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Vascular endothelial growth factor gene polymorphisms contribute to the risk of endometriosis: an updated systematic review and meta-analysis of 14 case-control studies

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ABSTRACT. Endometriosis is a chronic gynecological disease defined as the presence of the endometrium outside the uterine cavity. Endometriosis is a multifactorial and polygenic disease in which angiogenesis may be implicated. Angiogenesis is under the control of numerous inducers, including vascular endothelial growth factor (VEGF). Many studies have reported that VEGF plays a role in the progression of the disease, but individually published studies showed inconclusive results. We investigated the association between VEGF polymorphisms and the susceptibility to endometriosis. The MEDLINE, EMBASE, Web of Science, and CBM databases were searched for all articles published up to June 25, 2012, which addressed VEGF polymorphisms and endometriosis risk. We investigated the

potential association between VEGF polymorphisms and the risk of endometriosis. Fourteen studies were included with a total of 3313 endometriosis cases and 3393 healthy controls. Meta-analysis results showed that the rs699947 (A>C) and rs1570360 (G>A) polymorphisms in the VEGF gene were associated with a decreased risk of endometriosis, while rs3025039 (C>T) might increase the risk of endometriosis. However, the rs833061 (T>C) and rs2010963 (G>C) polymorphisms of the VEGF gene did not appear to have an influence on endometriosis susceptibility. Results from the meta-analysis suggest that the rs3025039 (C>T) polymorphism of the VEGF gene increases the risk of endometriosis, but the rs699947 (A>C) and rs1570360 (G>A) polymorphisms might be protective factors for endometriosis.

Key words: VEGF; Polymorphism; Endometriosis; Meta-analysis

INTRODUCTION

The endometrium is a complex tissue composed of different cells, including epithelial, stromal, inflammatory, perivascular, and blood vessel cells (Hsieh et al., 2004). Endometriosis is a chronic gynecological disease characterized by the growth of hormonally responsive, endometrial-like tissue outside the uterine cavity, causing diverse symptoms, including infertility, pelvic pain, and dysmenorrhea (Bhanoori et al., 2005). Histologically, endometriosis is a benign disease, but it can behave like a malignancy in terms of growing, infiltrating, and adhering to surrounding tissues (Varma et al., 2004). The prevalence of endometriosis ranges from 2 to 18% among women who seek tubal ligations, from 5 to 50% among infertile women, and from 5 to 20% among women with pelvic pain (Missmer and Cramer, 2003). The cause of endometriosis is likely multifactorial, involving environmental, immunological, endocrine, and genetic processes (Signorile and Baldi, 2010). The mechanisms underlying the disease remain unclear.

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is a heparin-binding glycoprotein with potent angiogenic and endothelial cell-specific mitogenic activities that appears to play an important role in a variety of estrogen target tissues by locally regulating endometrial angiogenesis (Girling and Rogers, 2005; Kim et al., 2005). The VEGF gene is located on chromosome 6p21.3 and consists of 8 exons with alternate splicing, forming a family of proteins (Ferrara et al., 2003). At least 30 single nucleotide polymorphisms (SNPs) in this gene have been described (Watson et al., 2000). Several transcription factor-binding sites are found in the VEGF 5'-untranslated region (UTR), and variation within this region increases transcriptional activity (Fukumura et al., 1998). Polymorphisms within the 5'-UTR lead to differences in VEGF expression between individuals and may influence the etiology of a variety of pathological conditions with which VEGF has been associated (Bhanoori et al., 2005).

Numerous researchers have investigated the association between endometriosis and VEGF gene polymorphisms. However, the results remain controversial. Bhanoori et al. (2005) reported that patients with endometriosis had a higher frequency of the +405G allele. Hsieh

et al. (2004) reported that the -460T allele was associated with higher susceptibility to endometriosis. Furthermore, a positive association was found between the VEGF 936T allele and severe endometriosis in a Japanese population (Ikuhashi et al., 2007) but not in a Korean population (Kim et al., 2008). Therefore, in this study, we evaluated whether the VEGF gene polymorphism is a useful marker for predicting susceptibility to endometriosis.

MATERIAL AND METHODS

Literature search strategy

Relevant papers published before June 25, 2012 were identified by searching the MEDLINE, EMBASE, Web of Science, and CBM databases using the following expression: ("VEGF" OR "Vascular endothelial growth factor A" OR "Vascular permeability factor" OR "Vascular endothelial growth factor") AND ("Endometriosis" OR "Endometrioses" OR "Adenomyosis") AND ("Genetic polymorphism" OR "Single nucleotide polymorphism" OR "SNP" OR "Mutant" OR "Gene variation" OR "Gene mutation"). The referenced manuscripts in the identified articles or textbooks were also reviewed to find other potentially important studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: i) case-control study focused on associations between VEGF gene polymorphisms and endometriosis risk; ii) all patients with the diagnosis of endometriosis confirmed by pathological or histological examination; iii) the frequencies of alleles or genotypes in case and control groups could be extracted, and iv) published in English or Chinese. The exclusion criteria were as follows: i) no control population; ii) duplicate of previous publication; iii) based on incomplete data; iv) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Using a standardized form, data from published studies were extracted independently by 2 reviewers to populate the necessary information. The following information was extracted from each of the articles included: 1st author, year of publication, country, language, ethnicity, study design, source of controls, number of cases and controls, mean age, sample, disease, genotype method, genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in the controls. In the case of conflicting evaluations, an agreement was reached following a discussion with a 3rd reviewer.

Quality assessment of included studies

Two reviewers independently assessed the quality of the papers according to modified STROBE quality score systems (von Elm et al., 2007; Zhang et al., 2011). Forty assessment items related with the quality appraisal were used in this meta-analysis, scores ranging from

0 to 40. Scores of 0-20, 20-30, and 30-40 were defined as low, moderate, and high quality, respectively. Disagreement was resolved by discussion.

Statistical analysis

The meta-analysis examined the association between VEGF gene polymorphisms and the risk of endometriosis. The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using Review Manager Version 5.1.6 (provided by the Cochrane Collaboration, available at: http://ims.cochrane.org/revman/download) and STATA Version 12.0 (Stata Corp, College Station, TX, USA). Inter-study variations and heterogeneities were estimated using the Cochran Q-statistic (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005) ($P < 0.05$ was considered a statistically significant heterogeneity). We also quantified the effect of heterogeneity using the I^2 test, which ranges from 0 to 100% and represents the proportion of inter-study variability attributed to heterogeneity rather than to chance. A significant Q-test ($P < 0.10$) or $I^2 > 50\%$ indicated heterogeneity among studies, and the random-effects model was then conducted for meta-analysis; otherwise, the fixed-effects model was used. We tested whether genotype frequencies of the controls were in HWE using the χ^2 test. Begg's funnel plots are often used to detect publication bias. However, due to the limitations of these plots, caused by varied sample sizes and subjective reviews, the Egger linear regression test, which measures funnel plot asymmetry using the natural logarithm scale of OR, was used to evaluate publication bias (Peters et al., 2006). When $P < 0.1$, publication bias was considered to be significant. All P values were 2-sided. To ensure reliability and accuracy, 2 reviewers populated the data in the statistical software programs independently; these 2 reviewers obtained the same results.

RESULTS

Studies included in the meta-analysis

According to the inclusion criteria, 14 studies were included (Hsieh et al., 2004; Bhanoori et al., 2005; Kim et al., 2005; Ikuhashi et al., 2007; Gentilini et al., 2008; Kim et al., 2008; Zhao et al., 2008; Cosin et al., 2009; Kang et al., 2009; Liu et al., 2009a,b; Attar et al., 2010; Lamp et al., 2010; Altinkaya et al., 2011). The flow chart of study selection is shown in Figure 1. The total endometriosis cases and healthy controls were 3313 and 3393, respectively, in the 14 case-control studies that evaluated the relationship between VEGF polymorphisms and the risk of endometriosis. The publication year of the involved studies ranged from 2004 to 2011. All cases fulfilled the diagnosis criteria of endometriosis confirmed by pathological or histological examination. There were 5 SNPs in the VEGF gene in these 14 studies, including rs833061 (T>C) in 10 studies, rs2010963 (G>C) in 9 studies, rs3025039 (C>T) in 7 studies, rs699947 (A>C) in 4 studies, and rs1570360 (G>A) in 3 studies. Eight of the 14 case-control studies were conducted with Asians and others were conducted with Caucasians. The HWE test was performed on the genotype distribution of the controls in all included studies, and all were in HWE ($P > 0.05$). The characteristics and methodological quality of the included studies are summarized in Table 1.

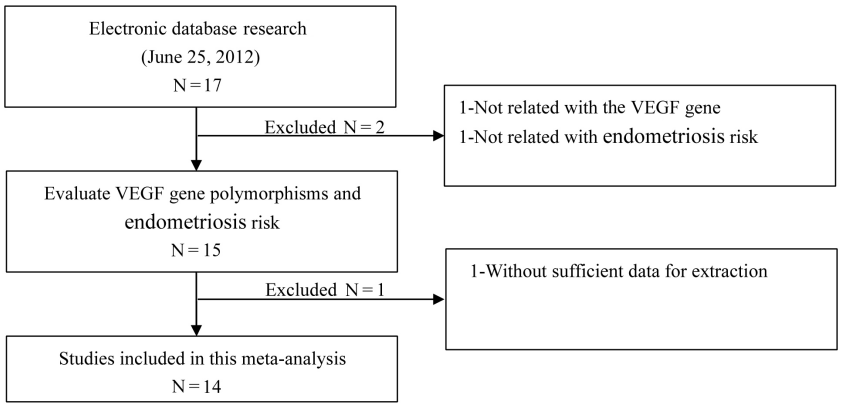

Figure 1. Flow chart shows study selection procedure.

Table 1. Baseline characteristics of studies included in the meta-analysis.

Reference	Country	Ethnicity	Case	Control	Source of control	Sample	Detection	SNP	Quality scores
Hsieh et al., 2004	China	Asian	122	131	Hospital-based	Blood	PCR-RFLP	rs833061 (T>C)	23
Bhanoori et al., 2005	India	Asian	215	210	Population-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (G>C)	24
Kim et al., 2005	Korea	Asian	215	219	Hospital-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (G>C)	22
Ikuhashi et al., 2007	Japan	Asian	147	181	Population-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (G>C) rs3025039 (C>T)	26
Gentilini et al., 2008	Italy	Caucasian	203	140	Hospital-based	Blood	PCR-RFLP	rs2010963 (G>C)	25
Kim et al., 2008	Korea	Asian	105	101	Hospital-based	Blood	PCR-RFLP	rs3025039 (C>T)	28
Zhao et al., 2008	Australia	Caucasian	958	959	Population-based	Blood	MassArray	rs699947 (A>C) rs833061 (T>C) rs2010963 (G>C) rs3025039 (C>T)	31
Cosín et al., 2009	Spain	Caucasian	186	180	Hospital-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (G>C) rs3025039 (C>T)	33
Kang et al., 2009	China	Asian	174	199	Population-based	Blood	PCR-RFLP	rs699947 (C>A) rs1570360 (G>A) rs833061 (T>C) rs3025039 (C>T)	32
Liu et al., 2009a	China	Asian	344	360	Population-based	Blood	PCR-RFLP	rs699947 (C>A) rs3025039 (C>T)	30
Liu et al., 2009b	China	Asian	344	360	Population-based	Blood	PCR-RFLP	rs833061 (T>C) rs1570360 (G>A)	32
Attar et al., 2010	Turkey	Caucasian	52	60	Population-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (C>G)	33
Lamp et al., 2010	Estonia	Caucasian	150	199	Hospital-based	Blood	PCR-RFLP	rs699947 (A>C) rs1570360 (G>A) rs2010963 (G>C) rs3025039 (C>T)	31
Altinkaya et al., 2011	Turkey	Caucasian	98	94	Hospital-based	Blood	PCR-RFLP	rs833061 (T>C) rs2010963 (G>C)	36

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism.

Association between VEGF polymorphisms and endometriosis risk

A summary of the meta-analysis findings of the association between VEGF gene

polymorphisms and endometriosis risk is provided in Table 2. No heterogeneity was found in the comparisons (P > 0.05); thus, the fixed-effects model was used.

Table 2. Genotype distribution of VEGF gene polymorphisms in case and control groups.

Reference	SNP	Case								Control								HWE test	
		Total	1	2	1/1	1/2	2/2	TA	MF	Total	1	2	1/1	1/2	2/2	TA	MF	χ^2	P
Hsieh et al., 2004	rs833061 (T>C)	122	190	54	68	54	0	244	0.22	131	179	83	48	83	0	262	0.32	28.166	0.000
Bhanoori et al., 2005	rs833061 (T>C)	215	224	206	56	112	47	430	0.48	210	224	196	56	112	42	420	0.47	1.071	0.301
	rs2010963 (G>C)	215	351	79	140	71	4	430	0.18	210	305	115	113	79	18	420	0.27	0.613	0.434
Kim et al., 2005	rs833061 (T>C)	215	309	121	113	83	19	430	0.28	219	323	115	120	83	16	438	0.26	0.099	0.753
	rs2010963 (G>C)	215	241	189	76	89	50	430	0.44	219	264	174	74	116	29	438	0.40	2.463	0.117
Ikuhashi et al., 2007	rs833061 (T>C)	147	211	83	72	67	8	294	0.28	181	244	118	80	84	17	362	0.33	0.570	0.450
	rs2010963 (G>C)	146	172	120	48	76	22	292	0.41	181	206	156	56	94	31	362	0.43	0.627	0.428
	rs3025039 (C>T)	147	216	78	80	56	11	294	0.27	181	289	73	118	53	10	362	0.20	1.485	0.223
Gentilini et al., 2008	rs2010963 (G>C)	203	244	162	69	106	28	406	0.40	140	193	87	67	59	14	280	0.31	0.036	0.849
Kim et al., 2008	rs3025039 (C>T)	105	169	41	66	37	2	210	0.20	105	169	41	66	37	2	210	0.20	1.547	0.214
Zhao et al., 2008	rs699947 (A>C)	958	973	943	-	-	-	1916	0.49	959	951	967	236	479	244	1918	0.50	0.001	0.976
	rs833061 (T>C)	953	956	950	227	502	224	1906	0.50	947	931	963	218	495	234	1894	0.51	1.978	0.160
	rs2010963 (G>C)	949	1306	592	442	422	85	1898	0.31	946	1331	561	459	413	74	1892	0.30	2.044	0.153
	rs3025039 (C>T)	957	1612	302	674	264	19	1914	0.16	945	1615	275	691	233	21	1890	0.15	0.068	0.795
Cosín et al., 2009	rs833061 (T>C)	186	197	175	50	97	39	372	0.47	180	182	178	48	86	46	360	0.49	0.354	0.552
	rs2010963 (G>C)	186	245	127	77	91	18	372	0.34	180	248	112	84	80	16	360	0.31	0.245	0.621
	rs3025039 (C>T)	186	313	59	132	49	5	372	0.16	180	325	35	146	33	1	360	0.10	0.355	0.551
Kang et al., 2009	rs699947 (C>A)	174	280	68	114	52	8	348	0.20	199	288	110	109	70	20	398	0.28	2.893	0.089
	rs1570360 (G>A)	174	297	51	128	41	5	348	0.15	199	302	96	117	68	14	398	0.24	0.880	0.348
	rs833061 (T>C)	174	276	72	109	58	7	348	0.21	199	310	88	123	64	12	398	0.22	0.874	0.350
	rs3025039 (C>T)	174	276	72	109	58	7	348	0.21	199	336	62	140	56	3	398	0.16	0.972	0.324
Liu et al., 2009a	rs699947 (C>A)	344	556	132	223	110	11	688	0.19	360	531	189	200	131	29	720	0.26	1.304	0.254
	rs3025039 (C>T)	344	568	120	234	100	10	688	0.17	360	599	121	248	103	9	720	0.17	0.194	0.660
Liu et al., 2009b	rs833061 (T>C)	344	532	156	201	130	13	688	0.23	360	572	148	229	114	17	720	0.21	0.333	0.564
	rs1570360 (G>A)	344	577	111	239	99	6	688	0.16	360	560	160	221	118	21	720	0.22	0.965	0.326
Attar et al., 2010	rs833061 (T>C)	52	68	36	27	14	11	104	0.35	60	71	49	30	11	19	120	0.41	23.107	0.000
	rs2010963 (C>G)	52	74	30	29	16	7	104	0.29	60	72	48	21	30	9	120	0.40	0.104	0.747
Lamp et al., 2010	rs699947 (A>C)	150	188	112	56	76	18	300	0.37	199	210	188	61	88	50	398	0.47	2.535	0.111
	rs1570360 (G>A)	150	175	125	52	71	27	300	0.42	199	251	147	78	95	26	398	0.37	0.122	0.727
	rs2010963 (G>C)	150	241	59	94	53	3	300	0.20	199	293	105	108	77	14	398	0.26	0.003	0.956
	rs3025039 (C>T)	150	251	49	104	43	3	300	0.16	199	330	68	137	56	6	398	0.17	0.009	0.924
Altinkaya et al., 2011	rs833061 (T>C)	98	190	6	92	6	0	196	0.03	94	186	2	92	2	0	188	0.01	0.011	0.917
	rs2010963 (G>C)	98	89	107	16	57	25	196	0.55	94	10	178	0	10	84	188	0.95	0.297	0.586

SNP = single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; 1 = wild allele; 2 = mutant allele; TA = total alleles; MF = minor allele frequency.

The meta-analysis results showed that the C allele, the C allele carrier, and CC genotypes of the rs699947 (A>C) polymorphism of the VEGF gene were associated with decreased risk of endometriosis (OR = 0.74, 95%CI = 0.58-0.94, P = 0.01; OR = 0.68, 95%CI = 0.55-0.84, P < 0.05; OR = 0.40, 95%CI = 0.27-0.60, P < 0.05, respectively). However, no association between rs699947 and endometriosis risk was found for the AC genotype (OR = 0.92, 95%CI = 0.74-1.14, P = 0.43). Moreover, the A allele carrier and the GA genotype of the rs1570360 (G>A) polymorphism might also decrease the risk of endometriosis (OR = 0.74, 95%CI = 0.55-0.99, P = 0.04; OR = 0.81, 95%CI = 0.67-0.97, P = 0.02, respectively). We also found that the A allele and the AA genotype of rs1570360 had no connection with the risk of endometriosis (OR = 0.74, 95%CI = 0.54-1.03, P = 0.07; OR = 0.49, 95%CI = 0.19-1.24, P = 0.13, respectively). Interestingly, the results showed that there were positive associations among the T allele, the T allele carrier, and the CT genotype of the rs3025039 (C>T) polymorphism with endometriosis risk (OR = 1.16, 95%CI = 1.04-1.30, P = 0.01; OR = 1.19, 95%CI = 1.05-1.36, P < 0.05; OR = 1.18, 95%CI = 1.03-1.35, P = 0.02, respectively). However, there

was no evidence that the rs833061 (T>C) and rs2010963 (G>C) polymorphisms of the VEGF gene were associated with risk of endometriosis (P > 0.05).

Sensitivity analysis was performed by sequential omission of individual studies with various contrasts. However, the significance of the pooled OR in all individual analyses was not significantly influenced.

Publication bias

Publication bias was accessed based on the rs3025039, rs699947, and rs1570360 polymorphisms in the VEGF gene by Begger's funnel plot and the Egger linear regression test. All funnel plots appeared symmetrical (Table 3). The Egger test also showed that there was no statistical evidence of publication bias (Table 4).

Table 3. Evaluation of publication bias by the Egger linear regression test.

SNP	Coefficient	SE	*t*	P	95%CI
rs3025039 (C>T)					
T allele	1.151	1.248	0.920	0.399	-2.057, 4.358
CT + TT	0.906	1.125	0.810	0.457	-1.986, 3.798
rs699947 (A>C)					
C allele	-4.135	0.676	-6.110	0.026	-7.046, -1.225
AC + CC	0.378	1.567	0.240	0.849	-19.527, 20.283
rs1570360 (G>A)					
A allele	1.902	5.743	0.330	0.772	-22.811, 26.614
GA + AA	-1.843	3.428	-0.540	0.645	-16.591, 12.904

SE = standard error; 95%CI = 95% confidence interval.

Table 4. Meta-analysis of the association between VEGF gene polymorphisms and endometriosis risk.

Polymorphisms	Case	Control	OR (95%CI)	P	Effect model
	n/N	n/N			
rs699947 (A>C)					
C	1255/3252	1454/3434	0.74 (0.58, 0.94)	0.01	Fixed
AC	238/668	289/758	0.92 (0.74, 1.14)	0.43	
CC	37/668	99/758	0.40 (0.27, 0.60)	<0.05	
AC+CC	275/668	388/758	0.68 (0.55, 0.84)	<0.05	
rs833061 (T>C)					
C	2015/5700	2088/5882	0.97 (0.90, 1.06)	0.53	Fixed
TC	1253/2850	1248/2941	1.06 (0.95, 1.18)	0.29	
CC	381/2850	420/2941	0.90 (0.77, 1.05)	0.16	
TC+CC	1634/2850	1668/2941	1.01 (0.90, 1.13)	0.91	
rs1570360 (G>A)					
A	398/2024	563/2236	0.74 (0.54, 1.03)	0.07	Fixed
GA	310/1012	399/1118	0.81 (0.67, 0.97)	0.02	
AA	44/1012	82/1118	0.49 (0.19, 1.24)	0.13	
GA+AA	354/1012	481/1118	0.74 (0.55, 0.99)	0.04	
rs2010963 (G>C)					
C	1465/4428	1536/4458	0.75 (0.54, 1.04)	0.09	Fixed
GC	981/2214	958/2229	1.12 (0.79, 1.60)	0.52	
CC	242/2214	289/2229	0.60 (0.29, 1.23)	0.16	
GC+CC	1223/2214	1247/2229	0.90 (0.69, 1.18)	0.43	
rs3025039 (C>T)					
T	721/4126	675/4338	1.16 (1.04, 1.30)	0.01	Fixed
CT	607/2063	571/2169	1.18 (1.03, 1.35)	0.02	
TT	57/2063	52/2169	1.19 (0.81, 1.74)	0.37	
CT+TT	664/2063	623/2169	1.19 (1.05, 1.36)	<0.05	

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

DISCUSSION

Endometriosis (or adenomyosis) is a non-neoplastic condition characterized by the presence of ectopic endometrium in the myometrium with hyperplasia of the adjacent smooth muscle. In women, endometriosis can result in debilitating pelvic pain (both cyclical and non-cyclical) and abnormal uterine bleeding and is paradoxically associated with both multiparity and infertility (Matalliotakis et al., 2005). Endometriosis, the most common tumor in women, has a prevalence of 10% in the general population and 30-40% in infertile women (Viganò et al., 2004). The establishment of new blood supply in the human exfoliated endometrium requires vascular proliferation and differentiation. Of known angiogenic factors, VEGF has emerged as important for the pathogenesis of endometriosis. VEGF is believed to play a central role in angiogenesis through a variety of mechanisms, including its effects on endothelial cell proliferation, survival, and migration (Ferrara, 2004).

Regulation of human VEGF is extremely complex and is a determinant of the rate and extent of angiogenesis, which is crucial for endothelial mitogenesis (Hsieh et al., 2004). VEGF is a potent angiogenic factor that promotes neovascularization, an important phenomenon involved in the implantation of endometrial cells in ectopic sites (Vigano et al., 2004). Polymorphisms in the 5'-UTR lead to differences in VEGF expression between individuals (Bhanoori et al., 2005). Recent studies have demonstrated a possible association between the VEGF gene polymorphism and endometriosis, where angiogenesis may be critical in disease development. Hsieh et al. (2004) demonstrated a significant association between the -460 C/T polymorphism and susceptibility to endometriosis. Zhao et al. (2008) investigated the possible association between endometriosis and VEGF polymorphisms with a large Australian population sample and observed that these polymorphisms were not associated with the risk of endometriosis.

Given the controversial results in the published studies, we conducted a meta-analysis to explore the association between VEGF genetic polymorphisms and the risk of endometriosis. In this meta-analysis, which included a total of 3313 endometriosis cases and 3393 healthy controls and was based on 14 independent publications, we focused on the association of 5 polymorphisms in the VEGF gene with endometriosis risk. We demonstrated that the rs3025039 (C>T) polymorphism in the VEGF gene was associated with increased risk of endometriosis, while rs699947 (A>C) and rs1570360 (G>A) might decrease the risk of endometriosis. However, the rs833061 (T>C) and rs2010963 (G>C) polymorphisms of the VEGF gene did not appear to influence endometriosis susceptibility. In interpreting the meta-analysis results, some limitations need to be noted. First, although the funnel plot and the Egger test did not show publication bias, selection bias could have occurred because only studies published in English or Chinese were included. Second, the number of published studies was not sufficient for analysis of specific cancer types. Third, our meta-analysis was based on unadjusted OR estimates because not all published articles contained adjusted ORs, or when they did, the ORs were not adjusted by the same potential confounders, such as pathological types, age, gender, geographic distribution. Finally, although all cases and controls are defined with similar inclusion criteria, potential factors that influence the results are not considered.

In summary, our meta-analysis of 14 case-control studies demonstrated that the rs3025039 (C>T) polymorphism of the VEGF gene might increase the risk of endometriosis, but rs699947 (A>C) and rs1570360 (G>A) might be protective factors. It is of importance to perform large sample studies to elucidate the influence of these polymorphisms on the susceptibility to endometriosis.

Conflicts of interest

We declare that we have no conflicts of interest.

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