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Review Article

Genetic association between vascular endothelial growth factor polymorphisms and endometriosis risk: a meta-analysis of 24 case-control studies

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Abstract: Many studies have investigated the association between vascular endothelial growth factor (VEGF) polymorphisms (-460C/T, +405G/C, +936T/C and -2578C>A) and endometriosis risk in various populations with inconsistent results. A systematic search in PubMed, Embase, ISI Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases were conducted up to February 1, 2017. Odds ratio (OR) and 95% confidence interval (CI) were used to pool the effect size. A funnel plot and Egger test were used to evaluate publication bias, and I^2 was applied to assess heterogeneity. Comprehensive meta-analysis of 24 case-control studies included 12,759 subjects (6,310 cases and 6,499 controls). The overall results suggest no significant association between -460C/T, +405G/C, +936T/C, and -2578C>A polymorphisms and endometriosis risk. However, -2578C>A polymorphism could confer an increased risk for endometriosis development in Asian populations. The +936T/C polymorphism could show significantly increased risk for endometriosis in stage III-IV, but not in stage I-II. Nevertheless, such association lost statistical significance after applying the Bonferroni correction for multiple testing. In summary, this meta-analysis suggests that the -2578C>A polymorphism is capable of causing endometriosis susceptibility in the Asian population.

Keywords: Vascular endothelial growth factor, polymorphism, endometriosis, meta-analysis

Introduction

Characterized by growth of hormonally responsive and endometrial-like tissue outside the uterine cavity resulting in pelvic pain and subfertility, endometriosis is a common gynecological and benign disorder [1, 2]. It is estimated that the prevalence of endometriosis is approximately 3-10% among females of reproductive age, and this disorder may be responsible for infertility in 30-50% of females [3-5]. Although the mechanism underlying this disease has not been completely clarified, there is abundant evidence that endometrial angiogenesis plays a key role in the tissue survival of ectopic endometrial implants, which is promoted by numerous inducers and growth factors, especially vascular endothelial growth factor (VEGF) [6, 7].

VEGF serves as a heparin-binding glycoprotein with endothelial cell-specific mitogenic and potent angiogenic activities. It is part of the biological system to regulate endometrial angiogenesis [6, 8, 9]. VEGF is encoded by the VEGF gene, which is located on Chromosome 6p21.3 and consists of eight exons with alternate splicing [6, 10, 11]. Several transcription factor-binding sites are identified in the VEGF 5'-untranslated region (UTR) [4, 8]. Single nucleotide polymorphisms (SNPs) within the region may increase the transcriptional activity and thereby affect enzyme activity or expression, which may have substantial effects on the process of VEGF-induced angiogenesis in the pathogenesis of endometriosis [1, 11, 12].

Many studies have investigated association of VEGF genetic polymorphisms and endometriosis risk in diverse populations. However, these studies have led to different conclusions. For instance, Perini et al. reported that *VEGF* -2578C>A, -460T>C, +405G>C may have a protective effect on the development of endome-

Table 1. Characteristics of 24 included studies in this meta-analysis

Author	Year	Ethnicity	Country	Cases/ Control	Sample size	Control source	Genotyping method	Diagnose	Quality score
Cardoso et al.	2017	Caucasian	Brazil	291/216	507	HB	TaqMan	Laparoscopy (ASPM)	8
Vodolazkaia et al.	2016	Caucasian	Belgium	1095/819	1914	HB	TaqMan	Laparoscopy (ASPM)	7
Henidi et al.	2015	Caucasian	Tunisia	105/150	255	HB	PCR-RFLP	Laparoscopy (ASPM)	8
Perini et al.	2015	Caucasian	Brazil	181/110	291	HB	TaqMan	Laparoscopy (AFSC)	7
Szczepanska et al.	2015	Caucasian	Poland	153/384	537	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Vanaja et al.	2013	Asian	India	302/324	626	HB	PCR-RFLP	Laparoscopy (ASPM)	8
Saliminejad et al.	2013	Caucasian	Iran	135/173	308	HB	PCR-RFLP	Laparoscopy (ASPM)	6
Emamifar et al.	2012	Caucasian	Iran	480/600	1080	PB	PCR-RFLP	Laparoscopy (ASPM)	7
Liu et al.	2012	Asian	China	116/116	232	HB	PCR-RFLP	Laparoscopy	7
Altinkaya et al.	2011	Caucasian	Turkey	98/94	192	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Attar et al.	2010	Caucasian	Turkey	52/60	112	PB	PCR-RFLP	Laparoscopy (ASPM)	8
Toktam et al.	2010	Caucasian	Iran	150/144	294	HB	PCR-RFLP	Laparoscopy	6
Lamp et al.	2010	Caucasian	Estonia	150/199	349	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Liu (B) et al.	2009	Asian	China	344/360	704	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Kang et al.	2009	Asian	China	174/199	373	HB	PCR-RFLP	Laparoscopy	6
Liu (A) et al.	2009	Asian	China	334/360	704	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Cosín et al.	2009	Caucasian	Spain	186/180	366	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Gentilini et al.	2008	Caucasian	Italy	203/140	343	HB	PCR-RFLP	Laparoscopy (ASPM)	7
Ikuhashi et al.	2008	Asian	Japan	147/181	328	PB	PCR-RFLP	Laparoscopy (ASPM)	7
Zhao et al.	2008	Caucasian	Australia	957/945	1902	PB	MassArray	Laparoscopy (AFSC)	8
Kim et al.	2008	Asian	Korea	105/105	210	HB	PCR-RFLP	Laparoscopy	7
Kim et al	2005	Asian	Korea	215/289	504	HB	PCR-RFLP	Laparoscopy	6
Bhanoori et al.	2005	Asian	India	215/210	425	PB	PCR-RFLP	Laparoscopy (AFSC)	7
Hsieh et al.	2004	Asian	China	122/131	253	HB	PCR-RFLP	Laparoscopy	7

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HB, hospital-based study; PB, population-based study; ASPM, American Society of Reproductive Medicine.

Table 2. Distributions of VEGF -460C/T, +405G/C, +936T/C and -2578C>A polymorphism allele and genotypes in different groups

Author	Case					Control					HWE
-460C/T (rs833061)	CC	CT	TT	C (%)	T (%)	CC	CT	TT	C (%)	T (%)	
Szczepanska et al.	48	68	38	164 (53.2)	144 (46.8)	96	197	92	389 (50.5)	381 (49.5)	0.64
Henidi et al.	15	53	37	83 (39.5)	127 (60.5)	29	67	54	125 (41.7)	175 (58.3)	0.32
Perini et al.	28	97	54	153 (42.7)	205 (57.3)	17	51	39	85 (39.7)	129 (60.3)	0.96
Emamifar et al.	65	187	228	317 (33)	643 (67)	72	228	300	372 (31)	828 (69)	0.01
Altinkaya et al.	0	6	92	6 (3.1)	190 (96.9)	0	2	92	2 (1.1)	186 (98.9)	0.92
Attar et al.	11	14	27	36 (34.6)	68 (65.4)	19	11	30	49 (40.8)	71 (59.2)	0.001
Liu (A) et al.	13	130	201	156 (22.7)	532 (77.3)	17	114	229	148 (20.6)	572 (79.4)	0.97
Kang et al.	7	58	109	72 (20.7)	276 (79.3)	12	64	123	88 (22.1)	310 (77.9)	0.35
Cosín et al.	39	97	50	175 (47)	197 (53)	46	86	48	178 (49.4)	182 (50.6)	0.55
Zhao et al.	225	502	227	952 (49.9)	956 (50.1)	234	495	218	963 (50.8)	931 (49.2)	0.16
Ikuhashi et al.	8	67	72	83 (28.2)	211 (71.8)	17	84	80	118 (32.6)	244 (67.4)	0.45
Kim et al	19	83	113	121 (28.1)	309 (71.9)	22	110	157	154 (26.6)	424 (73.4)	0.66
Bhanoori et al.	47	112	56	206 (47.9)	224 (52.1)	42	112	56	196 (46.7)	224 (53.3)	0.3
Hsieh et al.	0	54	68	54 (22.1)	190 (77.9)	0	83	48	83 (31.7)	179 (68.3)	0.001
+405G/C (rs2010963)	GG	GC	CC	G (%)	C (%)	GG	GC	CC	G (%)	C (%)	
Cardoso et al.	140	121	30	401 (68.9)	181 (31.1)	76	113	27	265 (61.3)	167 (38.7)	0.13
Vodolazkaia et al.	495	472	128	1462 (66.8)	728 (33.2)	394	321	104	1109 (67.7)	529 (32.3)	0.002
Szczepanska et al.	84	60	10	228 (74)	80 (26)	200	155	29	555 (72.3)	213 (27.7)	0.89
Henidi et al.	37	44	24	118 (56.2)	92 (43.8)	61	68	21	190 (63.3)	110 (36.7)	0.23

Perini et al.	83	75	23	241 (66.6)	121 (33.4)	38	56	16	132 (60)	88 (40)	0.53
Vanaja et al.	178	101	23	457 (75.7)	147 (24.3)	134	167	23	435 (67.1)	213 (32.9)	0.003
Saliminejad et al.	55	57	23	167 (61.9)	103 (38.1)	60	86	27	206 (59.5)	140 (40.5)	0.68
Emamifar et al.	97	230	153	424 (44.2)	536 (55.8)	258	276	66	792 (66)	408 (34)	0.54
Altinkaya et al.	16	57	25	89 (45.4)	107 (54.6)	0	10	84	10 (5.3)	178 (94.7)	0.59
Toktam et al.	48	80	22	176 (58.7)	124 (41.3)	83	48	13	214 (74.3)	74 (25.7)	0.13
Lamp et al.	94	53	3	241 (80.3)	59 (19.7)	108	77	14	293 (73.6)	105 (26.4)	0.96
Attar et al.	7	16	29	30 (28.8)	74 (71.2)	9	30	21	48 (40)	72 (60)	0.75
Cosín et al.	77	91	18	245 (65.9)	127 (34.1)	84	80	16	248 (68.9)	112 (31.1)	0.62
Zhao et al.	442	422	85	1306 (68.8)	592 (31.2)	459	413	74	1331 (70.3)	561 (29.7)	0.15
Gentilini et al.	69	106	28	244 (60.1)	162 (39.9)	67	59	14	193 (68.9)	87 (31.1)	0.85
Ikuhashi et al.	48	76	22	172 (58.9)	120 (41.1)	56	94	31	206 (56.9)	156 (43.1)	0.43
Kim et al	76	89	50	241 (56)	189 (44)	96	157	36	349 (60.4)	229 (39.6)	0.02
Bhanoori et al.	140	71	4	351 (81.6)	79 (18.4)	113	79	18	305 (72.6)	115 (27.4)	0.43
+936T/C (rs3025039)	TT	TC	CC	T (%)	C (%)	TT	TC	CC	T (%)	C (%)	
Vodolazkaia et al.	21	267	821	309 (13.9)	1909 (86.1)	17	196	608	230 (14)	1412 (86)	0.8
Szczepanska et al.	4	33	116	41 (13.4)	265 (86.6)	8	114	262	130 (16.9)	638 (83.1)	0.28
Henidi et al.	10	33	62	53 (25.2)	157 (74.8)	7	26	117	40 (13.3)	260 (86.7)	0.002
Perini et al.	4	41	120	49 (14.8)	281 (85.2)	1	27	67	29 (15.3)	161 (84.7)	0.34
Liu et al.	1	10	105	12 (5.2)	220 (94.8)	8	30	78	46 (19.8)	186 (80.2)	0.04
Lamp et al.	3	43	104	49 (16.3)	251 (83.7)	6	56	137	68 (17.1)	330 (82.9)	0.92
Liu (B) et al.	10	100	234	120 (17.4)	568 (82.6)	9	103	248	121 (16.8)	599 (83.2)	0.66
Kang et al.	7	58	109	72 (20.7)	276 (79.3)	3	56	140	62 (15.6)	336 (84.4)	0.32
Cosín et al.	5	49	132	59 (15.9)	313 (84.1)	1	33	146	35 (9.7)	325 (90.3)	0.55
Zhao et al.	19	264	674	302 (15.8)	1612 (84.2)	21	233	691	275 (14.6)	1615 (85.4)	0.79
Kim et al.	2	37	66	41 (19.5)	169 (80.5)	2	37	66	41 (19.5)	169 (80.5)	0.21
Ikuhashi et al.	11	56	80	78 (26.5)	216 (73.5)	10	53	118	73 (20.2)	289 (79.8)	0.22
-2578C>A (rs699947)	CC	CA	AA	C (%)	A (%)	CC	CA	AA	C (%)	A (%)	
Cardoso et al.	98	149	41	345 (59.9)	231 (40.1)	101	95	22	297 (68.1)	139 (31.9)	0.96
Vodolazkaia et al.	278	512	281	1068 (49.9)	1074 (50.1)	208	381	222	797 (49.1)	825 (50.9)	0.09
Perini et al.	61	90	27	212 (59.6)	144 (40.4)	50	47	14	147 (66.2)	75 (33.8)	0.57
Lamp et al.	18	76	56	112 (37.3)	188 (62.7)	50	88	61	188 (47.2)	210 (52.8)	0.11
Liu (B) et al.	223	110	11	556 (80.8)	132 (19.2)	200	131	29	531 (73.8)	189 (26.3)	0.25
Kang et al.	114	52	8	280 (80.5)	68 (19.5)	109	70	20	288 (72.4)	110 (27.6)	0.09

HWE, Hardy-Weinberg equilibrium.

triosis [13]. However, Hsieh et al. reported that the -460T allele may increase endometriosis risk [14]. Henidi et al. reported that VEGF +936 C/T polymorphism may be a risk factor for endometriosis [15].

To date, some previous meta-analyses based on different strategies tried to investigate the relationship of these polymorphisms and endometriosis risk with no conclusive results [16-18]. Jiang et al. reported that an increased risk of endometriosis with the variant allele of +405G/C or +936T/C [18]. Nevertheless, a recent meta-analysis by Fang et al. showed that VEGF +405G/C was not associated with the risk of endometriosis [16]. Unfortunately, these previous meta-analyses included some studies, in which the genotype distributions of controls did not follow Hardy-Weinberg equilibrium (HWE). Moreover, high heterogeneity was identified in any genetic model, but they only performed subgroup analysis based on ethnicity to investigate the origin of the high heterogeneity [16, 18]. Furthermore, no test was conducted to access statistical significance of multiple null hypotheses, such as Benjamini-Hochberg false discovery rate test. Henceforth, some new studies were performed to investigate the link between these polymorphisms and endometriosis risk on multiple ethnic populations [1, 5, 13, 15, 19-22]. However, the results remain inconclusive. Therefore, the data need to be updated and more reliable association of the polymorphisms with the risk of endometriosis are warranted.

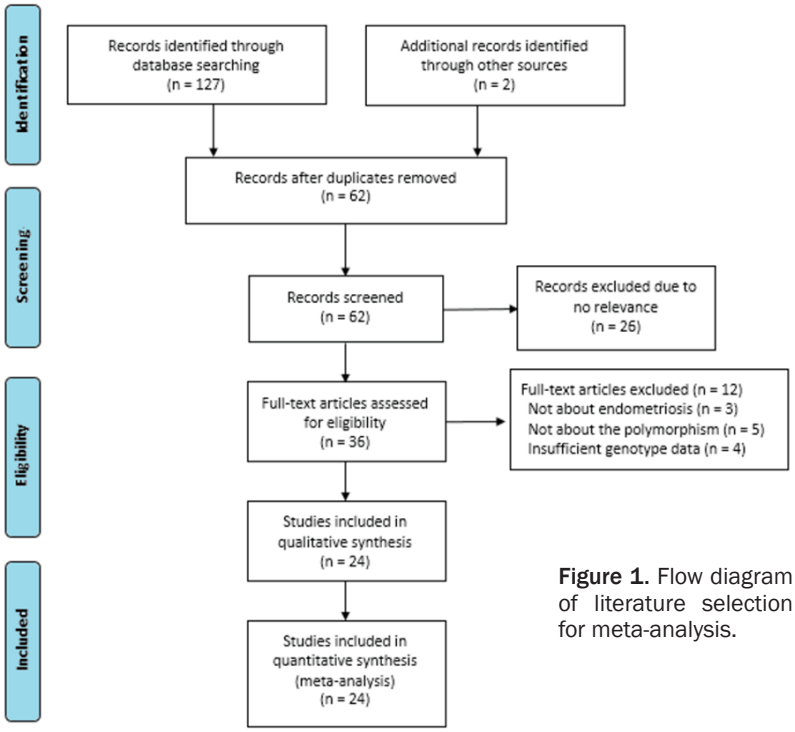

Figure 1. Flow diagram of literature selection for meta-analysis.

Due to the critical role of these polymorphisms in the pathogenesis of cancer and the inconsistency of previous meta-analysis, an updated meta-analysis was performed to evaluate association between -460C/T, +405G/C, +936T/C and -2578C>A in *VEGF* gene and endometriosis risk.

Materials and methods

The PRISMA protocol was prospectively conducted. Because we analyzed existing articles and did not need to handle individual patient data in this study and thus ethical approval was not deemed necessary.

Study selection

PubMed, Embase, ISI Web of Science, and the Chinese National Knowledge Infrastructure (CNKI) databases were systematically searched by two independent reviewers to identify relevant studies from inception to February 1, 2017, using the following search terms: 'vascular endothelial growth factor' or '*VEGF*' and 'vascular permeability factor' AND 'endometriosis' or 'endometrioses' AND 'polymorphism' or 'variant' or 'mutation' or 'polymorphisms' or 'variants' or 'mutations'. No publication date or languages restrictions were imposed. The inclusion criteria comprised of the following: (1) A case-control design; (2) Investigating the association between -460C/T (rs833061), +405G/C (rs2010963), +936T/C (rs3025039) and -2578C>A (rs699947) polymorphisms in *VEGF* gene and endometriosis risk; (3) Genotype distributions should be available for estimating the odds ratio with 95% confidence interval. Exclusion criteria: (1) Duplicative or overlapping publications; (2) Study with incomplete data; (3) Abstracts, conferences, letters, case reports or non-human studies. For multiple studies based on the same case series, only the study with the largest number of subjects were retained. The inspection of the references list of review or previous meta-analyses was performed for potentially relevant publications by two independent investigators.

Data extraction

To avoid errors in the pooled analysis, two independent investigators collected information for each included study. Items collected included author, publication date, country, ethnicity, control source, genotyping technology, genotype distributions, sample size, and diagnosis. Discrepancies were resolved by consensus. The information is shown in **Tables 1** and **2**.

Quality score assessment

The quality of each eligible study was evaluated based on Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The scale use a '-' rating system to evaluate quality by three points, including the selection of the study groups, comparability of the groups, and the ascertainment of the exposure or outcome of interest in the case-control study [23]. The total scores ranged 0-9. A study with scores of more than 7 points was regarded as a high-quality study (**Table 1**). Any disagreement was settled by discussion among the research team.

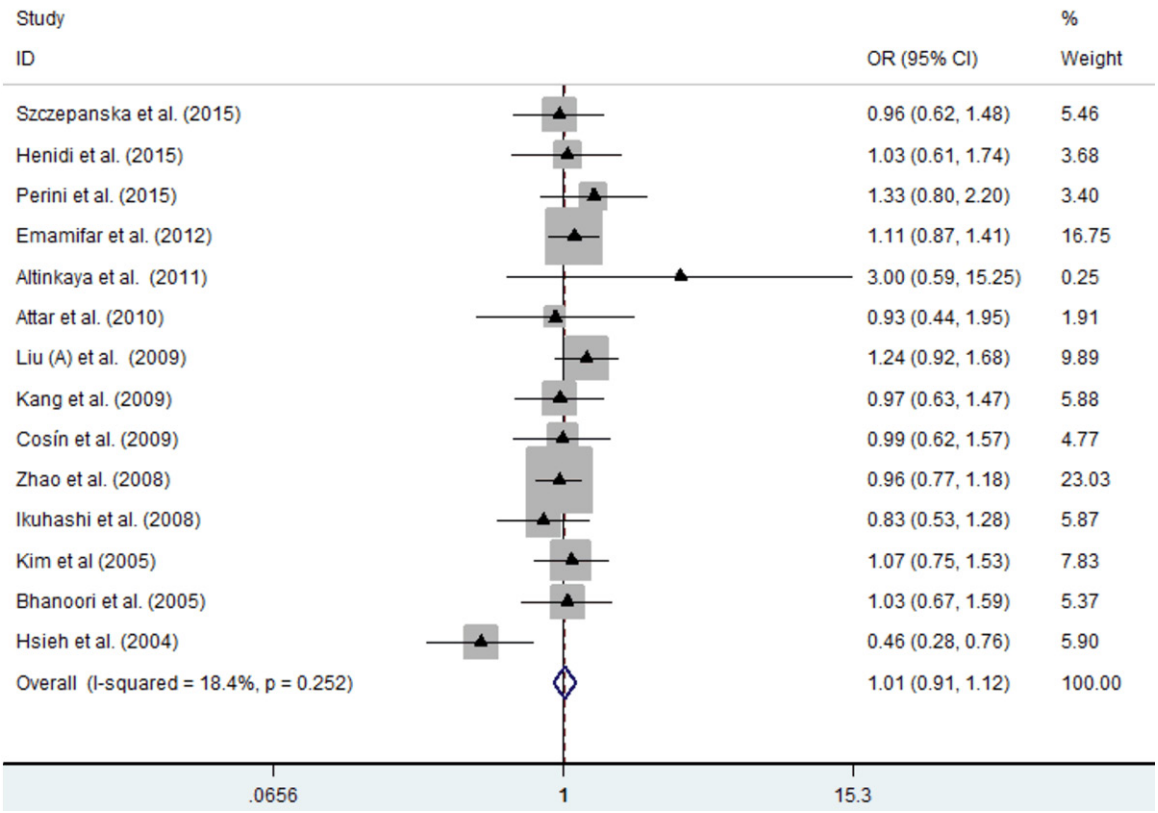

Figure 2. Forest plot of endometriosis risk associated with VEGF -460C/T polymorphism in dominant model (CC+CT vs. TT) for the overall population.

Statistical method

All data analysis was performed with STATA 12.0 software (Stata Corp LP, College Station, TX). All of the data were calculated as odds ratio (OR) with 95% confidence interval (CI) to evaluate the effectiveness of the association between *VEGF* polymorphisms and the risk of endometriosis. Heterogeneity was examined by Chi-squared-based Q-test and I^2 statistics and *P*-value < 0.10 was taken to indicate significance. The pooled OR was computed by the fixed-effects model (FEM) if no or low heterogeneity existed (P < 0.10). Otherwise, the random-effects model (REM) is preferred. Before this meta-analysis was performed, Hardy-Weinberg equilibrium (HWE) was recalculated using genotype data of the control groups by Pearson's Chi-square test. Stratification based on ethnicity (Asian and Caucasian), control source (hospital-based (HB) and population-based (PB) population) and disease stage (I-II and III-IV) was employed for group-wise analyses to investigate the potential origin of heterogeneity. In addition, sensitivity analyses were also performed by sequentially excluding individual studies to evaluate the stability of the results.

Potential publication bias was tested by Egger' linear regression and Begg's test, and P < 0.05 was considered to indicate statistically significant publication bias. Visual inspection of asymmetry in funnel plots was carried out to detect publication bias. Moreover, Benjamini-Hochberg false discovery rate (FDR) test was utilized to correct for multiple comparisons. When P_{corr} value < 0.05, FDR was considered to be significant.

Results

Study characteristics

In total, 129 articles complied with our search strategy. After removing duplications, scanning titles and abstracts and reading the full-text, a total of 24 case-control studies following our strict inclusion-exclusion criteria were eligible in this meta-analysis, which contained 12,759

Table 3. Summary of overall results and subgroup for the association between the VEGF -460C/T, +405G/C, +936T/C and -2578C>A polymorphism and endometriosis risk

	No.	Sample size (N)		OR (95% CI)	P_{OR}[a]	OR (95% CI)	P_{OR}[a]	OR (95% CI)	P_{OR}[a]	OR (95% CI)	P_{OR}[a]	OR (95% CI)	P_{OR}[a]
		Case	Control										
-460C/T (rs833061)				CC+CT vs. TT		CC vs. CT+TT		CC vs. TT		CT vs. TT		C vs. T	
Overall	14	3425	3893	1.01 (0.91-1.12)	0.87	0.97 (0.88-1.08)	0.59	0.98 (0.90-1.07)	0.69	1.01 (0.96-1.06)	0.68	0.99 (0.96-1.04)	0.86
HWE*	11	2771	3120	1.01 (0.97-1.04)	0.59	0.96 (0.86-1.08)	0.5	0.97 (0.88-1.06)	0.5	1.02 (0.97-1.07)	0.39	1.00 (0.93-1.08)	0.99
Control source													
PB	5	1848	1998	0.99 (0.97-1.04)	0.96	0.97 (0.85-1.10)	0.66	0.98 (0.88-1.09)	0.7	1.00 (0.95-1.06)	0.9	0.99 (0.94-1.04)	0.77
HB	9	1577	1895	1.00 (0.95-1.07)	0.77	0.97 (0.81-1.16)	0.76	0.99 (0.84-1.16)	0.86	1.02 (0.94-1.09)	0.64	1.00 (0.94-1.07)	0.94
Ethnicity													
Caucasian	8	2028	2523	1.01 (0.97-1.05)	0.6	0.98 (0.87-1.09)	0.72	0.99 (0.90-1.09)	0.85	1.02 (0.97-1.08)	0.48	1.00 (0.96-1.05)	0.89
Asian	6	1217	1370	0.99 (0.91-1.06)	0.7	0.94 (0.72-1.21)	0.63	0.94 (0.74-1.20)	0.62	0.99 (0.91-1.08)	0.84	0.98 (0.90-1.07)	0.62
Disease stage													
I-II	6	619	1265	1.08 (0.88-1.34)	0.44	0.95 (0.70-1.28)	0.73	1.02 (0.74-1.41)	0.91	1.11 (0.88-1.38)	0.38	1.03 (0.88-1.20)	0.69
III-IV	9	1345	1655	0.99 (0.85-1.15)	0.88	0.88 (0.69-1.12)	0.29	0.90 (0.69-1.19)	0.46	1.02 (0.87-1.20)	0.82	0.96 (0.86-1.08)	0.54
+405G/C (rs2010963)				GG+GC vs. CC		GG vs. GC+CC		GG vs. CC		GC vs. CC		G vs. C	
Overall	18	5107	5219	1.05 (0.71-1.56)	0.81	1.05 (0.71-1.56)	0.98	0.97 (0.65-1.45)	0.87	1.01 (0.71-1.46)	0.94	1.05 (0.84-1.32)	0.66
HWE*	15	3495	3787	1.14 (0.69-1.89)	0.61	0.96 (0.71-1.29)	0.77	1.02 (0.61-1.71)	0.95	1.13 (0.72-1.76)	0.61	1.06 (0.79-1.41)	0.69
Control source													
PB	5	1842	1997	0.82 (0.37-1.80)	0.61	0.85 (0.48-1.53)	0.59	0.83 (0.29-2.39)	0.73	0.81 (0.42-1.56)	0.53	0.84 (0.51-1.39)	0.51
HB	13	3265	3222	1.16 (0.76-1.81)	0.51	1.06 (0.82-1.39)	0.63	0.99 (0.71-1.39)	0.98	1.11 (0.71-1.72)	0.65	1.14 (0.89-1.45)	0.29
Ethnicity													
Caucasian	14	4229	4215	1.03 (0.65-1.65)	0.9	0.90 (0.68-1.19)	0.45	0.88 (0.55-1.41)	0.59	1.05 (0.69-1.59)	0.84	1.01 (0.77-1.31)	0.96
Asian	4	878	1004	1.12 (0.52-2.41)	0.77	1.05 (0.71-1.56)	0.024	1.35 (0.63-2.88)	0.45	0.92 (0.42-2.02)	0.84	1.23 (0.89-1.69)	0.21
Disease stage													
I-II	8	1339	2408	0.95 (0.42-2.15)	0.91	0.99 (0.54-1.85)	0.99	0.89 (0.35-2.24)	0.79	0.91 (0.44-1.90)	0.8	1.09 (0.65-1.84)	0.74
III-IV	9	1538	2037	1.29 (0.64-2.58)	0.48	1.16 (0.89-1.49)	0.27	1.09 (0.67-1.78)	0.72	1.17 (0.58-2.36)	0.66	1.24 (0.89-1.73)	0.2
+936T/C (rs3025039)				TT+TC vs. CC		TT vs. TC+CC		TT vs. CC		TC vs. CC		T vs. C	
Overall	12	3711	3735	1.07 (0.86-1.34)	0.53	1.11 (0.83-1.48)	0.49	1.15 (0.86-1.53)	0.36	1.07 (0.87-1.31)	0.54	1.07 (0.88-1.31)	0.51
HWE*	10	3490	3469	1.09 (0.95-1.28)	0.2	1.14 (0.83-1.56)	0.41	1.18 (0.86-1.61)	0.31	1.09 (0.94-1.25)	0.25	1.09 (0.97-1.24)	0.16
Control source													
PB	2	1104	1126	1.07 (0.97-1.19)	0.11	1.13 (0.62-1.72)	0.9	1.11 (0.67-1.86)	0.69	1.24 (0.98-1.58)	0.08	1.19 (0.94-1.51)	0.15
HB	10	2607	2609	1.02 (0.77-1.34)	0.9	1.15 (0.81-1.64)	0.45	1.16 (0.82-1.65)	0.41	1.01 (0.78-1.30)	0.95	1.03 (0.79-1.33)	0.85
Ethnicity													
Caucasian	7	2825	2774	1.13 (0.89-1.44)	0.31	1.12 (0.79-1.61)	0.52	1.16 (0.81-1.67)	0.41	1.11 (0.88-1.40)	0.38	1.13 (0.92-1.40)	0.25
Asian	5	886	961	0.93 (0.56-1.53)	0.77	1.08 (0.65-1.78)	0.77	1.11 (0.67-1.83)	0.69	0.95 (0.61-1.49)	0.83	0.92 (0.58-1.46)	0.71
Disease stage													
I-II	4	714	1332	1.29 (0.85-1.95)	0.23	0.90 (0.48-1.71)	0.75	0.95 (0.50-1.81)	0.884	1.37 (0.88-2.15)	0.16	1.16 (0.83-1.62)	0.38
III-IV	5	1160	1692	1.44 (1.02-2.05)	0.039	1.58 (1.03-2.44)	0.038	1.71 (1.10-2.64)	0.016	1.32 (0.98-1.78)	0.06	1.45 (1.04-2.04)	0.031
-2578C>A (rs699947)				CC+CA vs. AA		CC vs. CA+AA		CC vs. AA		CA vs. AA		C vs. A	
Overall	6	2205	1898	1.09 (0.76-1.57)	0.65	0.88 (0.61-1.26)	0.47	0.98 (0.56-1.71)	0.94	1.09 (0.92-1.30)	0.33	0.98 (0.75-1.27)	0.85
Ethnicity													
Caucasian	4	1687	1339	0.90 (0.71-1.13)	0.52	0.66 (0.44-0.99)	0.04	0.64 (0.38-1.01)	0.092	1.01 (0.85-1.22)	0.88	0.79 (0.62-1.02)	0.071
Asian	2	518	559	2.51 (1.46-4.32)	0.001	1.51 (1.19-1.93)	0.001	2.8 (1.61-4.87)	0.0001	2.06 (1.17-3.65)	0.013	1.52 (1.24-1.87)	0.0001
Disease stage													
III-IV	2	810	1171	1.54 (0.61-3.93)	0.36	1.18 (0.78-1.79)	0.44	1.62 (0.55-4.72)	0.38	1.39 (0.68-2.89)	0.37	1.21 (0.80-1.81)	0.37

OR, odds ratio; CI, confidence interval. *P* values in bold denotes significance. [a]The *P* values of Z test for odds ratios test. *The studies comply with Hardy-Weinberg equilibrium (HWE).

Table 4. Summary of the corrected *P* value for multiple testing and heterogeneity test in this meta-analysis

	No.	P_{Corr} [a]	I^2 (%)	P_{Het} [b]	P_{Corr} [a]	I^2 (%)	P_{Het} [b]	P_{Corr} [a]	I^2 (%)	P_{Het} [b]	P_{Corr} [a]	I^2 (%)	P_{Het} [b]	P_{Corr} [a]	I^2 (%)	P_{Het} [b]
-460C/T (rs833061)		CC+CT vs. TT			CC vs. CT+TT			CC vs. TT			CT vs. TT			C vs. T		
Overall	14	0.87	18.4	0.28	1.00	0	0.53	1.00	0	0.8	1.00	21.9	0.22	1.00	9.9	0.34
HWE*	11	0.74	0	0.79	0.83	0	0.55	1.00	0	0.81	1.00	0	0.73	0.99	0	0.74
Control source																
PB	5	0.96	0	0.8	1.00	4.2	0.38	1.00	0	0.41	1.00	0	0.88	1.00	0	0.45
HB	9	0.96	42	0.08	1.00	0	0.44	1.00	0	0.81	1.00	48	0.05	0.94	25	0.22
Ethnicity																
Caucasian	8	1.00	0	0.79	1.00	10.8	0.34	1.00	0	0.71	1.00	0	0.68	0.89	0	0.56
Asian	6	0.87	56.3	0.04	1.00	0	0.52	1.00	0	0.51	0.84	56	0.04	1.00	41	0.13
Disease stage																
I-II	6	1.00	0	0.71	0.91	12.9	0.33	0.91	0	0.54	1.00	0	0.67	1.00	0	0.47
III-IV	9	0.88	45	0.072	1.00	0	0.59	1.00	0	0.7	1.00	48	0.05	1.00	27	0.19
+405G/C (rs2010963)		GG+GC vs. CC			GG vs. GC+CC			GG vs. CC			GC vs. CC			G vs. C		
Overall	18	1.00	89	0.0001	0.98	87	0.0001	1.00	87	0.0001	1.00	85	0.0001	1.00	92	0.0001
HWE*	15	1.00	78	0.009	0.96	80	0.008	0.95	60	0.082	1.00	80	0.0001	1.00	84	0.0001
Control source																
PB	5	0.76	92	0.0001	0.98	92	0.0001	0.73	69	0.0001	1.00	86	0.0001	1.00	95	0.0001
HB	13	1.00	85	0.0001	1.00	82	0.0001	0.98	90	0.0001	0.81	83	0.0001	1.00	89	0.0001
Ethnicity																
Caucasian	14	1.00	90	0.0001	1.00	87	0.0001	1.00	82	0.0001	1.00	86	0.0001	0.96	93	0.0001
Asian	4	0.96	82	0.001	0.12	62	0.044	0.75	79	0.002	0.84	80	0.001	0.5	81	0.001
Disease stage																
I-II	8	1.00	91	0.0001	0.99	90	0.0001	1.00	91	0.0001	1.00	88	0.0001	1.00	90	0.0001
III-IV	9	0.8	90	0.0001	0.68	61	0.008	0.72	72	0.0001	0.83	89	0.0001	1.00	89	0.0001
+936T/C (rs3025039)		TT+TC vs. CC			TT vs. TC+CC			TT vs. CC			TC vs. CC			T vs. C		
Overall	12	0.66	73	0.0001	1.00	6.1	0.38	1.00	24	0.2	0.54	67	0.0001	0.85	75	0.0001
HWE*	10	0.5	35	0.13	0.41	0	0.77	0.39	0	0.7	0.42	28	0.18	0.8	34	0.14
Control source																
PB	2	0.28	36	0.203	0.9	0	0.43	0.86	0	0.32	0.4	20	0.26	0.25	37	0.21
HB	10	1.00	76	0.0001	1.00	17	0.28	1.00	33	0.14	0.95	61	0.0001	1.00	72	0.0001
Ethnicity																
Caucasian	7	0.78	67	0.006	0.52	0	0.49	0.51	9	0.36	0.63	62	0.014	1.00	62	0.005
Asian	5	0.96	82	0.0001	1.00	37	0.17	1.00	50	0.09	0.83	76	0.002	1.00	82	0.0001
Disease stage																
I-II	4	0.58	44	0.15	0.94	0	0.78	0.88	0	0.82	0.8	42	0.12	0.63	36	0.19
III-IV	5	0.05	72	0.006	0.06	32	0.21	0.08	48	0.11	0.06	57	0.05	0.08	78	0.001
-2578C>A (rs699947)		CC+CA vs. AA			CC vs. CA+AA			CC vs. AA			CA vs. AA			C vs. A		
Overall	6	1.00	67	0.01	1.00	83	0.0001	0.94	81	0.0001	1.00	18	0.29	1.00	85	0.0001
Ethnicity																
Caucasian	4	0.65	23	0.27	0.04	77	0.0001	0.15	74	0.009	0.88	0	0.88	0.18	76	0.006
Asian	2	0.001	0	0.81	0.002	0	0.81	0.0003	0	0.84	0.013	0	0.77	0.0005	0	0.83
Disease stage																
III-IV	2	1.00	83	0.013	0.44	77	0.04	0.48	87	0.006	0.61	72	0.06	0.93	86	0.007

P values in bold denotes significance. [a]*P* Values were corrected to adjust for multiple testing. [b]*P* value of the Q-test for heterogeneity test. *The studies comply with Hardy-Weinberg equilibrium (HWE).

subjects (6,310 cases and 6,499 controls) [1, 5, 13, 15, 19-22, 24-29] (**Figure 1**). Of the 24 included studies, ten studies involving 4359 subjects reported on Asians and fourteen studies on Caucasians. As for control source, 5 studies employed PB control, while 19 studies applied HB control. Moreover, the estimated quality of each included study ranged from 6 to 8 points. The main characteristics of the included studies are shown in **Tables 1** and **2**. All the cases involved in these studies were histologically confirmed. In addition, the controls were

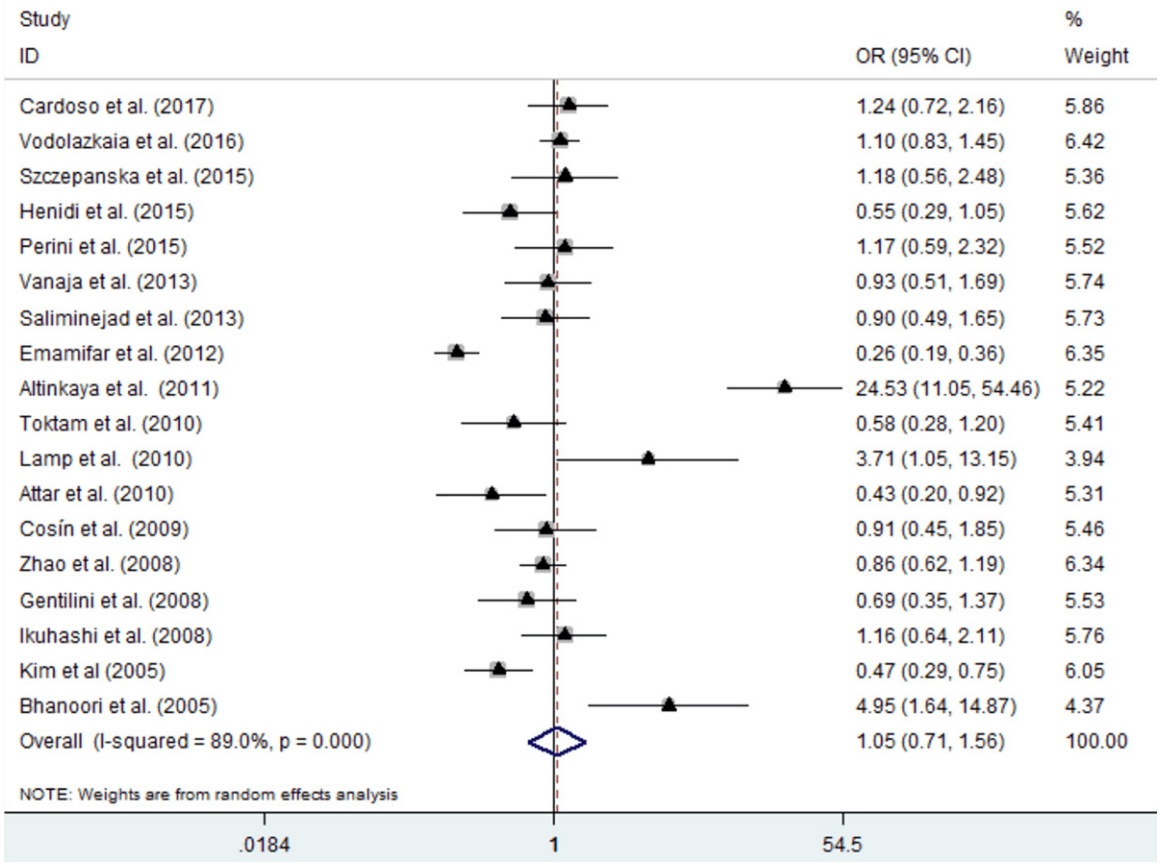

Figure 3. Forest plot of endometriosis risk associated with VEGF +405G/C polymorphism in dominant model (GG+GC vs. CC) for the overall population.

laparoscopically confirmed absence of endometriosis.

Association of -460C/T (rs833061) and endometriosis meta-analysis

All 7,318 participants from 14 case-control studies were involved in this meta-analysis to detect the association of *VEGF* -460C/T polymorphism and endometriosis risk [5, 13-15, 24, 25, 28, 30-36]. FEM was utilized to calculate the pooled OR in all genetic models due to absence of significant heterogeneity across all levels of analysis. Overall, no statistically significant associations were identified in any genetic model (CC+CT vs. TT: OR=1.01, P=0.87; CC vs. CT+TT: OR=0.97, P=0.59; CC vs. TT: OR=0.98, P=0.69; CT vs. TT: OR=1.01, P=0.68; C vs. T: OR=0.99, P=0.86) (**Figure 2**, **Table 3**).

The OR and 95% CI were pooled based on further subgroup analyses of ethnicity, control source, and disease stage to assess the potential effects of specific study characteristics on such association. Moreover, when stratified by ethnicity, a non-significant relationship was identified for the Asian (CC+CT vs. TT: OR=0.99, P=0.70) or Caucasian population (CC+CT vs. TT: OR=1.01, P=0.60) with low heterogeneity (**Table 3**). When stratified by control source, *VEGF* -460C/T had no association with endometriosis risk for HB or PB among all of genetic models. Based on stratification analysis by disease stage, no significant association between -460C/T in the VEGF gene and endometriosis was found for stage I-II or III-IV disease in five genetic models. Notably, no moderate heterogeneity was detected in any subgroup analysis. In addition, corrected *P* values for multiple testing did not change these results (**Table 4**).

Association of +405G/C (rs2010963) and endometriosis meta-analysis

All 18 studies involving 10,326 subjects were pooled to investigate the association between *VEGF* +405G/C and endometriosis risk [1, 5, 13, 15, 19-21, 24-29, 32]. For the presence of moderate heterogeneity across all levels of

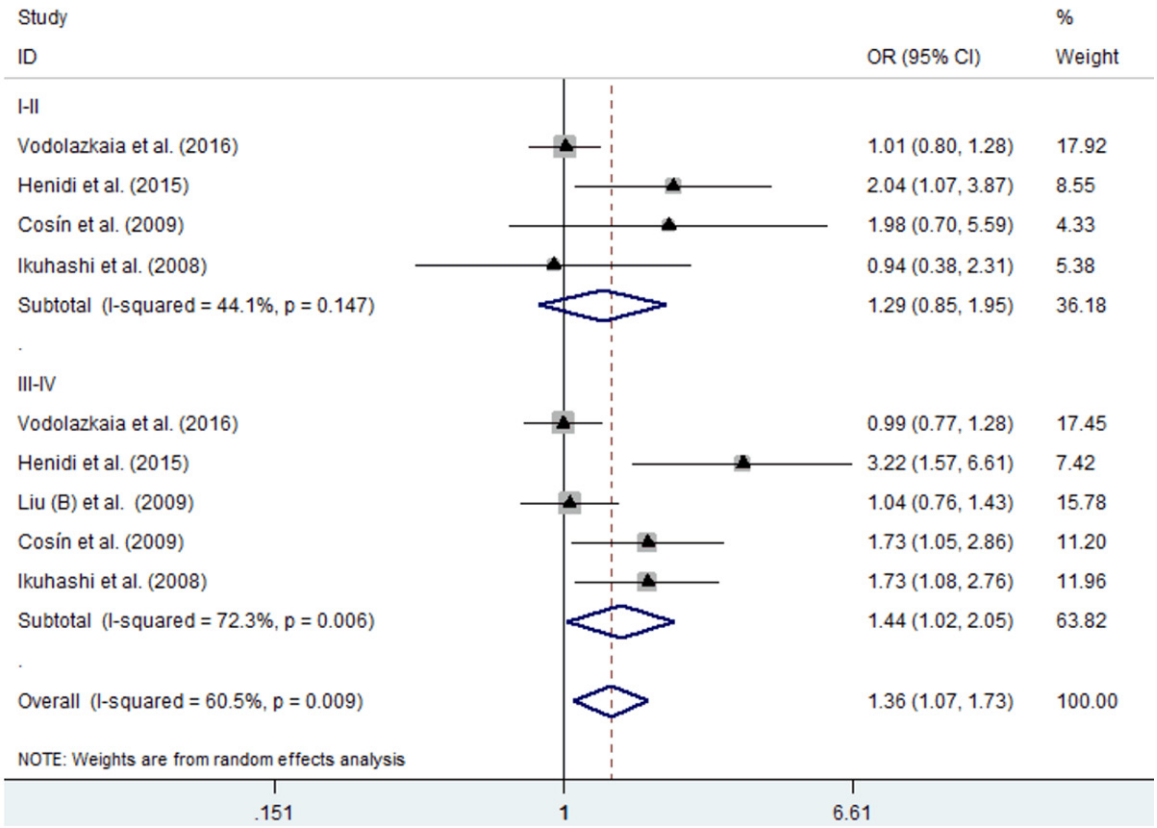

Figure 4. Forest plot of endometriosis risk associated with VEGF +936T/C polymorphism in dominant model (TT+TC vs. CC) for the subgroup analysis by disease stage (I-II and III-IV).

analysis, REM was utilized in all genetic models. In the overall analysis, no evidence was observed for significant association between +405G>C polymorphism and the risk of endometriosis in any genetic model (GG+GC vs. CC: OR=1.01, P=0.60) (**Figure 3**, **Table 3**).

Furthermore, in the stratified analysis by ethnicity, source of control and disease stage, there was no significant association. Moreover, the conclusion remained unchanged after *p* values were corrected using FDR test (**Table 4**).

Association of +936T/C (rs3025039) and endometriosis meta-analysis

Twelve studies involving 7,446 subjects were analyzed to assess the association between *VEGF* +936T/C and endometriosis risk [1, 5, 13, 15, 22, 27, 31-34, 37, 38]. Since there was significant heterogeneity in dominant, heterozygous and allelic model, REM was applied to estimate pooled ORs. And, FEM was utilized in other genetic models. The overall results suggest that there is no statistically significant association between +936T/C and the risk of endometriosis in any genetic comparison (**Table 3**).

When stratified by ethnicity and control source, *VEGF* +936T/C showed no significant association with the risk of endometriosis in any comparison. Moreover, in the stratified analysis by disease stage, statistically significant association was present in stage III-IV (TT+TC vs. CC: OR=1.44, P=0.039; TT vs. TC+CC: OR=1.58, P=0.038; TT vs. CC: OR=1.71, P=0.016; T vs. C: OR=1.45, P=0.031), but not in stage I-II in any genetic model (**Figure 4**, **Table 3**). However, the *VEGF* +936T/C polymorphism did not remain significant in all genetic comparison after multiple testing (TT+TC vs. CC: P_{Corr}=0.05; TT vs. TC+CC: P_{Corr}=0.06; TT vs. CC: P_{Corr}=0.08; T vs. C: P_{Corr}=0.08) (**Table 4**).

Association of -2578C>A (rs699947) and endometriosis meta-analysis

All 6 studies containing 4,103 subjects reported the association of *VEGF* -2578C>A polymorphism and endometriosis risk [1, 13, 19, 27, 31, 37]. For the absence of heterogeneity in

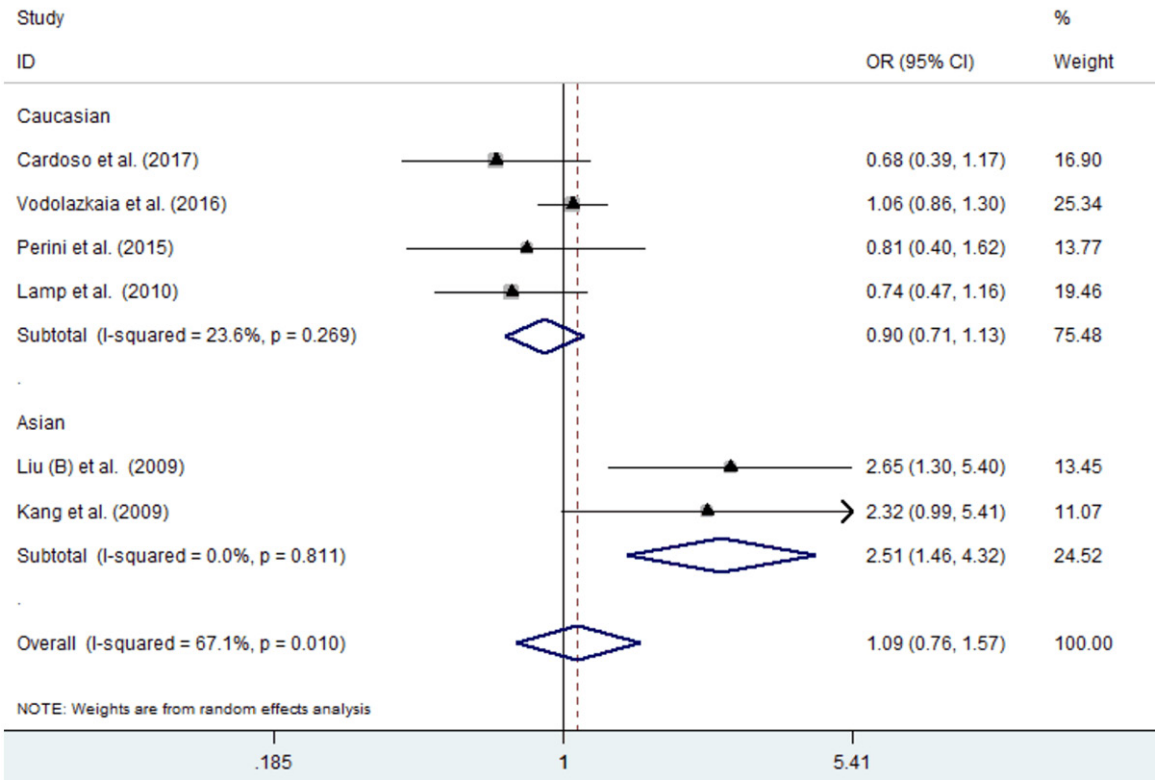

Figure 5. Forest plot of endometriosis risk associated with VEGF -2578C>A polymorphism in dominant model (CC+CA vs. AA) for the subgroup analysis by ethnicity (Caucasian and Asian).

heterozygous model, FEM was applied to estimate pooled ORs. And, REM was utilized in other genetic models. The overall results indicated that there was no statistically significant association between *VEGF* -2578C>A polymorphism and endometriosis risk in five genetic models (**Table 3**).

Furthermore, stratified analysis showed no significant association for stage III-IV. However, a significantly increased risk of endometriosis was associated with -2578C>A polymorphism in *VEGF* gene in Asians for all genetic model (CC+CA vs. AA: OR=2.51, P=0.001; CC vs. CA+AA: OR=1.51, P=0.001; CC vs. AA: OR=2.8, P=0.0001; CA vs. AA: OR=2.06, P=0.013; C vs. A: OR=1.52, P=0.0001), but not in Caucasians (**Figure 5**). Moreover, there were no significant variables after corrections for multiple comparisons (**Table 4**).

Publication bias

Publication bias was evaluated through the Begg's funnel plot and Egger's regression intercept tests. The result of Egger's test showed no significant publication bias in all comparisons of the overall population (data not shown). In addition, the shape of the Begg's funnel plot presented basically symmetric distribution (**Figure 6**).

Sensitivity analysis

Although stringent protocols were used to carry out all studies, some studies may have an effect on the results in the pooled analysis. Therefore, we performed sensitivity analyses to evaluate the stability of these results in this meta-analysis. First, sensitivity analysis was performed by sequentially excluding each study to evaluate the influence of any single study on the obtained conclusions and the corresponding pooled ORs was not significantly altered in all genetic models. Second, the genotype distributions of control groups in six studies did not comply with the HWE, but similar results were obtained by the exclusion of these studies (**Table 4**). Furthermore, the REM was compared with the FEM, and the conclusions were not altered. Therefore, the results of this meta-analysis were stable and robust.

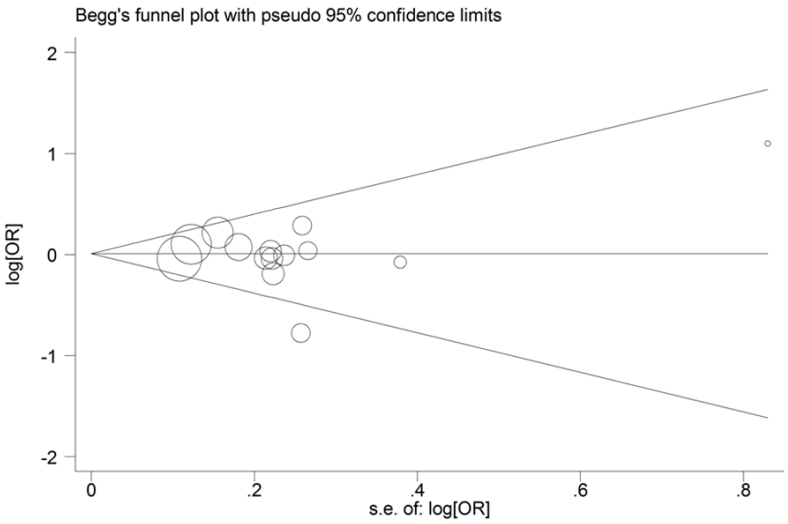

Figure 6. Begg's funnel plot of publication bias test for the association between VEGF -460C/T polymorphism and endometriosis risk under the dominant model (CC+CT vs. TT).

meta-analyses that +936T /C polymorphism may increase the susceptibility to endometriosis [17, 40]. The result can be explained by the following reasons: 1) We included larger sample size (12 case-control studies) regarding the relationship between the +936T/C and endometriosis risk, which may be closer to the real value; 2) The sensitivity analysis was performed by three different methods, and the corresponding pooled ORs were similar in each genetic comparison. Therefore, our results were more stable and credible.

Discussion

VEGF, an endothelial cell-specific angiogenic protein, serve as an important role in many estrogen target tissues to regulate endometrial angiogenesis and promote neovascularization, which seems to contribute to the implantation of endometrial cells in ectopic sites [4, 39]. VEGF gene is a potential candidate gene in the pathogenesis of endometriosis, which can regulate the expression of VEGF mRNA and thereby modulate the production of VEGF protein to play a crucial role in the formation of endometriosis [7, 11]. The VEGF genetic SNPs involved in angiogenesis contribute to the biological variability in VEGF gene expression and support endometriosis lesions development [1, 5, 20, 22]. Accumulating evidence has indicated that polymorphisms in the VEGF gene (-460C/T, +405G/C, +936T/C and -2578C>A) may be associated with endometriosis risk. However, some published studies yielded conflicting results [1, 5, 13, 15, 19-22, 24].

In this meta-analysis, we investigated four polymorphisms in the VEGF gene on gene locus with 24 separate case-control studies (6,310 cases and 6,499 controls) focusing on the relationship of these variants to the risk of endometriosis. The overall results revealed no significant associations were identified for four SNPs (-460C/T, +405G/C, +936T/C and -2578C>A) and endometriosis. Interestingly, the results was inconsistent with the previous

However, we must treat these results cautiously when referring to these findings. Because moderate heterogeneity was detected in this meta-analysis in some genetic models, which may be contributed to different ethnic populations, environmental exposure and clinical information of endometriosis architecture. First, accumulated evidence demonstrated that different populations living in different areas with different environments and life style might have different genetic backgrounds and linkage disequilibrium patterns, which may cause a bias and affect the results. Second, results from the population-based controls can represent the exposure situation of the overall population, which may be more reliable than the results form hospital-based populations. Third, different types and stages of endometriosis expressed different levels of VEGF, which indicated different pathways in the pathogenesis of endometriosis. Different disease stages may contribute to the moderate heterogeneity. Therefore, we performed subgroup analyses to investigate the origin of heterogeneity through ethnicity, control source, and disease stage.

When subgroup analyses were restricted to ethnicity and control source, no significant association was observed for all polymorphisms in any genetic model. However, the stronger and significantly increased risk of endometriosis was identified for +936T/C polymorphism in stage III-IV, not in stage I-II. Interestingly, such association between +936T/C in the VEGF

gene and the presence of endometriosis lost statistical significance after multiple testing (Bonferroni correction), which was contrary to the results of two previous meta-analyses [16, 40]. The contradictory result was explained by the following reasons: (1) Small sample was included in the previous two meta-analyses, which may reduce the power to reveal a reliable relationship; (2) Benjamini-Hochberg procedures was used to adjust for multiple comparisons in setting the level of significance, which was a routine and important method for controlling the type I error in the text of multiple hypothesis test. Therefore, the results after Bonferroni correction may reduce the false-positive associations and reveal a more credible relationship in this genetic association studies. However, Benjamini-Hochberg procedures may increase the risk of false-negative results. Therefore, these observations need further investigation with large sample size.

VEGF -2578C>A genetic polymorphism showed significant increased risk of endometriosis in Asian population, but not in Caucasian population. Such association remained significant after Benjamini-Hochberg correction and sensitivity analysis, suggesting the result were stable and credible. Natural selection and balance to other genetic variants may lead to different genotype frequencies and the difference between Caucasian and Asian populations. In addition, this discrepancy between Caucasians and Asians could be attributed to the genetic background, gene-environment and non-genetic risk factors. Growing evidence suggests that the -2578CC genotype increased the VEGF levels in serum samples [27, 31, 37, 41]. The presence of the -2578C allele in the promoter region of the VEGF gene was associated with enhanced protein and mRNA expression, which is in complete linkage with deletion/insertion of an 18 base pair (bp) fragment at -2549 of the promoter region [31, 37]. Therefore, we hypothesize that the CC genotype might increase serum VEGF levels and thereby VEGF protein and mRNA production, which have an effect on angiogenic activity in endometriotic implants. Interestingly, the result was consistent with a previous meta-analysis, but not with the other two meta-analysis [40]. Although we included larger sample size and used three different methods of sensitivity analysis and Bonferroni correction to investigate the association between this polymorphism and endometriosis risk with no heterogeneity, we must treat these results cautiously when referring to the findings. First, there were only two studies for Asian populations, which decrease the statistical power by pooling data to detect the association. Additionally, although laparoscopically verified control group can exclude endometriosis, these controls were selected from hospital, which may not represent the exposure situation of overall population and have unknown underlying confounding factors to a credible relationship.

We note several potential limitations when interpreting these results. First, further analyses were not performed to detect other risk factors for insufficient original data, such as age, gender and gene-environment/gene-gene interaction. Second, moderate heterogeneity was seen in some genetic comparisons. Further subgroup analysis showed that disease type and ethnicity might be the source of heterogeneity. Nevertheless, there is other inexplicable heterogeneity affecting the results. Third, some relevant published studies or unpublished studies with null results may have been missed. Fourth, studies eligible in this meta-analysis were conducted in Asian and Caucasian populations. Despite these limitations, we created a strict protocol, and performed study selection, data identification, and statistical analysis to reduce potential bias through the whole process. Thus, the objectivity and reliability of the results are guaranteed.

Conclusion

Our meta-analysis showed that no significant association between the SNPs in -460C/T and +405G/C and the presence of endometriosis was identified. The -2578C>A polymorphism was significantly associated with increased endometriosis risk in Asian populations. However, the association between +936T/C polymorphism in VEGF gene and the risk of endometriosis lost statistical significance after applying the Bonferroni correction for multiple testing. These observations thus need further investigation with larger sample size and more ethnic groups.

Disclosure of conflict of interest

None.

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