RESEARCH COMMUNICATION

VEGFA +936C/T and -634G/C Polymorphisms and Gastric Cancer Risk: a Meta-analysis

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Abstract

Aim: To estimate the association of vascular endothelial growth factor A (*VEGFA*) +936C/T and -634G/C polymorphisms and gastric cancer (GC) risk, a meta-analysis was performed. A total of nine studies were identified with 2,281 GC cases and 2,820 controls. This meta-analysis indicated significant associations between the *VEGFA* -634G/C polymorphism and GC risk were found for GC versus GG (OR 1.21, 95% CI 1.03-1.42) and GG+CC versus GC (OR 0.78, 95% CI 0.68-0.90) overall, for GC versus GG (OR 1.68, 95% CI 1.19-2.35) and GC+CC versus GG (OR 1.54, 95% CI 1.13-2.10) among Europeans, and for GG+CC versus GC (OR 0.82, 95% CI 0.70-0.96) among Asians. No association were observed between GC risk and the variant genotypes of VEGFA +936C/T in different genetic models. In summary, the results suggest that the *VEGFA* -634G/C polymorphism may contribute to GC susceptibility.

Keywords: Vascular endothelial growth factor - polymorphism - gastric cancer - meta-analysis

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Introduction

Gastric cancer (GC) is now the fourth most common and the second most deadly cancer worldwide (Crew and Neugut , 2006). The occurrence and development of GC is a complex process including many genetic and epigenetic changes. Among the known genetic alterations, angiogenesis is an essential process in the development, growth and metastasis of malignant tumors, including GC (Wu et al., 2009). Vascular endothelial growth factor A (VEGFA, originally known simply as VEGF) plays a central role in angiogenesis (Ferrara and Davis-Smyth , 1997). Extensive experimental and clinical data in GC support that increased VEGF expression is associated with the growth and metastasis of GC (Lazar et al., 2006; Wagner and Moehler, 2009).

The *VEGFA* gene is located on chromosome 6p21.3 and contains eight exons and seven introns. Several single-nucleotide polymorphisms (SNPs) have been described in *VEGFA* gene (Dassoulas et al., 2009). Among these, two VEGF SNPs, +936C/T (rs3025039) in the 3'-untranslated region and -634G/C (rs2010963) in the 5'-untranslated region, were known to modulate the protein expression of VEGF (Renner et al., 2000; Stevens et al., 2003).

Over the past decade, considerable epidemiological studies have focused on association between *VEGFA* +936C/T and -634G/C polymorphisms and GC susceptibility. However, the results remain controversial or inconclusive. To address these issues, we carried out a meta-analysis on all eligible case-control studies to estimate the GC risk of these two polymorphisms.

Materials and Methods

Search strategy

Search was applied to the following electronic databases: PubMed, EMBASE, Wanfang (Chinses), VIP (Chinses), and Chinese National Knowledge Infrastructure (CNKI) (up to July 1st, 2011). The following key words were used: (VEGFA OR VEGF OR "vascular endothelial growth factor") AND (haplotype OR polymorphism) AND ("gastric" OR "stomach") AND ("adenocarcinoma" OR "carcinoma" OR "cancer" OR "neoplasm" OR "tumor" OR "tumour"). The searching was done without restriction on language and conducted on human subjects. Additional studies were identified by a manual search of the references of original studies. Of the studies with overlapping data published by the same investigators, only the most recent or complete study was included in this meta-analysis.

Inclusion criteria

The inclusion criteria were as follows: (i) evaluated *VEGFA* +936C/T and/or -634G/C polymorphism and GC risk, (ii) case-control studies, and (iii) sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (CI).

Data extraction

Information was carefully extracted independently by two investigators according to the inclusion criteria noted above. For each study, the following characteristics were collected: the first author's surname, year of publication,

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country of origin, ethnicity, source of control groups, and the number of cases and controls for each *VEGFA* +936C/T or -634G/C genotype. Different ethnic descents were categorized as European, Asian, and African. If a study did not state the ethnic descendent or if it was not possible to separate participants according to such phenotype, the group reported was termed "mixed". According to sources of control, the studies were sorted as hospital-based study (HCC) (controls from hospitalized patients) or population-based study (PCC) (controls from healthy population).

Statistical analysis

To test for control population selective bias, a chi-square test was applied to determine if the genotype distribution of the control subjects of each individual population reported conformed to Hardy-Weinberg equilibrium (HWE; $P<0.05$ was considered significant). Sensitivity analysis was used to examine the effect of excluding specific studies such as studies with the controls not in HWE. Associations between *VEGFA* +936C/T or -634G/C polymorphism and GC risk were calculated by ORs and 95% CIs. The statistical significance of the summary OR was determined with the Z test, in which $P<0.05$ was considered significant. Between-study heterogeneity was estimated using the χ2-based Q statistic (Zintzaras and Ioannidis, 2005). Heterogeneity was considered statistically significant when $P<0.1$ or $I2>50\%$ (Higgins and Thompson, 2002). If heterogeneity existed, data was analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. The Begg's rank correlation method and the Egger's weighted regression method were used to assess the potential publication bias. All statistical analyses were performed with Stata software (version 11.0; Stata Corporation, College Station, TX), using two sided P values.

Results

Eligible studies and meta-analysis databases

With the retrieval strategy, 65 potentially relevant papers (20 in PubMed, 35 in Embase, 8 in Wanfang, 2 in VIP, and 0 in CNKI). As summarized in Table 1, nine studies (2,281 GC patients and 2,820 control subjects) were identified that examined the association between *VEGFA* +936C/T or -634G/C polymorphism and GC risk (Al-Moundhri et al., 2009; Bae et al., 2008; Chae et al., 2006; Guan et al., 2009; Ke et al., 2008; Tahara et al., 2009; Tzanakis et al., 2006; Xia et al., 2010; Zhou et al., 2011). Fifty-six studies were subjected to a full text review and excluded according to the selection criteria stated above. The lists of genotypes and allelic frequencies of the polymorphisms in the eligible studies are provided in Table 2. For +936C/T polymorphism, a total of nine eligible studies (2,281 GC patients and 2,820 control subjects) included (Chae et al., 2006; Tzanakis et al., 2006; Bae et al., 2008; Guan et al., 2009; Ke et al., 2008; Al-Moundhri et al., 2009; Tahara et al., 2009; Zhou et al., 2011). There were seven studies of Asians (Chae et al., 2006; Bae et al., 2008; Ke et al., 2008; Al-Moundhri et al., 2009; Tahara et al., 2009; Zhou et al., 2011), two studies of Europeans (Guan et al., 2009; Tzanakis et al., 2006), and no study of Africans. For -634G/C polymorphism, six eligible studies (1,504 GC patients and 1,707 control subjects) included (Chae et al., 2006; Tzanakis et al., 2006; Ke et al., 2008; Al-Moundhri et al., 2009; Guan et al., 2009; Zhou et al., 2011). There were four studies of Asians (Chae et al., 2006; Ke et al., 2008; Al-Moundhri et al., 2009; Zhou et al., 2011) and two studies of Europeans (Tzanakis et al., 2006; Guan et al., 2009). Two studies (Tzanakis et al., 2006; Xia et al., 2010) investigating +936C/T polymorphism and two studies investigating -634G/C polymorphism significantly deviated from HWE ($P<0.05$).

Association between VEGFA +936C/T and -634G/C polymorphisms and gastric cancer

In the overall analysis, no association could be observed between GC risk and the variant genotypes of *VEGFA* +936C/T in different genetic models when all the eligible studies were pooled into the meta-analysis. As shown in Table 3, no significant associations were found for T allele versus C allele, TT versus CC, CT versus CC, CT versus TT, CT+TT versus CC, TT versus CC+CT,

Table 1. Characteristics of Eligible Studies Included in the Meta-analysis

Author	Year	Country	Ethnicity	Controls (matched for)	Cases/Controls	Polymorphisms of VEGF
Chae	2006	Korea	Asian	Healthy	413/413	-460T/C (rs833061),-634G/C (rs2010963), +936C/T (rs3025039)
Tzanakis	2006	Greece	European	Healthy (age, sex, ethnicity)	100/100	-634G/C (rs2010963), -1154G/A (rs1570360), –2578C/A (rs699947), +936C/T (rs3025039)
Bae	2008	Korea	Asian	Thrombotic disease-/ cancer-free	154/229	+936C/T (rs3025039)
Ke	2008	China	Asian	cancer-free (age, sex, ethnicity, and residence)	540/561	-634G/C (rs2010963),-1498T/C (rs833061), –2578C/A (rs699947),+936C/T (rs3025039)
Al-Moundhri	2009	Oman	Asian	healthy (ethnicity and residence)	130/130	-460T/C (rs833061),-634G/C (+405G/C, rs2010963),+936C/T (rs3025039)
Guan	2009	USA	European	Cancer-free	171/353	-634G/C (rs2010963),-1498T/C (rs833061), +936C/T (rs3025039)
Tahara	2009	Japan	Asian	Cancer-free	385/459	+936C/T (rs3025039),+1612G/G
Xia	2010	China	Asian	Unclear (age, gender, ethnicity, and residence)	238/425	+936C/T (rs3025039), +9162C/T (rs3025021)
Zhou	2011	China	Asian	Healthy (ethnicity and residence)	150/150	-634G/C (rs2010963), +936C/T (rs3025039), +1612G>G

Table 2. Distribution of Genotypes and Allelic Frequencies in this Meta-analysis

First Author	Ethnicity	Cases					Controls					HWE
VEGFA+936C/T		CC	CT	TT	C alleles	T alleles	CC	CT	TT	C alleles	T alleles	
Chae	Asian	283	122	8	688	138	252	149	12	653	173	0.0691
Tzanakis	European	41	33	26	115	85	51	27	22	129	71	0.0000
Bae	Asian	89	58	7	236	72	169	57	3	395	63	0.4578
Ke	Asian	373	152	15	898	182	386	164	11	936	186	0.1775
Al-Moundhri	Asian	109	19	2	237	23	110	20	0	240	20	0.3420
Guan	European	127	41	3	295	47	276	70	7	622	84	0.3092
Tahara	Asian	256	118	11	630	140	300	140	19	740	178	0.6027
Xia	Asian	155	63	10	373	83	276	131	6	683	143	0.0283
Zhou	Asian	97	45	8	239	61	94	49	7	237	63	0.8497
VEGFA-634G/C CC		GG	GC	CC	G allele	C allele	GG	GC	CC	G allele	C allele	
Chae	Asian	129	253	31	511	315	106	223	84	435	391	0.0917
Tzanakis	European	41	40	19	122	78	52	39	9	143	57	0.6667
Ke	Asian	161	287	92	609	471	186	278	97	650	472	0.6920
Al-Moundhri	Asian	49	59	22	157	103	62	54	14	178	82	0.6641
Guan	European	69	72	30	210	132	180	99	74	459	247	0.0000
Zhou	Asian	74	47	29	195	105	76	44	30	196	104	0.0000

Table 3. Odds Ratios and 95% Confidence Intervals of *VEGFA* Polymorphisms and Gastric Cancer Risk

Group	No[a]	Case/Control	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]
VEGFA +936C/T			T vs. C allele		TT vs. CC		CT vs. CC		CT vs. TT		CT+TT vs. CC		TT vs. CC+CT		CC+TT vs. CT	
All	9	2281/2820	1.08(0.90-1.27)	0.39[c]	1.25(0.91-1.71)	0.16	1.03(0.85-1.24)	0.76[c]	0.84(0.61-1.17)	0.31	1.06(0.87-1.29)	0.54[c]	1.22(0.89-1.66)	0.20	0.99(0.83-1.18)	0.91[c]
All HWE	7	1943/2295	1.06(0.85-1.30)	0.60[c]	1.06(0.72-1.54)	0.75	1.03(0.82-1.29)	0.78[c]	0.99(0.86-1.13)	0.89	1.05(0.83-1.33)	0.68[c]	1.06(0.73-1.55)	0.73	0.98(0.79-1.20)	0.82[c]
Europeans	2	271/453	1.26(0.95-1.65)	0.10	1.34(0.72-2.47)	0.35	1.34(0.93-1.93)	0.10	1.10(0.56-2.15)	0.77	1.33(0.95-1.86)	0.09	1.16(0.65-2.09)	0.60	0.77(0.54-1.10)	0.15
Asians	7	2010/2367	1.04(0.85-1.27)	0.69[c]	1.22(0.85-1.75)	0.27	0.98(0.79-1.20)	0.81[c]	0.77(0.53,1.13)	0.19	1.01(0.80-1.25)	0.93[c]	1.24(0.86-1.78)	0.24	1.04(0.85-1.26)	0.70[c]
VEGFA -634G/C			C vs. G allele		CC vs. GG		GC vs. GG		GC vs. CC		GC+CC vs. GG		CC vs. GG+GC		GG+CC vs. GC	
All	6	1504/1707	1.08(0.85-1.38)	0.49[c]	1.05(0.59-1.84)	0.86[c]	1.21(1.03-1.42)	0.01	1.22(0.75-2.00)	0.41[c]	1.18(0.92-1.50)	0.17[c]	0.93(0.56-1.55)	0.79[c]	0.78(0.68-0.90)	0.00
All HWE	4	1183/1204	1.10(0.77-1.57)	0.59[c]	1.09(0.44-2.71)	0.84[c]	1.12(0.94-1.35)	0.19	1.10(0.52-2.32)	0.80[c]	1.14(0.82-1.58)	0.41[c]	1.00(0.44-2.26)	0.99[c]	0.82(0.70-0.97)	0.02
Europeans	2	271/453	1.28(1.02-1.60)	0.03	1.56(0.63-3.83)	0.33[c]	1.68(1.19-2.35)	0.00	0.98(0.27-3.53)	0.98[c]	1.54(1.13-2.10)	0.00	1.29(0.45-3.73)	0.62[c]	0.68(0.39-1.21)	0.19[c]
Asians	4	1233/1254	0.99(0.73-1.33)	0.96[c]	0.87(0.41-1.84)	0.72[c]	1.10(0.92-1.32)	0.25	1.31(0.70-2.45)	0.39[c]	1.05(0.80-1.39)	0.68[c]	0.81(0.42-1.59)	0.55[c]	0.82(0.70-0.97)	0.01

[a]Number of studies; [b]P value of Z test; [c]Random-effects model was used when P value for heterogeneity test P<0.1 or I2>50%; otherwise, fixed-effects model was used

and CC+TT versus CT. Similarly, in subgroup analysis, no significant results were observed in any of the genetic models. Sensitivity analysis did not alter the pattern of results.

The evaluation of association between *VEGFA* -634G/C polymorphism and GC risk is also presented in Table 3. Overall, *VEGFA* -634 GC genotype was associated with a significantly increased GC risk in GC versus GG model (codominant model, fixed-effects OR 1.21, 95% CI 1.03-1.42) and in GG+CC versus GC model (complete overdominant model, fixed-effects OR 0.78, 95% CI 0.68-0.90). In the stratified analysis by ethnicity, results showed that *VEGFA* -634 GG genotype was associated with a significantly decreased GC risk in GC versus GG model (fixed-effects OR 1.68, 95% CI 1.19-2.35) and GC+CC versus GG model (fixed-effects OR 1.54, 95% CI 1.13-2.10) among Europeans. The significantly elevated GC risk was associated with -634 GC genotype among Asians . Sensitivity analysis was performed after excluding studies conducted by Guan et al. (2009) and Zhou et al. (2011), because of the controls not in HWE. As shown in Table 3, the significant difference was observed between before and after results of GC versus GG (after: OR 1.12, 95% CI 0.94-1.35), and heterogeneity was significantly decreased (*P* heterogeneity=0.49, I2=0.00%).

Publication bias

The Begg's rank correlation method and Egger's weighted regression method were used to assess publication bias. As shown in Figure 1, there was no evidence of publication bias in *VEGFA* +936C/T polymorphism (CT+TT versus CC: Begg's test *P* =

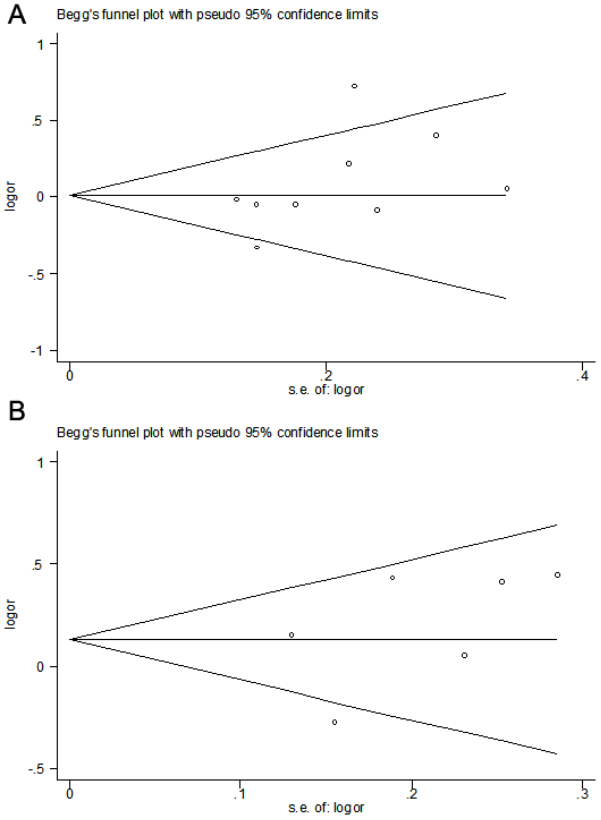

Figure 1. Begg's Funnel Plots of *VEGFA* +936C/T and -634G/C Polymorphisms and Gastric Cancer Risk. (A) For *VEGFA* +936C/T polymorphism (CT+TT versus CC, P=0.251). (B) For *VEGFA* -634G/C polymorphism (GC+CC versus GG, P = 0.707)

0.25, Egger's test P = 0.15) and -634G/C polymorphism (GC+CC versus GG: Begg's test P = 0.70, Egger's test P = 0.35).

Discussion

VEGF is the most important regulator of angiogenesis and overexpressed in various cancers tissues, including GC (Ferrara N, 2002; Wu et al., 2009). Polymorphisms that can alter VEGF expression and protein production may contribute to the risk of cancers. VEGF plasma levels are highly predictive for tumor growth and survival rate of patients (Carmeliet and Jain, 2000). *VEGFA* +936C/T polymorphism has previously been associated with lower VEGF plasma levels, showing strongly reduced levels in carriers of +936 T allele (Renner et al., 2000). There are conflicting reports in the literature on the exact function of *VEGFA* -634G/C polymorphism. The variant C allele of the -634G/C polymorphism has been associated with lower VEGF production, and the presence of C allele may disrupt the myeloid zinc finger 1 transcription factor-binding site (Watson et al., 2000). However, some studies reported that higher VEGF level or no association with the -634G/C genotype (Awata et al., 2002; Awata et al., 2005; Balasubramanian et al., 2007).

Several published studies were conducted in recent years to evaluate the association between VEGFA SNPs in terms of cancer risk predisposition and the prognostic value of VEGFA gene polymorphisms in different ethnic populations, but the results have been conflicting (Al-Moundhri et al., 2009; Bae et al., 2008; Chae et al., 2006; Guan et al., 2009; Ke et al., 2008; Tahara et al., 2009; Tzanakis et al., 2006; Xia et al., 2010; Zhou et al., 2011). Chae et al. (Chae et al., 2006) showed that VEGFA -634 C allele and CC genotype was associated with a significantly decreased susceptibility to GC. Guan et al. (Guan et al., 2009) suggested that -634 CG genotype and the combined -634 CG+CC genotypes were associated with a significantly elevated risk of GC. Moreover, several studies reported VEGFA +936 T allele was associated with a decreased susceptibility to GC (Bae et al., 2008; Chae et al., 2006).

In the present study, a meta-analysis was performed to examine the association between the *VEGFA* polymorphisms and GC risk by critically reviewing nine studies on *VEGFA* +936C/T polymorphism (a total of 2,281 GC patients and 2,820 controls) and six studies on -634G/C polymorphism (1,504 GC patients and 1,707 controls).

For *VEGFA* -634G/C polymorphism, our meta-analysis on the available studies showed that the -634 GC genotype was associated with a significant increase in GC risk. In the stratified analysis by ethnicity, it was found that -634 GG genotype was a protective factor on GC in Europeans, and -634 GC genotype was a risk factor on GC in Asians. It indicates the difference of genetic background among Asians and Europeans.

In this meta-analysis, it was found that *VEGFA* +936C/T polymorphism was not a risk factor to GC on the basis of all studies. When stratifying for the ethnicity, there were no significantly differences in genotype distribution between GC case and control among Asians and Europeans.

It should be noted that there were some limitations in this study. Firstly, because of the limitations of raw data and publication, some relevant studies were excluded in this meta-analysis. Secondly, the sample sizes in some subgroup analyses were extremely small. Thirdly, the sources of heterogeneity that existed among studies for most polymorphisms were not addressed. Finally, this meta-analysis was based on unadjusted data, while a more precise analysis could be performed if individual data were available.

In conclusion, in spite of several limitations above-mentioned, this meta-analysis suggested that *VEGFA* -634 GC genotype was associated with an increased risk of GC in overall and Asians, while -634 GG genotype was a protective factor on GC in Europeans. This meta-analysis also concluded that *VEGFA* +936C/T polymorphism showed no association with GC risk. More detailed and well-designed studies with larger population and different ethnicities are needed to further evaluate the associations.

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