Vascular endothelial growth factor +936C/T polymorphism and gastric cancer risk: A meta-analysis

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Abstract. The aim of this study was to determine whether the vascular endothelial growth factor (VEGF) +936C/T polymorphism confers susceptibility to gastric cancer (GC) by conducting a meta-analysis. Publications addressing the association between the VEGF +936C/T polymorphism and GC risk were selected from the Pubmed, Embase and CBM databases. Data were extracted from the studies by two independent reviewers. The meta-analysis was performed using RevMan 5.0.25 and STATA 9.2 software. From these data, the odds ratio (OR) with 95% confidence interval (CI) was calculated. Finally, 8 case-control studies were retrieved reporting a total of 2,131 gastrointestinal cancer patients and 2,670 controls. Meta-analysis results showed that there was no significant association between the VEGF +936C/T polymorphism and GC risk in all comparisons of the T allele vs. C allele (OR=1.08, 95% CI 0.90-1.30, P=0.42), CT+TT vs. CC (OR=1.08, 95% CI 0.87-1.34, P=0.49), TT vs. CC+CT (OR=1.14, 95% CI 0.85-1.53, P=0.37), TT vs. CC (OR=1.18, 95% CI 0.87-1.59, P=0.28) and TT vs. CT (OR=1.11, 95% CI 0.79-1.56, P=0.56). This meta-analysis confirms that there is a lack of association between the VEGF +936C/T polymorphism and GC risk.

Introduction

Despite a major decline in the incidence and mortality of gastric cancer (GC) over the past several decades, GC remains the fourth most common cancer and the second leading cause of cancer-related death in the world (1). The incidence of GC is particularly high in East Asia, Eastern Europe and parts of Central and South America (2). Male-to-female incidence ratios generally are in the 1.5-2.5 range, with higher ratios for intestinal than diffuse cancers and higher-risk populations (3). GC is a major health problem worldwide due to its high incidence, poor prognosis and limited treatment options (4).

GC is a multifactorial disease with environmental and lifestyle factors as major contributors (5). Epidemiological investigations have identified many risk factors for GC, including age, male gender, *Helicobacter pylori* (*H. pylori*) bacteria infection, smoking, obesity, radiation, diet and hereditary factors (4-6). The most important etiological factors implicated in gastric carcinogenesis are *H. pylori* infection, and dietary and hereditary factors (7-9). Individual variations in cancer risk have been associated with specific variant alleles of different genes (polymorphisms) that are present in a significant proportion of the normal population (10). Polymorphisms in a wide variety of genes may modify the effect of environmental exposures, and these gene-environmental interactions could explain the high variation in the GC incidence observed worldwide (11,12). However, the interaction between environmental factors and genetic susceptibility has not yet been adequately addressed.

Tumor angiogenesis is a vital process for the progression of a neoplasm from a small localized tumor to an enlarged tumor with the ability to metastasize (13). Vascular endothelial growth factor (VEGF) as a vascular permeability factor is the major mediator of physiologic and pathologic angiogenesis (14). Evidence from *in vitro* and *in vivo* experiments has shown that increased VEGF expression is associated with tumor growth and metastasis, whereas the inhibition of VEGF signaling results in suppression of both tumor angiogenesis and tumor growth (15). The VEGF gene is assigned to chromosome 6p12-p21 and consists of eight exons separated by seven introns that exhibit alternative splicing to form a family of proteins (16). In mammals, the VEGF family consists of seven secreted glycoproteins that are designated VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, placental growth factor (PIGF) and VEGF-F (17). VEGF and its receptors play an important role in the development of the vascular system, via angiogenesis mechanisms, as well as in the formation of the lymphatic vascular system (18). In the stomach, GC frequently displays high levels of VEGF expression which has been correlated with vascular involvement, and lymph node and liver metastasis (19,20). Moreover, high levels of VEGF expression have also been observed in gastric premalignant lesions, such as chronic atrophic gastritis and intestinal metaplasia, suggesting that alterations in VEGF expression may also contribute to the process of gastric carcinogenesis via angiogenesis (21).

Several polymorphisms in the VEGF gene involved in the development of GC have been described in the literature (22). Among these, VEGF +936C/T (rs3025039) in the 3'-untrans-

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                │  Pubmed, Embase and CBM      │
                │  databases research          │
                │  (December 2010)             │
                │        n=45                  │
                └──────────────┬──────────────┘
                               │
            Excluded n=33      │────────────┐
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                               │   ┌──────────────────────────────────────┐
                               │   │ 5 Letters or reviews                 │
                               │   │ 7 Not related to VEGF polymorphisms  │
                               │   │ 9 Not related to gastric cancer      │
                               │   │ 11 Not case-control study            │
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                │  Evaluate VEGF +936C/T       │
                │  polymorphism and            │
                │  gastric cancer risk         │
                │        n=12                  │
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            Excluded n=4       │────────────┐
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                               │   │ 1 Without sufficient genotype data for extraction│
                               │   │ 1 Family-based designs                           │
                               │   │ 2 Not related to +936C/T polymorphism            │
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                │  Studies included in this    │
                │  meta-analysis               │
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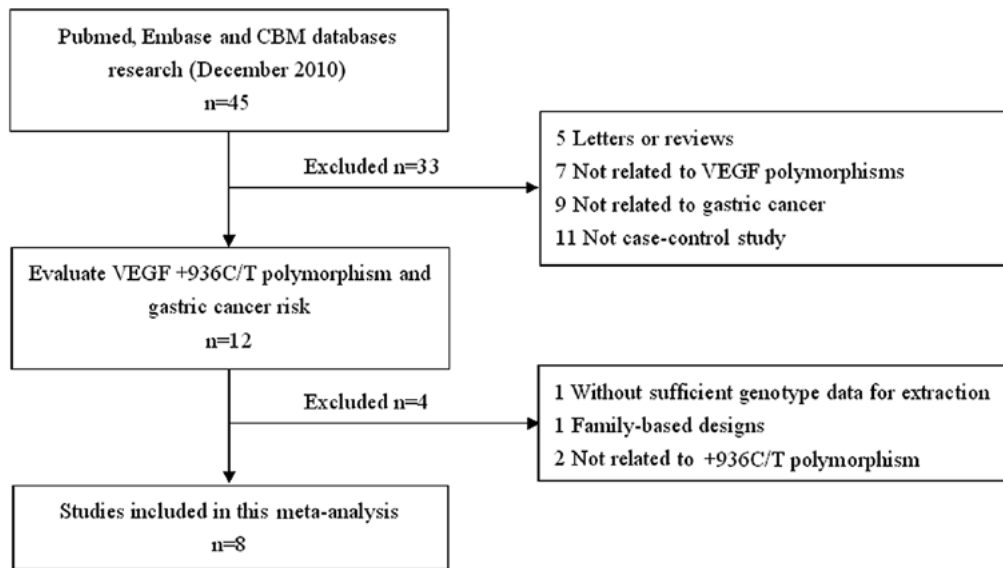
Figure 1. Flow chart showing the study selection procedure. Finally, 8 case-control studies were retrieved reporting a total of 2,131 gastrointestinal cancer patients and 2,670 controls.

lated region is one of the most common polymorphisms. Numerous studies have evaluated the association between the VEGF +936C/T polymorphism and GC risk. However, the results have been inconsistent. The aim of this meta-analysis was to investigate the association of VEGF polymorphisms with GC risk by conducting a meta-analysis from all eligible case-control studies published to date.

Materials and methods

Literature search. An electronic search of the Pubmed, Embase and CBM was performed to retrieve studies linking the VEGF +936C/T polymorphism and GC risk available by December 2010 without language restrictions, using the following query: ['Vascular Endothelial Growth Factor A' or 'Vascular Endothelial Growth Factor B' or 'Vascular Endothelial Growth Factor C' or 'Vascular Endothelial Growth Factor D' or 'Vascular Endothelial Growth Factor, Endocrine-Gland-Derived' or 'Vascular Endothelial Growth Factors' (Mesh)] and ['Polymorphism, Single Nucleotide' or 'Polymorphism, Restriction Fragment Length' or 'Polymorphism, Single-Stranded Conformational' or 'Genomic Structural Variation' or 'Polymorphism, Genetic' (Mesh)] and ['Gastric Cancer' or 'Gastric Neoplasm' or 'Stomach Neoplasms' (Mesh)]. The reference lists of major textbooks, reviews and included articles were identified through manual searches to find other potentially eligible studies. Studies reported by the same authors, yet published in different journals, were checked for possible overlapping participant groups. When pertinent data were not included or data that were presented were unclear, the authors were directly contacted.

Inclusion criteria and exclusion criteria. To be eligible for inclusion in this meta-analysis, the following criteria were established: i) case-control studies that addressed GC cases and healthy or benign disease controls; ii) studies that evaluated the association between the VEGF +936C/T polymorphism and

GC risk; iii) studies that included sufficient genotype data for extraction. Studies excluded were: i) not case-control studies that evaluated the association between the VEGF +936C/T polymorphism and GC risk; ii) case reports, letters, reviews and editorial articles; iii) studies based on incomplete raw data and no usable data reported; iv) studies containing duplicate data; v) family-based design.

Data extraction. Using a standardized form, data from the published studies were extracted independently by two reviewers (X.H. Dong and G.J. Jin) to populate the necessary information. From each of the included articles, the following information was extracted: first author, year of publication, country, language, ethnicity, study design, diagnostic criteria, source of cases and controls, number of cases and controls, sample, detection methods, polymorphisms and evidence of Hardy-Weinberg equilibrium (HWE) in controls. For conflicting evaluations, an agreement was reached following discussion.

Quality assessment of the included studies. The quality of the studies was also independently assessed by two reviewers (X.H. Dong and G.J. Jin) based on the STROBE quality score systems (23). Thirty items relevant to the quality appraisal were used for assessment in this meta-analysis, with scores ranging from 0 to 30. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (H. Shang).

Statistical analysis. The meta-analysis was carried out using the Review Manager version 5.0.25 (provided by The Cochrane Collaboration) and STATA package version 9.2 (Stata Corporation, College Station, TX, USA). The strength of the associations between the VEGF +936C/T polymorphism and GC risk was estimated using odds ratio (OR) and 95% confidence interval (95% CI). The following contrasts for the VEGF +936C/T polymorphism were evaluated: comparison of the variant allele with ancestral allele (T vs. C); comparison

of the variant homozygote combined with the heterozygote vs. ancestral homozygote (T/T+C/T vs. C/C); comparison of the variant homozygote combined with the heterozygote vs. ancestral homozygote (T/T vs. C/C+C/T); comparison of the variant homozygote vs. ancestral homozygote (T/T vs. C/C); comparison of the variant homozygote vs. heterozygote (T/T vs. C/T). Between-study heterogeneities were estimated using Cochran's Q test (24,25). We also quantified the effect of heterogeneity using the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q test (P<0.10) or I^2<50% indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used (26). Before the effect estimation of associations between the VEGF +936C/T polymorphism and GC risk, we tested whether genotype frequencies of the controls were in HWE using the χ^2 test. Subgroup analysis based on ethnicity was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by Begg's funnel plot, and funnel plot asymetry was assessed by Egger's linear regeression test (27). Statistical significance was considered when the P-value of Egger's test was ≤0.10. All P-values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (L.P. Zhou and H. Luan) populated the data in the statistical software programs independently and obtained the same results.

Results

Characteristics of the included studies. The search strategy retrieved 45 potentially relevant studies. According to the inclusion criteria, only 8 studies (28-35) with full-text were included in this meta-analysis and 37 studies were excluded. The flow chart of the study selection is summarized in Fig. 1. These 8 case-control studies selected included a total of 2,131 GC cases and 2,670 healthy or benign disease controls. All were case-control studies which evaluated the association between VEGF +936C/T polymorphism and GC risk. The year of publication of the included studies ranged from 2006 to 2010. All included articles were written in English except one in Chinese (35). The source of controls was mainly based on healthy population. Diverse genotyping methods mainly used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The baseline characteristics and methodological quality of all included studies are summarized in Table I. The genotype distribution and risk allele frequency are summarized in Table II.

Main meta-analysis results. A summary of the meta-analysis findings of the association between the VEGF +936C/T polymorphism and GC risk is provided in Table III. Meta-analysis results identified no significant association between the VEGF +936C/T polymorphism and GC risk in all comparisons of T allele vs. C allele (OR=1.08, 95% CI 0.90-1.30, P=0.42), CT+TT vs. CC (OR=1.08, 95% CI 0.87-1.34, P=0.49), TT vs. CC+CT (OR=1.14, 95% CI 0.85-1.53, P=0.37), TT vs. CC (OR=1.18, 95% CI 0.87-1.59, P=0.28) and TT vs. CT (OR=1.11,

Table I. Baseline characteristics of the studies included in the meta-analysis.

First author (ref.)	Year	Country	Ethnicity	Source of controls	Source of cases	Detection method	No. of subjects		Gender (male/female)		Age, in years (mean±SD)	
							Cases	Controls	Cases	Controls	Cases	Controls
Tzanakis, et al (28)	2006	Greece	Caucasian	Population-based	Hospital-based	PCR-RFLP	100	100	58/42	-	65.0±12.3	-
Chae, et al (29)	2006	Korea	Asian	Population-based	Hospital-based	PCR-RFLP	413	413	313/100	333/80	60.2±10.3	60.2±9.0
Bae, et al (30)	2008	Korea	Asian	Population-based	Hospital-based	PCR-RFLP	154	229	91/63	112/117	58.1±12.7	59.6±11.8
Ke, et al (31)	2008	China	Asian	Population-based	Population-based	PCR-RFLP	540	561	371/169	384/177	60.4±9.5	59.5±10.2
Al-Moundhri, et al (32)	2009	Oman	Caucasian	Population-based	Hospital-based	PCR-RFLP	130	130	75/55	-	56.8±12.2	41.3±11.6
Guan, et al (33)	2009	USA	Caucasian	Population-based	Hospital-based	PCR-RFLP	171	353	56/115	104/249	59.7±12.6	57.6±11.2
Tahara, et al (34)	2009	Japan	Asian	Hospital-based	Hospital-based	PCR-RFLP	385	459	271/114	267/192	65.5±11.0	61.5±13.0
Xia, et al (35)	2010	China	Asian	Population-based	Hospital-based	-	238	425	191/47	336/89	61.0±9.4	60.6±8.4

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SD, standard deviation.

Table II. Genotype distribution and risk allele frequency of all studies included.

First author (Ref.)	Cases								Controls								HWE test (P-value)
	Total	CC	CT	TT	Total allele	C	T	AF	Total	CC	CT	TT	Total allele	C	T	AF	
Tzanakis, *et al* (28)	100	41	33	26	200	115	85	0.425	100	51	27	22	200	129	71	0.355	0.000
Chae, *et al* (29)	413	283	122	8	826	688	138	0.167	413	252	149	12	826	653	173	0.209	0.069
Bae, *et al* (30)	154	89	58	7	308	236	72	0.234	229	169	57	3	458	395	63	0.138	0.458
Ke, *et al* (31)	540	373	152	15	1,080	898	182	0.169	561	386	164	11	1,122	936	186	0.166	0.177
Al-Moundhri, *et al* (32)	130	109	2	19	260	220	40	0.154	130	110	0	20	260	220	40	0.154	0.000
Guan, *et al* (33)	171	127	41	3	342	295	47	0.137	353	276	70	7	706	622	84	0.119	0.309
Tahara, *et al* (34)	385	256	118	11	770	630	140	0.182	459	300	140	19	918	740	178	0.194	0.603
Xia, *et al* (35)	238	155	63	10	476	373	83	0.174	425	276	131	6	850	683	143	0.168	0.021

AF, allele frequency; HWE, Hardy-Weinberg equilibrium.

95% CI 0.79-1.56, P=0.56). In the subgroup analysis based on ethnicity, the subjects of all included studies were divided into Caucasian and Asian populations. Results of subgroup analysis confirmed that there was also no association between the VEGF +936C/T polymorphism and GC risk in both Caucasian and Asian populations. Sensitivity analysis was performed by sequential omission of individual studies. The significance of the pooled OR in all individual analyses and subgroup analyses was not influenced excessively by omitting any single study. In addition, we also performed sensitivity analysis by omission of studies without HWE, but the results were also not influenced.

Publication bias. Publication bias of the literature was assessed using the Begg's funnel plot and Egger's linear regression test. Egger's linear regression test was used to measure the asymmetry of the funnel plot. The results of Egger's linear regression test are shown in Table IV. Results showed that there was no publication bias (all P>0.05).

Discussion

Evidence suggests that VEGF plays an important role in the carcinogenesis pathway, such as in the inhibition of apoptosis, tumor growth, angiogenesis, invasion and metastasis (36). The specific function of VEGF in the formation of prostaglandins makes it a strong candidate for increasing the susceptibility to common cancers, such as GC, colorectal, lung, breast, prostate cancer and other solid tumors (37-40). As is known, genetic polymorphisms altering the level of protein expressed are anticipated to have a substantial influence on disease activity (41). Several polymorphisms in VEGF have been previously reported, although some of these polymorphisms are not functionally significant and not associated with a susceptibility to GC.

Our meta-analysis quantitatively assessed the association between the VEGF +936C/T polymorphism and GC risk. Finally, 8 case-control studies were included and comprised a total of 2,131 GC cases and 2,670 healthy or benign disease controls. The main meta-analysis results showed that there was no association between the VEGF +936C/T polymorphism and GC risk in all comparisons of T allele vs. C allele, CT+TT vs. CC, TT vs. CC+CT, TT vs. CC and TT vs. CT, suggesting that the VEGF +936C/T polymorphism is not a risk factor for GC. Similarly, in the subgroup analysis by ethnicity, no association was found between the VEGF +936C/T polymorphism and GC risk in all comparisons in both Caucasian and Asian populations. Between-study heterogeneity was found in the comparisons of the T allele vs. C allele and CT+TT vs. CC; the random effects model was used. No heterogeneity was found in other comparisons; the fixed effects model was used. No evidence of publication bias was noted in this meta-analysis for the VEGF +936C/T polymorphism.

There were some limitations in our meta-analysis. Firstly, due to incomplete raw data or publication limitations, several relevant studies could not be included. Secondly, we were not able to address the sources of heterogeneity existing among studies for most polymorphisms. However, we could not perform subgroup stratifications analysis for the limited number of published studies. Thirdly, the lack of genotype frequency information provided by some published studies did not allow the estimation of the best genetic model of inheri-

Table III. Meta-analysis of the association between the VEGF +936C/T polymorphism and gastric cancer risk.

Comparisons	OR	95% CI	P-value	Heterogeneity		Effects model
				I^2	P-value	
T vs. C	1.08	0.90-1.30	0.42	64%	0.007	Random
Caucasian	1.18	0.93-1.51	0.17	0%	0.650	
Asian	1.05	0.82-1.34	0.72	76%	0.002	
T/T+C/T vs. C/C	1.08	0.87-1.34	0.49	63%	0.008	Random
Caucasian	1.27	0.94-1.72	0.12	0%	0.730	
Asian	1.02	0.77-1.35	0.88	75%	0.003	
T/T vs. C/C+C/T	1.14	0.85-1.53	0.37	32%	0.170	Fixed
Caucasian	1.07	0.68-1.66	0.78	0%	0.810	
Asian	1.21	0.82-1.79	0.34	59%	0.050	
T/T vs. C/C	1.18	0.87-1.59	0.28	41%	0.100	Fixed
Caucasian	1.15	0.73-1.82	0.55	0%	0.660	
Asian	1.20	0.81-1.77	0.37	64%	0.030	
T/T vs. C/T	1.11	0.79-1.56	0.56	27%	0.220	Fixed
Caucasian	0.82	0.43-1.57	0.55	0%	0.590	
Asian	1.25	0.83-1.87	0.28	47%	0.110	

OR, odds ratio; 95% CI, 95% confidence interval.

Table IV. Evaluation of publication bias by Egger's linear regression test.

Comparison	Coefficient	Standard error	t	P> |t|	95% CI
T vs. C	3.69	2.07	1.78	0.13	-1.38-8.76
T/T+C/T vs. C/C	3.12	1.77	1.76	0.13	-1.22-7.46
T/T vs. C/C+C/T	1.87	1.71	1.09	0.32	-2.32-6.06
T/T vs. C/C	2.11	1.91	1.11	0.31	-2.57-6.80
T/T vs. C/T	-0.21	1.37	-0.16	0.88	-3.58-3.15

95% CI, 95% confidence interval.

tance to follow. Although we actively contacted the authors, they did not provide a comprehensive set of data. In addition, the small sample size available was not ideal for detecting small genetic effects. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original studies and also the confounding factors addressed across the different studies were variable.

In conclusion, our meta-analysis of 8 case-control studies demonstrated that there was lack of association between the VEGF +936C/T polymorphism and GC risk. Therefore, the necessity to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results should be emphasized.

Acknowledgements

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