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Vascular endothelial growth factor -634 G/C polymorphism and risk of cancer: an updated meta-analysis

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ABSTRACT. The association between vascular endothelial growth factor (*VEGF*) gene polymorphisms and risk of cancer has been investigated in several studies published previously; however, the individual results are inconclusive. Therefore, we performed a meta-analysis to establish evidence for an association between the *VEGF* -634 G/C polymorphism and risk of cancer. We searched PubMed, Medline, and Korean Studies Information Service System databases and identified 29 case-control studies, containing data of 25,324 individuals, for this meta-analysis. The odds ratio (OR) and 95% confidence interval (95%CI) were used to determine the strength of the association. Overall, no significant association was detected in the allele model (G allele *vs* C allele, OR = 0.98, 95%CI = 0.93-1.03), dominant model (G/G+G/C *vs* C/C, OR = 1.00, 95%CI = 0.90-

1.11), or recessive model (G/G *vs* G/C+C/C, OR = 0.96, 95%CI = 0.89-1.03). The meta-analysis results suggest that the *VEGF* -634 G/C polymorphism may not be related to the development of cancer. However, additional studies with larger sample size are required in order to provide supporting evidence.

Key words: Vascular endothelial growth factor; Meta-analysis; Cancer; Polymorphism

INTRODUCTION

Cancer commonly refers to a broad group of diseases that involve unregulated cell growth. Although the causes of cancer are diverse, the condition is attributable to the complex interaction between lifestyle, environment, and genetic makeup of the individual. Several factors are known to increase the risk of cancer, including tobacco use, dietary factors, certain infections, exposure to radiation, lack of physical activity, obesity, and environmental pollutants (Anand et al., 2008). Several recent studies have revealed that gene polymorphisms may be associated with cancer development, either independently or in combination with other carcinogenic factors. Therefore, identification of gene polymorphisms may help to predict the individual risk of cancer (Zaridze, 2008).

Vascular endothelial growth factor (VEGF) is a signal protein that stimulates vasculogenesis and angiogenesis. VEGF belongs to a sub-family of growth factors, specifically the platelet-derived growth factor family of cystine-knot growth factors (Niu and Chen, 2010). Overexpression of VEGF has been associated with tumor progression and poor prognosis in cancer (Hicklin and Ellis, 2005).

Recently, increasing number of studies have highlighted the association between the *VEGF* -634 G/C polymorphism and various cancers including lung, gastric, colorectal, and cervical cancer (Jin et al., 2005; Lee et al., 2005; 2006; Jacobs et al., 2006; Kataoka et al., 2006; Sfar et al., 2006; Tzanakis et al., 2006; Balasubramanian et al., 2007; Garcia-Closas et al., 2007; Hsiao et al., 2007; Amano et al., 2008; Chae et al., 2006, 2008; Hofmann et al., 2008; Ke et al., 2008; Zhai et al., 2008a,b; Al-Moundhri et al., 2009; Dassoulas et al., 2009; Guan et al., 2009; Maltese et al., 2009; Ungerbäck et al., 2009; Bruyère et al., 2010; Kim et al., 2010; Li et al., 2011; Zhou et al., 2011; Supic et al., 2012; Deng et al., 2013; Luo et al., 2013; Wang et al., 2014). Due to the substantial differences in sample size, these studies failed to accurately define the genetic susceptibility of the *VEGF* -634 G/C polymorphism in development of cancer.

In this study, we performed a meta-analysis using these published data to establish statistical evidence for an association between the *VEGF* -634 G/C polymorphism and cancer risk.

MATERIAL AND METHODS

Search strategy

Case and control studies were sought in PubMed, Medline, and Korean Studies

Information Service System (KISS) databases, up to March 2014 without language restrictions. Relevant studies were identified using the terms: "vascular endothelial growth factor or VEGF" and "polymorphism or polymorphisms or variant" and "cancer or carcinoma". The search was restricted to studies in man. Additional studies were identified by a manual search of print articles comprising both, original research and reviews. If data or data subsets were published in more than one article, the publication with the largest sample size was included.

Inclusion criteria and data extraction

Studies were included if they met the following criteria: 1) evaluated the association between *VEGF* polymorphism (-634 G>C) and cancer, 2) case-control study design, and 3) contained detailed genotype frequency data of cases and controls. Data were extracted independently by two investigators, who then reached a consensus on all items. If the two investigators generated different results, they would check the data again and have a discussion to come to an agreement. Data extracted from the selected articles included the first author's name, year of publication, country of origin, ethnicity of study population, and number of cases and controls. The ethnicity was divided into Asian and Caucasian populations.

Statistical analysis

Before determining the role of *VEGF* polymorphism in cancer, we calculated whether genotype frequencies of controls were in agreement with the Hardy-Weinberg equilibrium (HWE) using the chi-square test (http://www.had2know.com/academics/hardy-weinberg-equilibrium-calculator-2alleles.html). Meta-analysis was performed using the Comprehensive Meta Analysis software (Corporation, NJ, USA). The pooled odds ratio (OR) and 95% confidence interval (95%CI) was used to determine the association between cancer and *VEGF* polymorphism (-634 G>C). The random-effect model or the fixed-effect model was used. OR with the corresponding 95%CI was calculated for the additive model (G/G *vs* G/C, GG *vs* C/C), dominant model (G/G and G/C *vs* C/C), recessive model (G/G *vs* G/C and C/C), and allele (G *vs* C).

A chi-square test-based Q-statistic test was performed to assess heterogeneity of the study. We also estimated the effect of heterogeneity by the I^2 test, where a significant Q-test ($P \leq 0.05$) or $I^2 > 50\%$ indicated heterogeneity among studies. The random-effect Mantel-Haenszel method was adopted if the result of the Q-test was $P < 0.05$ or $I^2 > 50\%$, which indicated statistically significant heterogeneity between studies. Otherwise, the fixed-effect Mantel-Haenszel method was adopted. Finally, potential publication bias was investigated using the Begg and Mazumdar rank correlation test and the Egger regression test. $P < 0.05$ was regarded as statistically significant.

RESULTS

Study characteristics

A total of 558 studies were screened from publication databases: Pubmed, Med-

line, and KISS. As shown in Figure 1, 29 articles including 12,559 cases and 12,765 controls were selected and study characteristics from selected studies regarding the *VEGF* -634 G>C polymorphism and cancer are summarized in Table 1. The studies covered several types of cancer including bladder cancer (1), breast cancer (5), cervical cancer (1), colorectal cancer (5), endometrial carcinoma (1), esophageal cancer (1), gastric cancer (6), glioma (1), lung cancer (3), oral squamous cell carcinoma (1), osteosarcoma (1), prostate cancer (1), renal cell carcinoma (1), and thyroid cancer (1). The overall frequencies of the G allele were found to be higher in control and multiple-cancer groups in the Caucasian population than those in the Asian population (the G allele frequencies in Asian and Caucasian populations were 0.58 and 0.64 in the control group, whereas they were 0.58 and 0.66 in the multiple-cancer group, respectively; Figure 2).

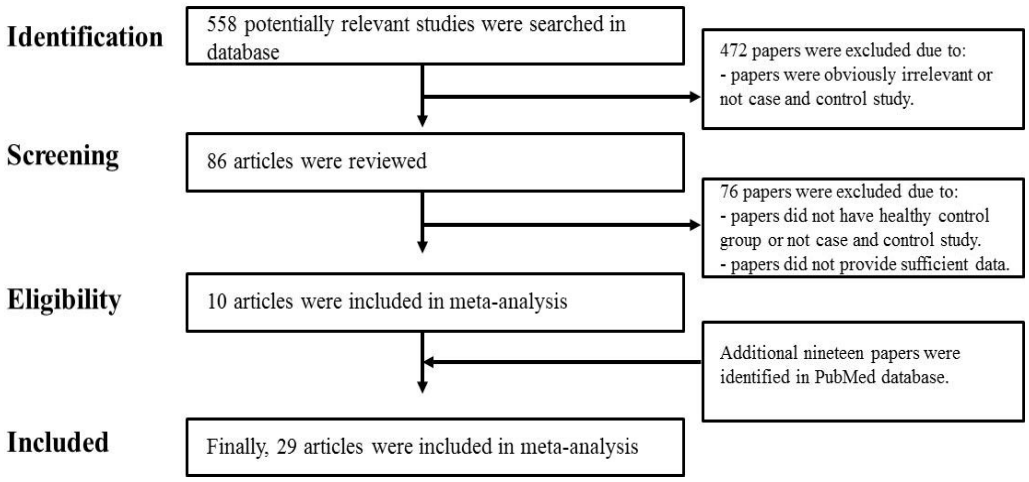

Figure 1. Flow chart illustrating the search strategy used to identify relevant studies of the VEGF -634 G>C polymorphism and cancer for meta-analysis.

Quantitative synthesis

Table 2 shows the results of the overall meta-analysis. The results indicate that the *VEGF* -634 G>C polymorphism may not be associated with risk of developing cancer (G/G *vs* G/C+C/C, OR = 0.96, 95%CI = 0.89-1.03, P = 0.26; G/G+G/C *vs* C/C, OR = 1.00, 95%CI = 0.90-1.11, P = 0.98; G/G *vs* G/C, OR = 0.96, 95%CI = 0.89-1.03, P = 0.25; G/G *vs* C/C, OR = 0.98, 95%CI = 0.87-1.09, P = 0.66; G *vs* C, OR = 0.98, 95%CI = 0.93-1.03, P = 0.41; Table 2). The results did not change after excluding 4 studies (Guan et al., 2009; Dassoulas et al., 2009; Zhou et al., 2011 and Luo et al., 2013) that did not agree with HWE. In the stratified analysis by cancer type, a weak association was found between the *VEGF* -634 G>C polymorphism and gastric cancer (G/G *vs* G/C, OR = 0.82, 95%CI = 0.70-0.97, P = 0.016; Table 3). These results suggest that the *VEGF* -634 G>C polymorphism may not contribute to development of cancer.

Table 1. Genotype and allele distribution of the VEGF- 634 G>C polymorphism in multiple-cancer patients and controls.

Study	Type of cancer	Ethnicity	Case/Control	Case	Control	Case	Control	HWE P
				GG/GC/CC	GG/GC/CC	G/C	G/C	
Jin et al., 2005	Breast cancer	Caucasian	936/941	488/363/85	492/367/82	1339/533	1351/531	0.17
Lee et al., 2005	Lung cancer	Asian	431/432	108/247/76	108/232/92	463/399	448/416	0.11
Jacobs et al., 2006	Breast cancer	Caucasian	495/500	221/222/52	232/221/47	664/326	685/315	0.59
Sfar et al., 2006	Prostate cancer	Caucasian	101/100	29/57/15	44/46/10	115/87	134/66	0.69
Kataoka et al., 2006	Breast cancer	Asian	1095/1198	395/508/192	418/598/182	1298/892	1434/962	0.18
Tzanakis et al., 2006	Gastric cancer	Caucasian	100/100	41/40/19	52/39/9	122/78	143/78	0.67
Chae et al., 2006	Gastric cancer	Asian	413/413	129/253/31	106/223/84	511/315	435/391	0.09
Hsiao et al., 2007	Thyroid cancer	Asian	313/230	104/160/49	67/119/44	368/258	253/207	0.49
Balasubramanian et al., 2007	Breast cancer	Caucasian	490/498	226/207/57	209/225/64	659/321	643/353	0.78
Garcia-Closas et al., 2007	Bladder cancer	Caucasian	881/876	388/395/98	387/396/93	1171/591	1170/582	0.58
Hofmann et al., 2008	Colorectal cancer	Caucasian	427/427	193/192/47	192/195/43	578/286	579/281	0.52
Zhai et al., 2008a	Esophageal cancer	Caucasian	308/546	115/124/29	233/251/62	354/182	717/375	0.65
Zhai et al., 2008b	Lung cancer	Caucasian	1900/1458	805/848/247	650/644/164	2458/1342	1944/972	0.81
Ke et al., 2008	Gastric cancer	Asian	540/561	161/287/92	186/278/97	609/471	650/472	0.69
Amano et al., 2008	Endometrial carcinoma	Asian	105/179	25/52/28	58/79/42	102/108	195/163	0.14
Chae et al., 2008	Colorectal cancer	Asian	465/413	166/193/106	106/223/84	525/405	435/391	0.09
Ungerbäck et al., 2009	Colorectal cancer	Caucasian	302/336	135/130/37	167/137/32	400/204	471/201	0.61
Guan et al., 2009	Gastric cancer	Caucasian	171/353	69/72/30	180/99/74	210/132	459/247	<0.0001
Dassoulas et al., 2009	Colorectal cancer	Caucasian	312/362	128/125/59	145/141/76	381/243	431/293	0.003
Maltese et al., 2009	Colorectal cancer	Caucasian	301/91	118/135/48	30/46/15	371/231	106/76	0.71
Al-Moundhri et al., 2009	Gastric cancer	Asian	130/130	49/59/22	62/54/14	157/103	178/82	0.66
Bruyère et al., 2010	Renal cell carcinoma	Caucasian	48/198	15/25/8	86/92/20	55/41	264/132	0.52
Kim et al., 2010	Cervical cancer	Asian	196/215	63/102/31	76/103/36	228/164	255/175	0.91
Li et al., 2011	Glioma	Asian	760/800	247/393/120	306/379/115	887/633	991/609	0.89
Zhou et al., 2011	Gastric cancer	Asian	150/150	74/47/29	76/44/30	195/105	196/104	<0.0001
Supic et al., 2012	Oral squamous cell carcinoma	Caucasian	114/126	48/55/11	61/49/16	151/77	171/81	0.22
Deng et al., 2013	Lung cancer	Asian	65/110	19/32/14	30/55/25	70/60	115/105	0.98
Luo et al., 2013	Breast cancer	Asian	680/680	338/205/137	341/204/135	881/479	886/474	<0.0001
Wang et al., 2014	Osteosarcoma	Asian	330/342	115/165/50	118/166/58	395/265	402/282	0.98

HWE, Hardy-Weinberg equilibrium.

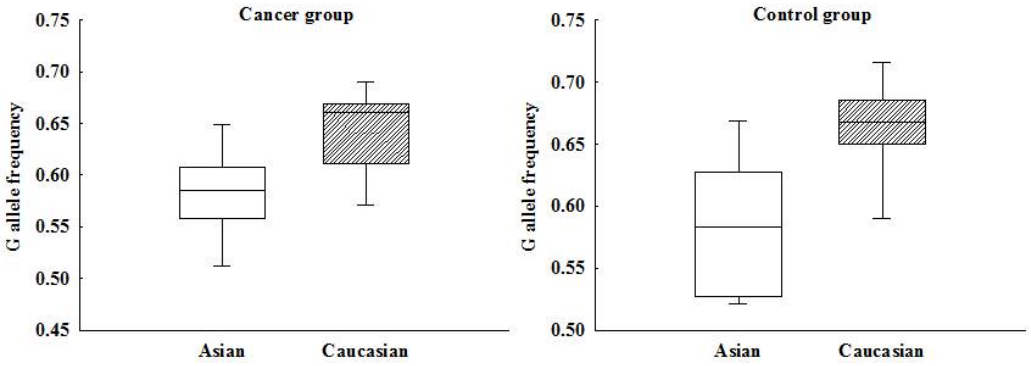

Figure 2. G allele frequencies of the VEGF -634 G>C polymorphism in Asian and Caucasian populations.

Table 2. Results of the meta-analysis from different comparative genetic models in the subgroup analysis by ethnicity.

Genetic comparison	Population	OR (95%CI)	P	Heterogeneity		Model
				P	I^2	
G/G *vs* G/C+C/C	All	0.96 (0.89-1.03)	0.26	0.011	41.75	Random
	Asians	0.96 (0.88-1.12)	0.94	0.011	52.57	Random
	Caucasians	0.94 (0.88-1.01)	0.09	0.144	28.46	Fixed
G/G+G/C *vs* C/C	All	1.00 (0.90-1.11)	0.98	0.008	42.80	Random
	Asians	1.07 (0.90-1.27)	0.48	0.001	63.62	Random
	Caucasians	0.93 (0.84-1.04)	0.20	0.638	0.00	Fixed
G/G *vs* G/C	All	0.96 (0.89-1.03)	0.25	0.012	41.16	Random
	Asians	0.98 (0.86-1.20)	0.80	0.012	52.12	Random
	Caucasians	0.95 (0.88-1.02)	0.17	0.135	29.48	Fixed
G/G *vs* CC	All	0.98 (0.87-1.09)	0.66	0.003	46.85	Random
	Asians	1.06 (0.87-1.28)	0.59	0.001	63.52	Random
	Caucasians	0.91 (0.81-1.01)	0.09	0.397	4.95	Fixed
G *vs* C	All	0.98 (0.93-1.03)	0.41	0.006	44.25	Random
	Asians	1.01 (0.93-1.10)	0.77	0.005	56.14	Random
	Caucasians	0.95 (0.91-1.00)	0.03	0.195	23.38	Fixed

Analysis for heterogeneity and publication bias

The results showed high extent of heterogeneity among the studies analyzed (Table 2). As cancer type and ethnicity could influence the results, we performed subgroup analysis by these parameters (Table 3). The results suggest that Asian population, colorectal cancer, and gastric cancer may contribute to heterogeneity. The Begg and Mazumdar rank correlation test and the Egger regression test were performed to assess the publication bias. The shape of the funnel plot showed the evidence of funnel plot symmetry in all genetic models (data not shown). The results of Begg and Mazumdar rank correlation and Egger regression tests suggested no potential publication bias (G/G *vs* G/C+C/C, $P_{begg} = 0.08$, $P_{egger} = 0.24$; G/G+G/C *vs* C/C, $P_{begg} = 0.93$, $P_{egger} = 0.78$; G/G *vs* G/C, $P_{begg} = 0.44$, $P_{egger} = 0.81$; G/G *vs* C/C, $P_{begg} = 0.44$, $P_{egger} = 0.81$; G *vs* C, $P_{begg} = 0.18$, $P_{egger} = 0.39$; data not shown). These results indicate that there was no publication bias for multiple cancers in the meta-analysis.

Table 3. Results of the meta-analysis from different comparative genetic models in the subgroup analysis by cancer type.

Cancer type	Genetic comparison	OR (95%CI)	P	Heterogeneity		Model
				P	I^2	
Breast cancer	G/G *vs* G/C+C/C	1.02 (0.93-1.12)	0.62	0.70	0.00	Fixed
	G/G+G/C *vs* C/C	0.93 (0.82-1.06)	0.28	0.75	0.00	Fixed
	G/G *vs* G/C	1.05 (0.95-1.15)	0.38	0.71	0.00	Fixed
	G/G *vs* C/C	0.96 (0.83-1.04)	0.55	0.76	0.00	Fixed
	G *vs* C	0.99 (0.93-1.06)	0.85	0.69	0.00	Fixed
Colorectal cancer	G/G *vs* G/C+C/C	1.11 (0.88-1.42)	0.38	0.026	63.88	Random
	G/G+G/C *vs* C/C	0.93 (0.88-1.12)	0.46	0.72	0.00	Fixed
	G/G *vs* G/C	1.15 (0.87-1.52)	0.32	0.011	69.36	Random
	G/G *vs* C/C	1.04 (0.85-1.28)	0.69	0.45	0.00	Fixed
	G *vs* C	1.03 (0.93-1.14)	0.53	0.25	25.43	Fixed
Gastric cancer	G/G *vs* G/C+C/C	0.85 (0.66-1.08)	0.17	0.036	58.15	Random
	G/G+G/C *vs* C/C	1.07 (0.64-1.74)	0.80	<0.01	83.05	Random
	G/G *vs* G/C	0.82 (0.70-0.97)	0.016	0.17	35.03	Fixed
	G/G *vs* C/C	0.95 (0.54-1.67)	0.87	<0.01	83.73	Random
	G *vs* C	0.92 (0.72-1.17)	0.50	<0.01	79.74	Random
Lung cancer	G/G *vs* G/C+C/C	0.93 (0.83-1.06)	0.27	0.77	0.00	Fixed
	G/G+G/C *vs* C/C	0.95 (0.80-1.14)	0.60	0.14	49.38	Fixed
	G/G *vs* G/C	0.95 (0.83-1.08)	0.39	0.93	0.00	Fixed
	G/G *vs* C/C	0.91 (0.75-1.10)	0.33	0.23	32.15	Fixed
	G *vs* C	0.95 (0.87-1.04)	0.30	0.30	18.71	Fixed

DISCUSSION

VEGF plays an essential role in angiogenesis and has been linked with the development and metastasis of common cancers (Amankwah et al., 2012). Therefore, it has been implicated in the cause for poor prognosis in cancer. Numerous studies show decreased overall survival and disease-free survival rates in tumors overexpressing VEGF. Russo et al. (2012) demonstrated that VEGF is an important factor in prostate cancer progression, being critical to tumorigenicity and metastasis. Additionally, Jacobsen et al. (2004) reported a correlation between VEGF expression and tumor size as well as stage, showing significantly decreased survival of renal cell carcinoma patients with VEGF-overexpressing tumors.

VEGF is located at chromosome 6p12-p21, where several genetic polymorphisms have been identified (Jain et al., 2009). Of note is *VEGF* -634 G/C, located in the 5'-untranslated region that is thought to be closely associated with VEGF protein expression and involved in tumor angiogenesis (Watson et al., 2000; Koukourakis et al., 2004). The association between *VEGF* -634 G/C and cancer risk has been investigated in a broad range of studies with either a relatively small or large sample size of different ethnic populations. However, due to the difference in size and genetic background of the sample, the evidence provided by each study is not sufficient to draw a convincing conclusion. This inconclusive association motivated us to perform a meta-analysis consisting of all published data to date, to verify if any association existed between cancer risk and the *VEGF* -634 G/C polymorphism.

In a previous published meta-analysis focused on *VEGF* -634 G/C genetic variants and several types of cancer, no significant association was determined (Liu et al., 2011). The limited sample size in this study may have masked any true association, resulting in false-negative findings. However, our meta-analysis based on a large dataset from independent studies also showed that there is no association between the *VEGF* -634 G/C polymorphism and increased risk of cancer. Also, subgroup analysis by ethnicity demonstrated no significant association in terms of

Asian and Caucasian populations. While our findings were no different from those reported by Liu et al., a widely expanded sample size could improve the reliability of our estimates.

Our meta-analysis did have certain limitations and the results should be interpreted with caution. First, meta-analysis is a type of secondary and retrospective study, limited by the quality of the primary studies. Therefore, the reliability of our meta-analysis was also limited by the quality of the studies analyzed herein. Second, we could not perform an analysis on gene-gene and gene-environment interactions. Third, although we have performed a fairly comprehensive search, a weak publication bias was detected.

In conclusion, this study investigated the relationship between *VEGF* -634 G/C polymorphism and the occurrence of cancer. We found that *VEGF* -634 G/C polymorphisms may not contribute to increased cancer susceptibility. Further, larger studies considering gene-gene and gene-environment interactions may demonstrate more precise evidence regarding the association between the *VEGF* -634 G/C polymorphism and risk of cancer.

Conflicts of interest

The authors declare no conflict of interest.

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