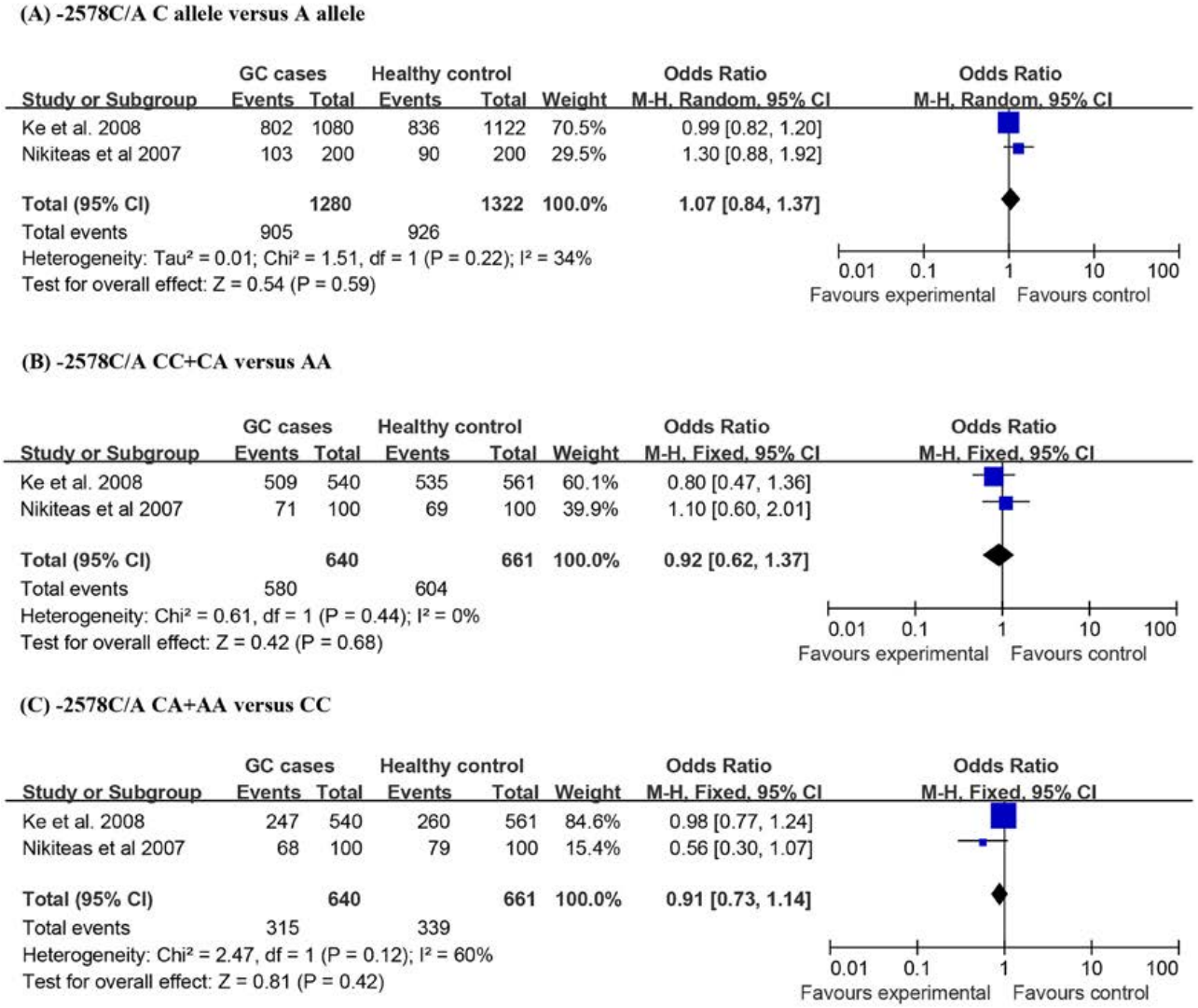

Figure 6. Forest plot showing the association between -2578C/A polymorphism and gastric cancer risk. **(A)** -2578C/A C allele versus A allele; **(B)** -2578C/A CC + CA versus AA; **(C)** -2578C/A CA + AA versus CC.

Due to the contradictory results concluded from published meta-analyses, in this study we performed a meta-analysis to summarize all of the available data, to assess comprehensively the relationship between VEGF polymorphisms and the risk of gastric cancer. Apart from the extensively studied SNPs (+936C/T, -634G/C) , we gathered all available data to assess the association between gastric cancer and some seldom investigated SNPs (+1612 G/A -2578C/A, -460G/C and -1154 G/A). In concordance with previous meta-analyses [31-33], our results showed that +936C/T polymorphism had no significant effect on gastric cancer risk and we found -634G/C polymorphism was associated with gastric cancer susceptibility, as reported by Cao et al. [32].

This meta-analysis, with 2,281 cases and 2,280 controls derived from 9 case–control studies, was performed to examine the association between gastric cancer risk and the polymorphisms of VEGF +936C/T, -634G/C, -460T/C, +1612G/A, -2578C/A and -1154G/A. Our results showed that VEGF -634G/C and +1612G/A polymorphisms were associated with gastric cancer susceptibility. It was also found that the -634G allele carrier (GG+GC) wss linked with increased risk of gastric cancer. For the VEGF +1612G/A polymorphism, our data showed that the +1612G allele and the G allele carrier (GG +GA) were associated with a significant decrease in gastric cancer risk. However, due to the limited number of studies available for the meta-analysis, the association should be confirmed by further studies based on larger populations. In the present study, there was no significant difference in the SNPs allele or genotype distribution of VEGF +936C/T, -460 C/T,-2578C/A and -1154 G/A between gastric cancer patients and controls.

Some limitations in our study should not be ignored. Firstly, the susceptibility to gastric

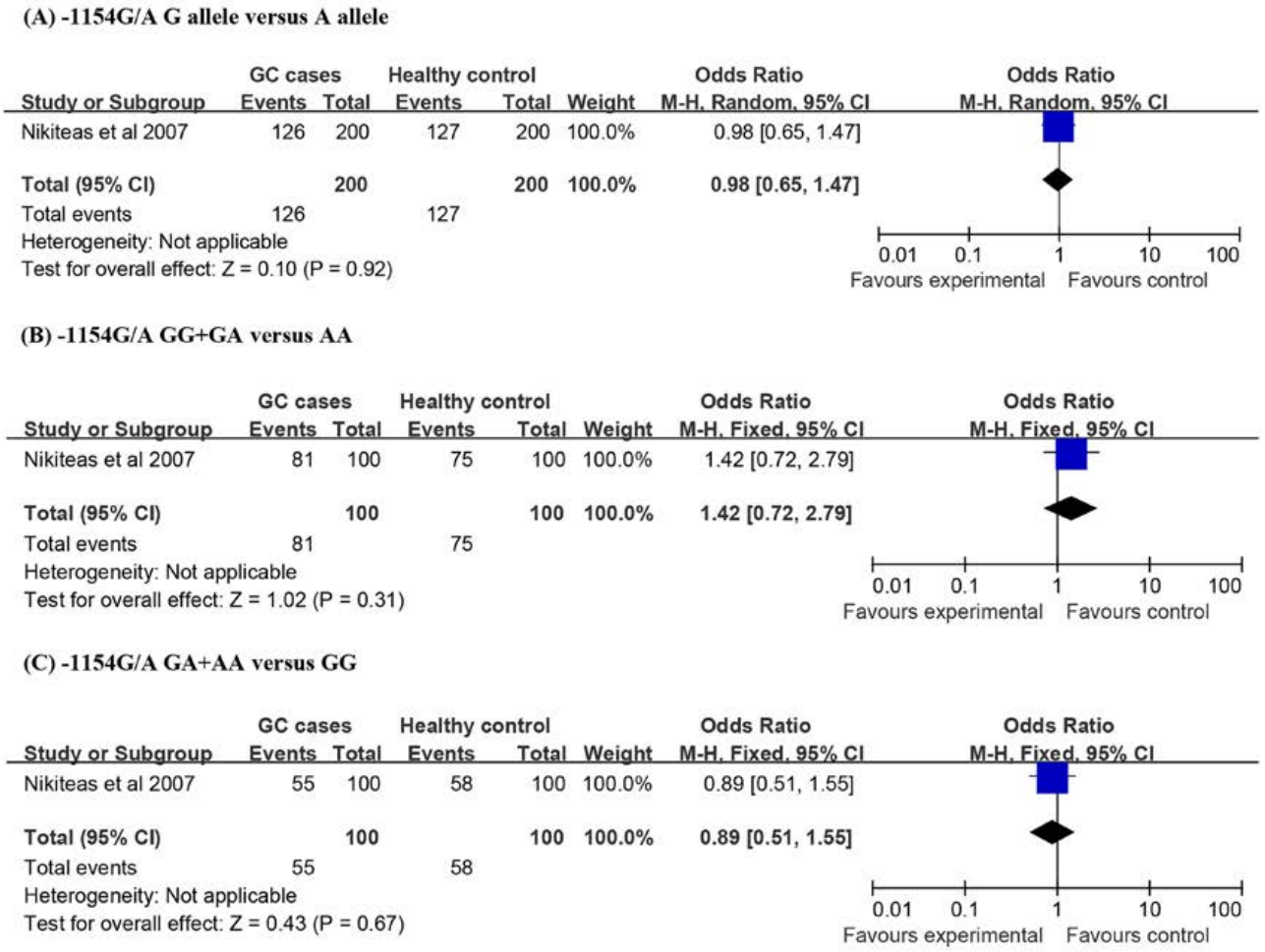

Figure 7. Forest plot showing the association between -1154G/A polymorphism and gastric cancer risk. **(A)** -1154G/A G allele versus A allele; **(B)** -1154G/A GG + GA versus AA; **(C)** -1154G/A GA + AA versus GG.

cancer may be modulated by some other genetic markers and other related factors such as age, gender, major histological types and Helicobacter pylori infection**.** Subgroup analyses have not been conducted due to lack of relevant data. Therefore, these possible risk factors should be taken into account in the future studies. Secondly, our results should be interpreted with caution, because most of the included studies were conducted in Asians, and more races need to be further studied. Thirdly, although no noticeable publication bias was found in our meta-analysis , publication bias was inevitable for negative findings which were rarely published.

Despite these limitations, this meta-analysis provides evidence that the VEGF-634 G allele carrier is associated with increased GC risk and the VEGF +1612 G allele and G allele carrier decrease the risk. Further prospective researches with larger sample size and more details are expected to confirm these findings and make more comprehensive conclusions.

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Conflict of interests

The authors declare no confict of interests.

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