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GENETICS

The cytochrome P4501A1 gene polymorphisms and endometriosis: a meta-analysis

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Abstract
Purpose Cytochrome P450 1A1 (*CYP1A1*) polymorphisms were implicated in endometriosis risk, but individual published studies showed inconclusive results. Thus, a meta-analysis was performed to clarify the effect of *CYP1A1* polymorphisms on endometriosis risk.
Methods PubMed, Embase, and CNKI databases were searched to identify the eligible studies focusing on the associations between *CYP1A1 MspI* and *Ile462Val* polymorphisms and susceptibility to endometriosis. Summary odds ratios (ORs) and 95 % confidence intervals (95 % CIs) for *CYP1A1* polymorphisms and endometriosis were calculated.
Results Pooled analysis of 12 studies involved a total of 1555 cases and 2868 controls showed that in all genetic models, no significant association between *CYP1A1 MspI* polymorphism and endometriosis risk was observed in the overall, Asians and Caucasians population, respectively. Interestingly, increased endometriosis risk was associated with carrying the C allele of *CYP1A1* combined with *GSTM1* null genotypes. For *CYP1A1 Ile462Val* polymorphism, eight studies were available (878 cases and 1991 controls). In the overall analysis, *CYP1A1 Ile462Val* polymorphism had a statistically significant association with increased endometriosis risk in allele contrast and all genetic models except the model of Val/Ile vs. Ile/Ile. In the subgroup analysis by ethnicity, significant elevated endometriosis risk was associated with *CYP1A1 Ile462Val* polymorphism in Asians but not in Caucasians under all genetic models. No publication bias was found in the present studies.
Conclusions This meta-analysis suggested that *CYP1A1 Ile462Val* polymorphism was associated with an increased risk of endometriosis, particularly in Asians. *CYP1A1 MspI* polymorphism may not be associated with endometriosis risk, but *GSTM1* and *CYP1A1 MspI* polymorphism may have a joint effect on endometriosis risk.

Keywords Endometriosis · Cytochrome P450 1A1 · Polymorphism · Meta-analysis

Capsule This meta-analysis suggested that *CYP1A1 Ile462Val* polymorphism was associated with an increased risk of endometriosis, particularly in Asians.

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Introduction

Endometriosis is one of the most common gynecological disorders in women that is defined as the presence of endometrial glands and stroma outside the uterine cavity. It is associated with a spectrum of symptoms of which chronic pelvic pain and infertility are the most common [1]. The disease affects 5 to 15 % of women in reproductive age, while the prevalence in infertile women is 30 to 50 % [2]. Although endometriosis has been intensively studied, the exact cause of the disorder is still unclear. Endometriosis is considered as a multifactor disease affected by hormonal, immunological, environmental, and genetic factors. Numerous studies have shown that the genetic factors were importantly involved in the susceptibility to endometriosis [3].

Cytochrome P450 1A1 (CYP1A1) enzyme is a member of the CYP superfamily and prone to mutation [4]. Multiple polymorphic sites within the *CYP1A1* gene have been reported, while *MspI* (rs4646903 T>C) and *Ile462Val* (rs1048943 A>G) are the two most common polymorphisms. Several studies have investigated the relationships between *CYP1A1*

MspI and *Ile462Val* polymorphisms and endometriosis risk [5–8] However, the results were inconclusive. Hence, to acquire a more precise estimation of these associations, a meta-analysis of all eligible case–control studies was needed. A previous meta-analysis (based on only 480 cases and 475 controls from three studies in 2001, 2002, 2003, respectively) investigating the relationship of *CYP1A1 MspI* polymorphism and endometriosis was conducted in 2006 [9]. It was suggested that women with *CYP1A1 MspI* +/− and +/+ genotype have about 40 % of increased risk of endometriosis as compared with women of *MspI* −/− genotype, but the relationship of *CYP1A1 Ile462Val* polymorphism and endometriosis was not mentioned. In the past 10 years, several more replication studies which were performed to reevaluate the effect of *CYP1A1 MspI* polymorphisms on endometriosis offered some new data and diverse conclusions. In order to perform a more comprehensive estimation of the associations between *CYP1A1* gene polymorphisms and endometriosis susceptibility, we conducted the meta-analysis to assess the associations between *CYP1A1 MspI* and *Ile462Val* polymorphisms and the risk of endometriosis.

Materials and methods

Literature search

All eligible studies were identified by searching the PubMed, Embase, and China National Knowledge Infrastructure (CNKI) (last update Jan 10, 2016) using the terms as follows: ('polymorphism' or 'mutation' or 'variant' or 'variation' or 'genotype' or 'genetic') and ('*CYP1A1*' or 'cytochrome P450 1A1') and (endometriosis). No language restriction was applied. Manual search of reference lists from potentially relevant articles was also performed to identify other potential studies.

Inclusion and exclusion criteria

The following criteria were used to select the eligible studies: (1) the studies evaluated the associations between *CYP1A1 MspI* and *Ile462Val* polymorphisms and the risk of endometriosis, (2) case-control studies, (3) the studies provided sufficient data to estimate an odds ratio (OR) and 95 % confidence interval (95 % CI). Only published studies with full text articles were included. If more than one article from the same group occurred, we only included the most recent or complete article to avoid overlapping.

The following exclusion criteria were applied for excluding studies: (1) no control population; (2) studies contained duplicate data; (3) no available genotype or allele frequency; (4) publication only as an abstract or as conference proceedings, (5) case reports or reviews; (6) unpublished study.

Data extraction

The following information were extracted: the first author, year of publication, ethnicity, country, number of subjects, diagnostic criteria of cases, genotyping methods, the minor allele frequency and genotypes, sites of mutation and Hardy-Weinberg equilibrium (HWE) in controls. Data were extracted independently by two investigators and discrepancies were resolved by consensus including a third author.

Statistical analysis

The STATA version 10.0 (Stata Corp, College Station, TX) software was used for meta-analysis. The HWE of genotypes in the control group was assessed by using a χ^2 test. The possible associations between *CYP1A1 MspI* and *Ile462Val* polymorphisms and endometriosis risk were evaluated by ORs and 95 % CI under allele contrast (MspI: C vs. T; Ile462Val: Val vs. Ile), homozygote (MspI:CC vs. TT; Ile462Val: Val/Val vs. Ile/Ile), heterozygote (MspI: CT vs. TT; Ile462Val: Val/Ile vs. Ile/Ile), recessive (MspI: CC vs. CT + TT; Ile462Val: Val/Val vs. Val/Ile + Ile/Ile), and dominant (MspI: CC + CT vs. TT; Ile462Val: Val/Val + Val/Ile vs. Ile/Ile) models. Studies providing the combined genotypes (CC + CT; Val/Val + Val/Ile) rather than the separate ones were only included in the dominant model evaluation.

The Q-statistic and I^2 test were used to evaluate potential heterogeneity between studies. $I^2 < 25$ % represents no heterogeneity, $I^2 = 25$–50 % represents moderate heterogeneity, $I^2 = 50$–75 % represents large heterogeneity, and $I^2 > 75$ % represents extreme heterogeneity [10]. If the result of the Q test was $P < 0.10$, suggesting the existence of between-study heterogeneity, ORs were pooled by random-effects model (DerSimonian and Laird method). Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used. Subgroup analyses were utilized to explore the potential sources of heterogeneity across studies. Potential publication bias was estimated by the Begg rank correlation test and Egger weighted regression test. $P < 0.05$ was considered to represent statistically significant publication bias.

Results

Literature search and study selection

According to the search criteria, a total of 70 articles relevant to the searched keywords were initially identified, of which 48 irrelevant papers were excluded after reading the title and abstract. After the full-text evaluation, five articles were excluded with reasons for no available data ($n = 1$) [11], irrelevance to endometriosis ($n = 1$) [12], duplicate publications ($n = 3$) [13–15]. An article providing data for two different

subgroups (Caucasian and Asian) was counted as two separate studies [6]. Finally, 18 studies (12 articles in English [5, 7, 16–25] and others in Chinese [6, 8, 26–28]) were included in this meta-analysis. For the *CYP1A1 MspI* polymorphism, 12 studies involved a total of 1555 cases and 2868 controls. For the *CYP1A1 Ile462Val* polymorphism, eight studies were available, including a total of 878 cases and 1991 controls. There were four articles (including five studies) about the association between combinations of *CYP1A1 MspI* polymorphism and the glutathione S-transferases M1 (*GSTM1*) null mutation and the risk of endometriosis [5, 6, 22, 24].

Study characteristics were summarized in Tables 1 and 2 (Table 1 for MspI, Table 2 for *Ile462Val*). Among these publications about the *CYP1A1 MspI* polymorphism, seven studies involved Asian subjects, four studies involved Caucasian subjects, and one study involved unknown subjects (Table 1). A total of eight separate comparisons (five Asian and three Caucasian) were considered for *CYP1A1 Ile462Val* polymorphism (Table 2). Four genotype methods were used among these studies, including DNA sequencing, TaqMan, polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP), and allele-specific PCR (AS-PCR). Only three studies were confirmed as endometriosis by surgery [7, 18, 22], and other studies were confirmed as endometriosis by histological study.

CYP1A1 MspI polymorphism and endometriosis risk

For *CYP1A1 MspI* polymorphism, no significant difference in risk was seen between endometriosis and controls in the overall meta-analysis (C vs. T: OR = 1.02, 95 % CI 0.84–1.24, $I^2 = 56.1$ %, $P_{\text{heterogeneity}} = 0.02$; CC vs. TT: OR = 0.98, 95 % CI 0.64–1.49, $I^2 = 41.5$ %, $P_{\text{heterogeneity}} = 0.09$; CT vs. TT: OR = 1.06, 95 % CI 0.90–1.25, $I^2 = 31.2$ %, $P_{\text{heterogeneity}} = 0.17$; dominant model: OR = 1.02, 95 % CI 0.88–1.17, $I^2 = 29.8$ %, $P_{\text{heterogeneity}} = 0.15$; and recessive model: OR = 0.87, 95 % CI 0.65–1.16, $I^2 = 31.6$ %, $P_{\text{heterogeneity}} = 0.17$). Stratification analysis by ethnicity also showed neither significant association between the *CYP1A1 MspI* polymorphism and endometriosis in the population of Asian nor in that of Caucasian origin under allele contrast and all genetic models (Table 3). In the subgroup analysis by HWE in controls, no obvious association was found yet (data not shown).

CYP1A1 Ile462Val polymorphism and endometriosis risk

In the overall population, meta-analysis revealed significant association between the *CYP1A1 Ile462Val* polymorphism and endometriosis in allele contrast and all genetic models except the model of *Val/Ile* vs. *Ile/Ile* (Table 4). In the subgroup analysis by ethnicity, significant association between the *CYP1A1 Ile462Val* polymorphism and endometriosis was found in the population of Asian origin under allele contrast and all genetic models (Table 4). We did not observe significant association between the *Ile462Val* polymorphism and endometriosis in Caucasian population (Table 3). For the studies within HWE in controls, there was still significant association between the *Ile462Val* polymorphism and endometriosis susceptibility (data not shown).

Association of genotypes of CYP1A1-GSTM1 with endometriosis risk

Taking the genotype of TT for *CYP1A1 MspI* and *GSTM1* present as the reference, genotypes of TC or TC + CC for *CYP1A1* and *GSTM1* null deletion were significantly associated with endometriosis risk (TC/GSTM− vs. TT/GSTM+: OR = 1.44, 95 % CI 1.06–1.96, $I^2 = 36.1$ %, $P_{\text{heterogeneity}} = 0.18$; TC + CC/GSTM− vs. TT/GSTM+: OR = 1.45, 95 % CI 1.08–1.94, $I^2 = 38.1$ %, $P_{\text{heterogeneity}} = 0.17$) (Table 5). Hadfield et al. also reported a similar finding [25] to ours, which was not included in our meta-analysis because of lack of data about the interaction of CYP1A1 *MspI* polymorphism and *GSTM1* null mutation on the endometriosis risk.

Gene–gene interaction cannot be assessed for combinations of CYP1A1 Ile462Val polymorphism and *GSTM1* null mutation on the risk of endometriosis in the pooled analysis because there was only one study about the interaction [27], in which taking the subjects with the genotype of Ile/Ile for *CYP1A1* and *GSTM1* present as the reference, the OR was 4.40 (95 % CI, 1.55–12.45) for subjects with genotype of Ile/Val for *CYP1A1* and *GSTM1* null, and 9.90 (95 % CI, 1.80–54.45) for subjects with genotype of Val/Val for *CYP1A1* and *GSTM1* null.

Heterogeneity analysis

For the *CYP1A1 MspI* polymorphism, there was moderate or large heterogeneity among studies in overall comparisons. To explore sources of heterogeneity across studies, subgroup analyses by ethnicity (Asian or Caucasian) and Hardy-Weinberg equilibrium (HWE) in controls (yes or not) were conducted. There was no heterogeneity in the studies of Asian in most comparisons; however, there was still large heterogeneity in the studies of Caucasian in most comparisons (Table 3). HWE in controls could not explain the heterogeneity (data not shown).

For the *CYP1A1 Ile462Val* polymorphism, there was large heterogeneity among studies in most comparisons. To explore sources of heterogeneity across studies, subgroup analyses by ethnicity (Asian or Caucasian) and HWE in controls (yes or not) were conducted. There was no heterogeneity in the studies of Asian or Caucasian in most comparisons (Table 4).

Table 1 Characteristics of studies about MspI included in the present meta-analysis

Study	Year	Ethnicity (country)	Numbers		Diagnosis method	Genotype method	Minor allele frequency		Cases			Controls			*P* value (HWE test)
			Case	Control			Case	Control	TT	TC	CC	TT	TC	CC	
Wu CH et al.	2012	Asian (China)	121	171	Laparoscopy and histological examination	TaqMan	Cannot calculate		TT 60	TC + CC 61		TT 84	TC + CC 87		Cannot calculate
Trabert B et al.	2011	Caucasian (USA)	255	567	Surgical examination	PCR-RFLP	0.118	0.138	202	46	7	423	132	12	0.65
Rozati R et al.	2008	Asian (India)	97	102	Laparoscopy examination	PCR-RFLP	0.232	0.230	56	37	4	61	35	6	0.74
Juo SH et al.	2006	Asian (China)	104	299	Laparoscopy and histological examination	PCR-RFLP	0.346	0.401	42	52	10	107	144	48	0.97
Huber A et al.	2005	Caucasian (Austria)	32	790	Surgical and histological examination	PCR-sequencing	Cannot calculate		TT 28	TC + CC 4		TT 650	TC + CC 140		Cannot calculate
Babu KA et al.	2005	Asian (India)	310	215	Laparoscopy examination	PCR-RFLP	0.311	0.356	145	137	28	93	91	31	0.26
Arvanitis DA et al.	2003	Caucasian (Greece)	275	346	Surgical or laparoscopy, histological examination	PCR-RFLP	0.202	0.143	173	93	9	253	87	6	0.64
Iizuka S et al.	2003	Asian (Japan)	35	37	Histological examination	PCR-RFLP	0.371	0.405	17	10	8	15	14	8	0.19
Hadfield RM et al.	2001	Unknown (UK)	129	49	Surgical and histological examination	PCR-RFLP	Cannot calculate		TT 102	TC + CC 27		TT 37	TC + CC 12		Cannot calculate
Chen ZF et al.	2005	Caucasian (China)	41	107	Surgical or laparoscopy, histological examination	PCR-RFLP	Caucasian		Caucasian						Caucasian 0.79
							0.378	0.299	16	19	6	52	46	9	Asian 0.77
		Asian (China)	80	105					Asian						
									34	41	5	44	49	12	
							Asian								
							0.319	0.348							
Peng DX et al.	2002	Asian (China)	76	80	Surgical or laparoscopy, histological examination	PCR-RFLP	0.447	0.35	23	38	15	34	36	10	0.92

Table 2 Characteristics of studies about Ile/Val included in the present meta-analysis

Study	Year	Ethnicity (country)	Numbers		Diagnosis method	Genotype method	Minor allele frequency		Cases			Controls			*P* value (HWE test)
			Case	Control			Case	Control	Ile/Ile	Ile/Val	Val/Val	Ile/Ile	Ile/Val	Val/Val	
Matsuzaka Y et al.	2012	Asian (Japan)	95	137	Laparoscopy and histological examination	PCR-sequencing	0.242	0.223	Ile 144		Val 46	Ile 213		Val 61	Cannot calculate
Trabert B et al.	2011	Caucasian (USA)	255	567	Surgical examination	PCR-RFLP	0.053	0.053	231	21	3	510	54	3	Ile/Val 0.24
Tsuchiya M et al.	2007	Asian (Japan)	79	59	Laparoscopy and histological examination	PCR-RFLP	Cannot calculate		Ile/Ilel 50		Ile/Val + Val/Va 29	Ile/Ile 40		Ile/Val + Val/Val 19	Cannot calculate
Huber A et al.	2005	Caucasian (Austria)	32	790	Surgical and histological examination	PCR-sequencing	Cannot calculate		Ile/Ile 32		Ile/Val + Val/Val 0	Ile/Ile 735		Ile/Val + Val/Val 52	Cannot calculate
Ivashchenko TE et al.	2003	Caucasian (Russia)	74	40	Laparoscopy and histological examination	PCR-RFLP	0.034	0.05	69	5	0	36	4	0	0.74
An XF et al.	2011	Asian (China)	216	216	Surgical and histological examination	AS-PCR	0.407	0.282	72	112	32	110	90	16	0.68
Cao YH et al.	2008	Asian (China)	51	102	Surgical or laparoscopy, histological examination	AS-PCR	0.431	0.255	16	26	9	58	36	8	0.47
Peng DX et lal.	2003	Asian (China)	76	80	Surgical or laparoscopy, histological examination	AS-PCR	0.395	0.25	29	34	13	46	28	6	0.55

Table 3 Analyses of the association between *CYP1A1 MspI* polymorphism with endometriosis

Comparisons	No. of studies	Subgroup	OR (95 % CI)	Test of heterogeneity		Publication bias	
				P value	I^2 (%)	Begg's test	Egger's test
C vs. T	9	All	1.02 (0.84, 1.24)	0.02	56.1	0.35	0.56
		Ethnicity					
	6	Asian	0.90 (0.77, 1.06)	0.28	19.8		
	3	Caucasian	1.20 (0.79, 1.82)	0.02	74.0		
CC vs. TT	9	All	0.98 (0.64, 1.49)	0.09	41.5	0.60	0.16
		Ethnicity					
	6	Asian	0.72 (0.51, 1.02)	0.24	26.4		
	3	Caucasian	1.72 (0.95, 3.13)	0.65	0		
CT vs. TT	9	All	1.06 (0.90, 1.25)	0.17	31.2	1.00	0.99
		Ethnicity					
	6	Asian	1.03 (0.82, 1.28)	0.75	0		
	3	Caucasian	1.13 (0.65, 1.97)	0.01	77.0		
Dominant model	12	All	1.02 (0.88, 1.74)	0.15	29.8	0.95	0.80
		Ethnicity					
	7	Asian	0.96 (0.79, 1.16)	0.65	0		
	4	Caucasian	1.10 (0.68, 1.78)	0.02	69.9		
	1	unknown					
Recessive model	9	All	0.87 (0.65, 1.16)	0.17	31.6	0.75	0.14
		Ethnicity					
	6	Asian	0.72 (0.52, 1.00)	0.33	12.6		
	3	Caucasian	1.13 (0.66, 1.93)	0.23	32.9		

HWE in controls still could not explain the heterogeneity (data not shown).

There were two studies about the relationship between the CYP1A1 *MspI* polymorphism and endometriosis risk in Indians, and no study on the relationship between CYP1A1 *Ile462Val* polymorphism and endometriosis risk in Indians. It was really one problem that Indians are counted as Asians or Caucasians in stratified analysis. In stratified analysis, there was no difference between the results no matter Indians were counted as Asians or not. Thus, we only showed the results of stratified analysis in which Indians are counted as Asians, while the results of stratified analysis in which Indians are counted as Caucasians are not showed in the article.

Publication bias

Begg's funnel plot and Egger's test were performed to assess possible publication bias (Tables 2, 3, and 4; Figs. 1 and 2), which showed no publication bias for studies published on the *CYP1A1 MspI* and *Ile462Val* polymorphisms.

Discussion

Environmental toxins, including dioxin, have been implicated as risk factors of endometriosis [29]. It was stated that phase I drug-metabolizing enzymes (DMEs) metabolized toxic compounds to genotoxic electrophilic intermediates, and phase II DMEs conjugate the intermediates to water-soluble deriva

Table 4 Analyses of the association between *CYP1A1 Ile462Val* polymorphism with endometriosis

Comparisons	No. of studies	Subgroup	OR (95 % CI)	Test of heterogeneity		Publication bias	
				P value	I^2 (%)	Begg's test	Egger's test
Val vs. Ile	6	All	1.48 (1.12, 1.97)	0.06	52.8	1.00	0.43
		Ethnicity					
	4	Asian	1.68 (1.38, 2.05)	0.17	39.9		
	2	Caucasian	0.96 (0.62, 1.49)	0.57	0		
Val/Val vs. Ile/Ile	4	All	3.20 (1.98, 5.19)	0.94	0	1.00	0.87
		Ethnicity					
	3	Asian	3.32 (2.00, 5.50)	0.91	0		
	1	Caucasian	2.21 (0.44, 11.02)				
Val/Ile vs. Ile/Ile	5	All	1.52 (0.97, 2.39)	0.05	58.3	1.00	0.73
		Ethnicity					
	3	Asian	2.02 (1.47, 2.77)	0.75	0		
	2	Caucasian	0.83 (0.51, 1.36)	0.71	0		
Dominant model	7	All	1.52 (1.01, 2.30)	0.03	57.0	0.37	0.31
		Ethnicity					
	4	Asian	2.04 (1.54, 2.68)	0.40	0		
	3	Caucasian	0.83 (0.52, 1.31)	0.55	0		
Recessive model	4	All	2.31 (1.46, 3.65)	0.99	0	0.73	0.47
		Ethnicity					
	3	Asian	2.32 (1.44, 3.74)	0.95	0		
	1	Caucasian	2.24 (0.45,11.17)				

tives, completing the detoxification cycle [30]. Cytochrome P450s are the most important phase I enzymes. The products of CYP1A1 are involved in estrogen and PAH metabolism. It was shown that CYP1A1 was involved in metabolism of dioxin, which may increase the incidence and severity of endometriosis in monkeys [29]. Moreover, CYP1A1 is also involved in estrogen metabolism, catalyzing the hydroxylation of 17β-estradiol at the C-2 position [31]. Considering that estrogenic components play key roles in endometriosis [32], CYP1A1 may be associated with endometriosis. The *CYP1A1 MspI* polymorphism can alter the level of gene expression or mRNA stability, resulting in a highly inducible activity of the enzyme [33]. For the *Ile462Val* polymorphism, it was found that mean mRNA (induced/basal) levels of CYP1A1 increased with number of Val variants [34]. Heterozygotes for both 3801C and Val variants had twofold increased basal CYP1A1 expression compared with homozygotes for the 3801T and Ile alleles [35]. Hence, certain variant genotypes of the *CYP1A1* gene which may cause enhanced enzymatic activity appear to play a role in susceptibility to endometriosis in theory. To date, several studies reported the role of *CYP1A1* polymorphisms in endometriosis. However, the results were inconclusive. Therefore, we performed a meta-analysis to acquire a more precise estimation of these associations.

In the meta-analysis, we investigated the associations between *CYP1A1 MspI* and *Ile462Val* polymorphisms and endometriosis risk. To the best of our knowledge, this is the first meta-analysis of the assessment for the relationships between both the two *CYP1A1* gene polymorphisms and the risk of endometriosis (the previous meta-analysis (2006) assessed

Table 5 Analyses of the association between combinations of *CYP1A1 MspI* polymorphism and the *GSTM1* null mutation and the risk of endometriosis

Comparisons	No. of studies	OR (95 % CI)	Test of heterogeneity	
			P value	I^2 (%)
TT GSTM− vs. TT GSTM+	5	1.02 (0.77, 1.35)	0.13	44.6
TC GSTM− vs. TT GSTM+	5	1.44 (1.06, 1.96)	0.18	36.1
CC GSTM− vs. TT GSTM+	5	1.35 (0.75, 2.43)	0.53	0
CC + TC GSTM− vs. TT GSTM+	5	1.45 (1.08, 1.94)	0.17	38.1

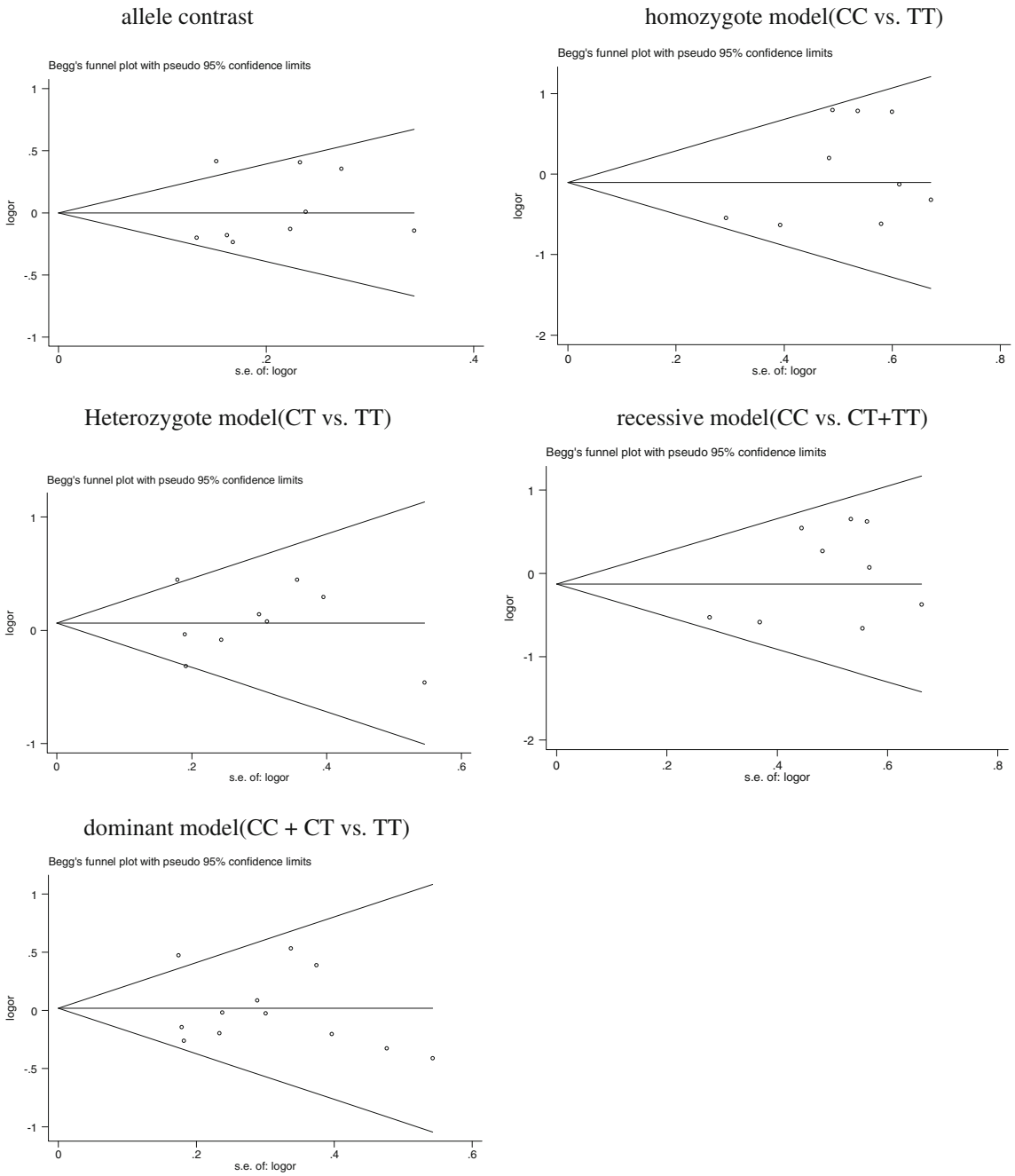

Fig. 1 Begg's funnel plot of publication bias test on the relationship between CYP1A1 *MspI* polymorphism and endometriosis risk. Each point represents a separate study for the indicated association

the association between only *CYP1A1 MspI* polymorphism and endometriosis risk). Meta-analysis of the *CYP1A1 MspI* polymorphism showed no association with endometriosis in all genetic models and allele contrast in the overall, Asians and Caucasians population, respectively. Interestingly, when gene–gene interaction was taken into account, increased endometriosis risk was associated with carrying the C allele of *CYP1A1* combined with *GSTM1* null genotypes. It was speculated that *GSTM1* and *CYP1A1 MspI* polymorphism may have a joint effect on endometriosis risk.

Meta-analysis of the *CYP1A1 Ile462Val* polymorphism showed a significantly increased risk of endometriosis in the overall population. In the stratified analysis by ethnicity, the significant association of *Ile462Val* polymorphism and endometriosis was observed in Asians but not in Caucasians. However, there were only small number of studies on Caucasians for this polymorphism, and it was suggested that *Val* variant occurred more frequently in Asian than in Caucasians [36]. Therefore, it was possible that the observed ethnic difference in the association of *Ile462Val* polymor

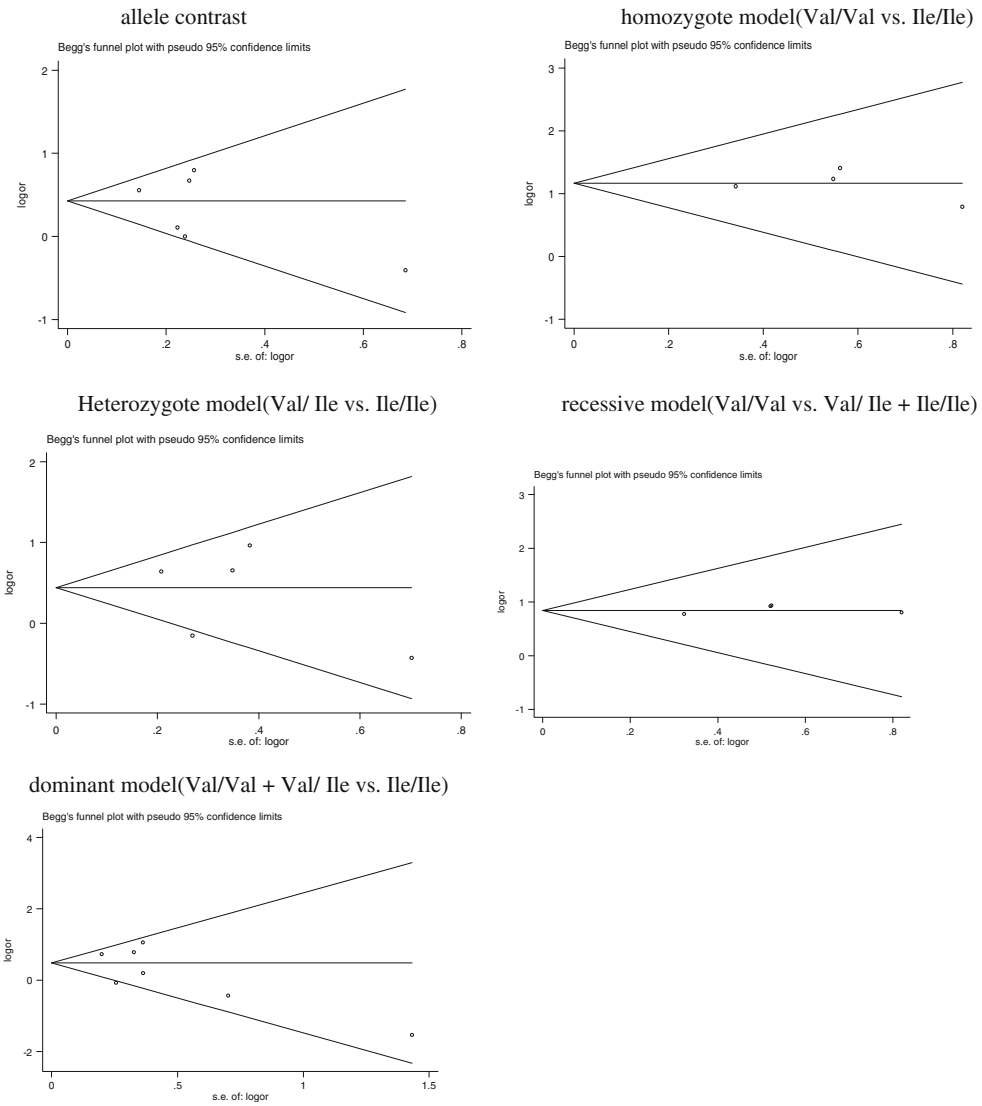

Fig. 2 Begg's funnel plot of publication bias test on the relationship between CYP1A1 *Ile462Val* polymorphism and endometriosis risk. Each point represents a separate study for the indicated association

phism and endometriosis might be the result of small samples. More studies with the Caucasians population are needed to validate the effect of the *CYP1A1 Ile462Val* polymorphism on endometriosis risk in Caucasians.

Heterogeneity is one of the important issues, which may affect the interpretation of the results. In our meta-analysis, between-study heterogeneity was significant in most comparisons. It was suggested that genetic associations for complex diseases may be spurious if the distribution of genotypes in the healthy control groups in genetic case-control studies deviates from HWE [37]. So it was important to utilize the sub-group analysis by HWE in controls to explore the potential genetic associations for complex diseases. However, HWE in controls was unable to identify the sources of heterogeneity. For *CYP1A1 MspI* polymorphism, in the subgroup analyses by ethnicity, although there was still large heterogeneity in the studies of Caucasian in most comparisons, there was no heterogeneity in the studies of Asian in most comparisons. For *CYP1A1 Ile462Val* polymorphism, in the subgroup analyses by ethnicity, there was no heterogeneity in the studies of Asian or Caucasian in most comparisons. Therefore, it was possible that the ethnic difference might partly be the source of heterogeneity. Furthermore, endometriosis was a complex disease. Both environmental and genetic factors could affect the endometriosis risk in different populations. Wherefore, contributors to heterogeneity in this meta-analysis may also be related to the gene–environment interactions.

Some limitations of our study should be considered. Firstly, the included studies were carried out mainly in Asians and Caucasians. Further studies in other ethnic groups are needed to confirm the results of this meta-analysis. Secondly, the meta-analysis was based primarily on unadjusted ORs as the result of the lack of available information, and confounding factors might influence the precision of effect estimates. Thirdly, endometriosis is a complex disorder influenced by both genetic and environmental factors. *CYP1A1* polymor

phisms may be only one risk of endometriosis, and there are many other genetic and environmental factors that participate in the development of endometriosis [38–40]. Gene–gene interaction may influence the results of endometriosis risk. It was suggested that increased risk of developing endometriosis was not found in women with *GSTM1* null genotype when compared with women with other genotypes in a meta-analysis of the association between GSTM1 polymorphism and endometriosis risk [41]. In our meta-analysis, *CYP1A1 MspI* polymorphism may not be associated with endometriosis risk, but *GSTM1* null genotypes combined with the C allele of *CYP1A1* were associated with increased risk for endometriosis. Thus, there is synergy between *GSTM1* and *CYP1A1 MspI* polymorphism on endometriosis risk. So more studies were needed to confirm whether other gene polymorphisms combined with *CYP1A1* polymorphisms were associated with the endometriosis risk or not. Gene–environment interactions were not addressed in this meta-analysis, since no related data were provided in the included studies. Fourthly, although Begg's test and Egger's test did not show any conspicuous publication bias, selection bias may have occurred because we only included published articles in this meta-analysis. Finally, some significant heterogeneity across studies was detected in the meta-analysis. Nevertheless, this may not be a principal issue because our results showed that the related summarized ORs were not substantially altered after subgroup analyses by ethnicity which may be the main source of heterogeneity, especially in Asians, and this indicated obvious statistical robustness of our results.

In conclusion, this study suggested that *CYP1A1 Ile462Val* polymorphism was associated with an increased risk of endometriosis, particularly in Asians. *CYP1A1 MspI* polymorphism may not be associated with endometriosis risk; however, genotypes combined of the C allele of *CYP1A1* and *GSTM1* null were associated with increased risk for endometriosis. Considering the small number of studies included, more studies are needed to validate these findings, especially in different populations.

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