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The association between MTHFR polymorphisms and cervical cancer risk: a system review and meta analysis

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Abstract
Purpose Methylenetetrahydrofolate reductase (MTHFR) plays an important role in determining the proportions of folate coenzymes for DNA synthesis or DNA methylation. Published data on the association between the MTHFR polymorphisms and cervical risk are controversial. A meta-analysis was performed to assess whether the polymorphisms of MTHFR are associated with cervical cancer risk.
Methods Medline, Embase, China National Knowledge Infrastructure and Chinese Biomedicine Databases were searched to identify eligible studies. Pooled odds ratios (ORs) and 95 % confidence intervals (CIs) for MTHFR C677T and MTHFR A1298C polymorphisms and cervical cancer were appropriately derived from fixed-effects or random effects models. Five different ORs were calculated: (1) allele contrast (C vs. T), (2) homozygous comparison (CC vs. TT), (3) heterozygous comparison (CC vs. CT), (4) dominant model (CC vs. CT+TT) and (5) recessive model (CC+CT vs. TT).
Results A total of 13 studies, which included 12 studies for MTHFR C677T (2332 cases and 3000 controls) and five studies for A1298C polymorphisms (677 cases and 1191 controls), were enrolled in this meta-analysis. The pooled analyses revealed that MTHFR C677T polymorphism was not associated with cervical cancer risk; while the A1298C polymorphism had a significant association with increased cervical cancer risk in allele contrast, heterozygote comparison and dominant model (A C, OR = 0.84, 95 % CI = 0.71–0.98; AA vs. CC OR = 0.72, 95 % CI = 0.59–0.89; AA vs. AC+CC, OR = 0.72, 95 % CI = 0.59–0.88). The significant associations between MTHFR A1298C polymorphism and cervical cancer were found among Asians and population-based case–control studies.
Conclusions This study indicated that the MTHFR C677T may be no associated with cervical cancer risk, and yet the MTHFR A1298C polymorphism may be a risk factor for cervical cancer.

Keywords Methylenetetrahydrofolate reductase (MTHFR) · Polymorphism · Cervical cancer · Meta-analysis

Introduction

Cervical cancer is the third most common cancer among women and continues a serious threat to women throughout the world. It accounts for 250,000 deaths annually and most of cancer cases occur in developing regions of Earth [1]. Epidemiological and molecular biological data established an aetiological link between high-risk human papilloma virus (HR-HPV) infection and cervical cancer [2, 3]. However, in the majority of HPV infected women, this virus is cleared by the immune system and only a small portion of HPV infected women develop cervical cancer, so HPV alone cannot be entirely to blame. It appears that genetic or lifestyle factors may play an important role in the persistence of HPV infection and in the malignant conversion of cervical epithelial cells [4, 5].

Susceptibility to cervical cancer may also depend on epigenetic changes, especially DNA synthesis and

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methylation. Methylenetetrahydrofolate reductase (MTHFR) is a critical enzyme in determining the proportions of folate coenzymes for DNA synthesis or DNA methylation [6, 7]. Two common functional polymorphisms in MTHFR are known. The most common is a C-to-T transition at nucleotide 677 (C677T) in exon 4, resulting in an alanine-to-valine substitution that affects the catalytic domain of the enzyme, leading to reduced enzyme activity [8, 9]. Another common variant is an A-to-C transversion at position 1298 in exon 7 (A1298C), resulting in a substitution of glutamate with alanine at codon 429. This polymorphism also reduces enzyme activity, although to a lesser extent. Therefore, the MTHFR gene may be one of the candidate genes for susceptibility of cervical cancer.

Over the last two decades, a number of studies have assessed the association between the MTHFR polymorphisms and cervical cancer in different populations; however, the results are inconsistent and inconclusive [10–16]. Because a single study might have been underpowered to detect the overall effects, a quantitative synthesis of the accumulated data from different studies was deemed noteworthy to provide evidence on the association of MTHFR polymorphisms with cervical cancer. To address such questions, we performed a meta-analysis of published studies to determine potential associations between MTHFR (C677T and A1298C) with the risk of cervical cancer.

Materials and methods

Publication search

We searched the PubMed, Embase, CNKI (China National Knowledge Infrastructure) and Chinese Biomedicine databases for all articles on the association between MTHFR polymorphism and cervical cancer risk (last search update 16th March 2015). The following terms were used in this search: ''MTHFR'' or "C677T" or "A1298C" and ''polymorphism'' or ''variant'' or "allele" or "genotype" and ''cervical cancer'' or ''cervical neoplasm*'' or "cervical tumor". All searched studies' bibliographies were checked for other relevant publications. Review articles were hand-searched to find additional eligible studies. Only published studies with full text articles were included. When overlapping data of the same population were included in more than one publication, the most recent or most complete study was used in this meta analysis.

Inclusion and exclusion criteria

All human-associated studies, regardless of sample size, were included if they met the following criteria: (1) evaluation of at least one of the two polymorphisms (C667T and A1298C) and cervical cancer risk, (2) case–control studies and (3) sufficient data for examining an odds ratio (OR) with 95 % confidence interval (95 % CI). The major exclusion criteria were: (1) abstract, comment, review and editorial, (2) studies which evaluated the association between MTHFR polymorphism and cervical cancer with chemotherapy and (3) no sufficient data were reported.

Data extraction

Two investigators (Y. K. and Y. LY) extracted information from all eligible publications independently according to the inclusion criteria listed above. Disagreements were resolved by discussion between the two investigators. The following characteristics were collected from each study: first author, year of publication, country of the first or corresponding author, ethnicity, source of control groups (hospital-based, population-based controls), genotypes, genotyping methods, number of cases and controls, minor allele frequency (MAF), evidence of Hardy–Weinberg equilibrium (HWE). Ethnicities were categorized as Asian, Caucasian or Mixed. Hospital-based case–control study (HCC) were from hospitalized patients, and population-based case–control study (PCC) was defined as controls from healthy people.

Statistical analysis

We first assessed HWE in the controls for each study using the goodness-of-fit test (χ^2 or Fisher's exact test) and a $P < 0.05$ was considered as significant disequilibrium. The strength of the association between cervical cancer and the MTHFR C677T and A1298C polymorphisms was estimated using the OR and corresponding 95 % CI. Take the MTHFR C677T polymorphism as example, five different ORs were calculated: (1) allele contrast (C vs. T), (2) homozygous comparison (CC vs. TT), (3) heterozygous comparison (CC vs. CT), (4) dominant model (CC vs. CT+TT) and (5) recessive model (CC+CT vs. TT). We also carried out the stratified analyses by ethnicity (Caucasians/Asians) and source of control groups (population-based, hospital-based controls).

Both the Cochran Q statistic to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated [17]. A P value of more than the nominal level of 0.05 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of a fixed-effects model (the Mantel–Haenszel method [18]); otherwise, the random-effects model (the DerSimonian and Laird method) was used [19]. Sensitivity analysis and cumulative meta-analyses were performed to assess the reliability of the results.

Evidence of publication bias was assessed using the Begg's rank correlation method and the Egger's weighted regression method by visual inspection of the funnel plot ($P < 0.05$ was considered statistically significant) [20, 21]. All analyses were done using STATA software, version 13.0 (STATA Corp., College Station, TX, USA).

Result

Characteristics of studies

Through literature search and selection, 44 articles were identified as potentially relevant studies, of these, 23 were excluded after screening the titles and abstracts. Then, 21 studies were retrieved for full-text articles assessed and 8 articles were excluded for various reasons [one study was a review article, five studies were related to cervical intraepithelial neoplasia (CIN) and two studies were correlated to neoadjuvant chemotherapy]. Finally, a total of 13 case control studies in 12 publications [10–16, 22–27], which included 12 studies for C677T and five studies for A1298C polymorphisms, were found to examine the MTHFR polymorphisms and cervical cancer susceptibility and identified based on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [28].

The characteristics of selected studies are exhibited in Table 1. There were six studies of subjects of Caucasian descent, six studies of subjects of Asian descent and one study of subjects Mixed descent. Studies had been carried out in China, Korea, India, Greece, Germany, The Netherland and Poland. The cases definition used in the individual studies were histologically or pathologically diagnosed with cervical cancer. Controls were mainly from healthy populations and matched for geographical area and/or age, of which three studies were hospital-based and ten studies were population-based. All control samples of studies included were in HWE excepted for one study for the A1298C polymorphism [22].

Quantitative analysis

Association of the MTHFR C677T polymorphism with cervical cancer susceptibility. A total of 12 case–control studies with 2332 cases and 3000 controls for MTHFR C677T were included eventually [11–16, 22–27]. The main results of this pooled analysis are presented in Table 2 and the forest plot evaluating the association of MTHFR polymorphisms with cervical risk is presented in Fig. 1a.

Overall, no significant association was found between cervical cancer and MTHFR C677T polymorphism in all models: allele contrast (C vs. T), OR = 1.05, 95 % CI = 0.85–1.30; homozygote (CC vs. TT), OR = 1.01, 95 % CI = 0.69–1.48; heterozygote (CC vs. CT), OR = 1.10, 95 % CI = 0.86–1.40; dominant model (CC vs. CT+TT), OR = 1.08, 95 % CI = 0.83–1.40; recessive model (CC+CT vs. TT), OR = 0.97, 95 % CI = 0.71–1.34).

To underestimate the true effect of the association between MTHFR polymorphisms and cervical cancer risk, stratified analyses were performed by ethnicity and source of controls. In stratified analyses, no significant associations were observed in the allele contrast, homozygote, heterozygous, dominant model and recessive model in any subgroup (Table 2).

Association of the MTHFR A1298C polymorphism with cervical cancer susceptibility.

A total of five case–control studies including 677 cases and 1191 controls for MTHFR A1298C were enrolled eventually [10, 11, 13, 22, 26]. The evaluations of the association of MTHFR A1298C polymorphism with cervical cancer are presented in Table 3 and Fig. 1b. A significantly increased cervical cancer risk associated with the MTHFR A1298C polymorphism was found in three models: allele contrast (A vs. C), OR = 0.84, 95 % CI = 0.71–0.98; heterozygote (AA vs. AC), OR = 0.72, 95 % CI = 0.59–0.89; dominant model (AA vs. AC+CC), OR = 0.72, 95 % CI = 0.59–0.88. However, the association was not found in the homozygote comparison and recessive model (homozygote comparison (AA vs. CC), OR = 2.02, 95 % CI = 0.75–5.41; recessive model (AA+AC vs. CC), OR = 2.37, 95 % CI = 0.79–7.09.

When stratified for ethnicity, we found a significantly increased cervical cancer risk among Asian descent in allele contrast, heterozygote comparison and dominant model [allele contrast (A vs. C), OR = 0.84, 95 % CI = 0.71–0.98; heterozygote comparison (AA vs. AC), OR = 0.72, 95 % CI = 0.59–0.89; dominant model (AA vs. AC+CC), OR = 0.72, 95 % CI = 0.59–0.88]. And yet, significantly decreased cervical cancer risk was observed in homozygote comparison and recessive model [homozygote comparison (AA vs. CC), OR = 3.21, 95 % CI = 0.57–6.71; recessive model (AA+AC vs. CC), OR = 3.99, 95 % CI = 2.01–7.94]. Since only one study of MTHFR A1298C polymorphism and cervical cancer risk in Caucasian population was published, the result of Caucasian population could not be reliable.

When stratified for source of controls, a significantly increased cervical cancer risk was found among PCC studies in allele contrast, heterozygote comparison and dominant model [allele contrast (A vs. C), OR = 0.81, 95 % CI = 0.67–0.97; heterozygote comparison (AA vs. AC), OR = 0.71, 95 % CI = 0.56–0.91; dominant model (AA vs. AC+CC), OR = 0.72, 95 % CI = 0.57–0.91]. The associations were not found in the homozygote comparison and recessive model [homozygote comparison (AA

Table 1 Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	SNPs studied	Source of controls	Simple size (case/control)	Genotyping methods	MAF in controls	HWE
Lanbropoulos	2003	Greece	Caucasian	C677T	PCC	21/91	PCR-PFLP	0.34	0.40
Sull	2004	Korea	Asian	C677T	PCC	246/454	SNapShot	0.42	0.99
Ma	2005	China	Asian	C677T	HCC	111/111	PCR-PFLP	0.43	0.29
Zoodsma	2005	The Netherland	Caucasian	C677T	PCC	636/592	Taqman SNP	0.32	0.61
Kang	2005	Korea	Asian	C677T, A1298C	PCC	79/74; 79/84	PCR-PFLP	0.38; 0.16	0.49; 0.34
Shekari	2008	India	Caucasian	C677T	PCC	200/200	PCR-PFLP	0.21	0.54
Kohaar	2010	India	Caucasian	C677T, A1298C	PCC	164/231	SNapShot	0.16; 0.37	0.60; 0.13
Tong	2011	Korea	Asian	C677T, A1298C	HCC	146/427; 148/428	Taqman SNP	0.41; 0.20	0.37; 0.64
Yang	2011	China	Asian	C677T, A1298C	PCC	157/199	PCR-PFLP	0.33; 0.20	0.47; 0.03
Keyserling	2011	Germany	Caucasian	C677T	HCC	386/328	LDR-PCR	0.29	0.89
Prasad	2011	India	Mixed	C677T	PCC	62/125	PCR-PFLP	0.04	0.06
Mostowska	2011	Poland	Caucasian	C677T	PCC	124/168	PCR-PFLP	0.35	0.42
Fan	2014	China	Asian	A1298C	PCC	129/214	PCR-PFLP	0.16	0.20

SNPs single nucleotide polymorphisms, *HCC* hospital-based case–control, *PCC* population-based case–control, *PCR–RFLP* polymerase chain reaction-restriction fragment length polymorphism, *LDR-PCR* ligation detection reaction-polymerase chain reaction, *MAF* minor allele frequency, *HWE* Hardy–Weinberg equilibrium

vs. CC), OR = 2.88, 95 % CI = 0.67–12.66; recessive model (AA+AC vs. CC), OR = 3.21, 95 % CI = 0.74–13.98].

Heterogeneity analysis

A substantial heterogeneity of MTHFR C677T polymorphism and cervical cancer was observed among studies in overall comparisons [allele contrast (C vs. T), $P_{\text{heterogeneity}} < 0.001$; homozygote comparison (CC vs. TT), $P_{\text{heterogeneity}} = 0.002$; heterozygote comparison (CC vs. CT), $P_{\text{heterogeneity}} < 0.001$; dominant model (CC vs. CT+TT), $P_{\text{heterogeneity}} < 0.001$; recessive model (CC+CT vs. TT), $P_{\text{heterogeneity}} = 0.011$]. For MTHFR A1298C polymorphism, heterogeneity was also observed in homozygote comparison and recessive model (homozygote comparison, $P_{\text{heterogeneity}} = 0.011$; recessive model, $P_{\text{heterogeneity}} = 0.002$).

Galbraith plot analyses were utilized to explore sources of heterogeneity across studies. Five studies were found to be contributors of heterogeneity for allele contrast of C677T polymorphism [14, 15, 23, 25, 27]. The heterogeneity decreased significantly after excluding the five outlier studies (C vs. T: $P_{\text{heterogeneity}} = 0.516$). Four studies were found to be contributors of heterogeneity for heterozygote comparison of C677T polymorphism [14, 15, 22, 25]. The heterogeneity decreased significantly after excluding the four outlier studies (CC vs. TT: $P_{\text{heterogeneity}} = 0.628$). Three studies were found to be contributors of heterogeneity for heterozygote comparison of C677T polymorphism [15, 23, 25]. The heterogeneity decreased significantly after excluding the three outlier studies (CC vs. CT: $P_{\text{heterogeneity}} = 0.975$). Four studies were found to be contributors of heterogeneity for dominant model of C677T polymorphism [14, 15, 23, 25]. The heterogeneity decreased after excluding the four outlier studies (CC vs. CT+TT: $P_{\text{heterogeneity}} = 0.835$). Two studies were found to be contributors of heterogeneity for recessive model of C677T polymorphism [14, 22]. The heterogeneity decreased after excluding the two outlier studies (CC+CT vs. TT: $P_{\text{heterogeneity}} = 0.301$).

For MTHFR A1298C polymorphism, two studies were found to be contributors of heterogeneity for heterozygote comparison and recessive model [10, 13]. We re-evaluated the association after excluding these two outlier studies with reduced heterogeneity (AA vs. CC: $P_{\text{heterogeneity}} = 0.191$; AA+AC vs. CC: $P_{\text{heterogeneity}} = 0.214$).

Sensitivity analysis

Sensitivity analyses were performed to evaluate the influence of each study on the overall pooled OR. The study of Zoodsma et al. was considered to be the most influenced study on the pooled OR for the association of the MTHFR C677T with cervical cancer risk (Fig. 2) [15]; however, the result of sensitivity analysis remained nonsignificant after the removal of that study. Regarding the association of the MTHFR A1298C with cervical cancer risk, the study of Fan et al. was considered to be the most influenced study on the pooled OR [10]. The result of sensitivity analysis revealed that the pooled ORs were 0.72 (95 % CI: 0.59, 0.89) and 0.77 (95 % CI: 0.61, 0.97) before and after

Table 2 Quantitative analyses of the MTHFR C677T polymorphism on the cervical cancer risk

Genetic model			Allele contrast		Homozygote		Heterozygote		Dominant model		Recessive model	
Variables	Sample size		C vs. T		CC vs. TT		CC vs. CT		CC vs. CT+TT		CC+CT vs. TT	
	N^a	Case/control	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}
Total	12	2332/3000	1.05 (0.85, 1.30)	0.000	1.01 (0.69, 1.48)	0.002	1.10 (0.86, 1.40)	0.000	1.08 (0.83, 1.40)	0.000	0.97 (0.71, 1.34)	0.011
Ethnicity												
Asian	5	739/1265	0.86 (0.66, 1.11)	0.000	0.76 (0.42, 1.39)	0.004	0.96 (0.78, 1.18)	0.818	0.89 (0.70, 1.14)	0.216	0.78 (0.47, 1.30)	0.007
Caucasian	6	1531/1610	1.27 (0.92, 1.76)	0.009	1.31 (0.88, 1.94)	0.226	1.28 (0.84, 1.95)	0.000	1.31 (0.86, 1.99)	0.000	1.22 (0.92, 1.61)	0.636
Mixed	1	62/125	0.99 (0.33, 2.97)	–	1.48 (0.06, 36.92)	–	0.79 (0.25, 2.51)	–	0.88 (0.28, 2.76)	–	1.51 (0.06, 37.51)	–
Source of control												
PCC	9	1689/2134	1.19 (0.92, 1.53)	0.000	1.28 (0.80, 2.04)	0.016	1.23 (0.93, 1.62)	0.003	1.23 (0.92, 1.65)	0.000	1.17 (0.78, 1.75)	0.045
HCC	3	643/866	0.79 (0.59, 1.05)	0.044	0.64 (0.34, 1.21)	0.040	0.81 (0.62, 1.06)	0.300	0.77 (0.56, 1.07)	0.154	0.71 (0.41, 1.22)	0.050

HCC hospital-based case–control, *PCC* population-based case–control

[a] Number of comparisons

[b] *P* value of *Q* test for heterogeneity test. Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used

excluding that study, respectively. In addition, one study of MTHFR A1298C polymorphism was not consistent with HWE (Hardy–Weinberg equilibrium) [22]. When analysis was limited to the trials within HWE, the estimated association remained unchanged.

Cumulative meta-analysis

Cumulative meta-analyses of the two associations were performed by sorting of the included studies according to the publication time. The cumulative meta-analysis for the association of the MTHFR C677T with cervical cancer risk demonstrated that the null results were consistent and remained unchanged over time (Fig. 3a). As for the cumulative meta-analysis of association of the MTHFR A1298C with cervical cancer risk, the results showed that increased significant associations were found with accumulation of more data over time, although no associations were observed initially (Fig. 3b).

Publication bias

Begg's and Egger's tests were conducted to assess publication bias of the literatures.

The shapes of the Begg's funnel plots did not show any evidence of obvious asymmetry. In addition, no potential publication bias were observed in the statistical results [(1) MTHFR C677T, allele contrast (C vs. T): Begg's test $P = 0.73$, Egger's test $P = 0.96$; homozygote comparison (CC vs. TT): Begg's test $P = 0.64$, Egger's test $P = 0.57$; heterozygote comparison (CC vs. CT): Begg's test $P = 0.54$, Egger's test $P = 0.68$; dominant model (CC vs. CT+TT): Begg's test $P = 0.84$, Egger's test $P = 0.66$; recessive model (CC+CT vs. TT): Begg's test $P = 0.28$, Egger's test P = 0.34; (2) MTHFR A1298C, allele contrast (A vs. C): Begg's test $P = 0.46$, Egger's test $P = 0.86$; homozygote comparison (AA vs. CC): Begg's test $P = 1.00$, Egger's test $P = 0.61$; heterozygote comparison (AA vs. AC): Begg's test $P = 1.00$, Egger's test $P = 0.60$; dominant model (AA vs. AC+CC): Begg's test $P = 0.81$, Egger's test $P = 0.67$; recessive model (AA+AC vs. CC): Begg's test $P = 1.00$, Egger's test $P = 0.73$].

Discussion

Present study based on 13 case–control studies demonstrates a variety of associations implicating MTHFR polymorphisms and cervical cancer. Both the polymorphisms of C677T and A1298C seemed capable of conferring additional risk for cervical cancer.

No associations were found between the MTHFR C677T polymorphism and cervical cancer risk in all

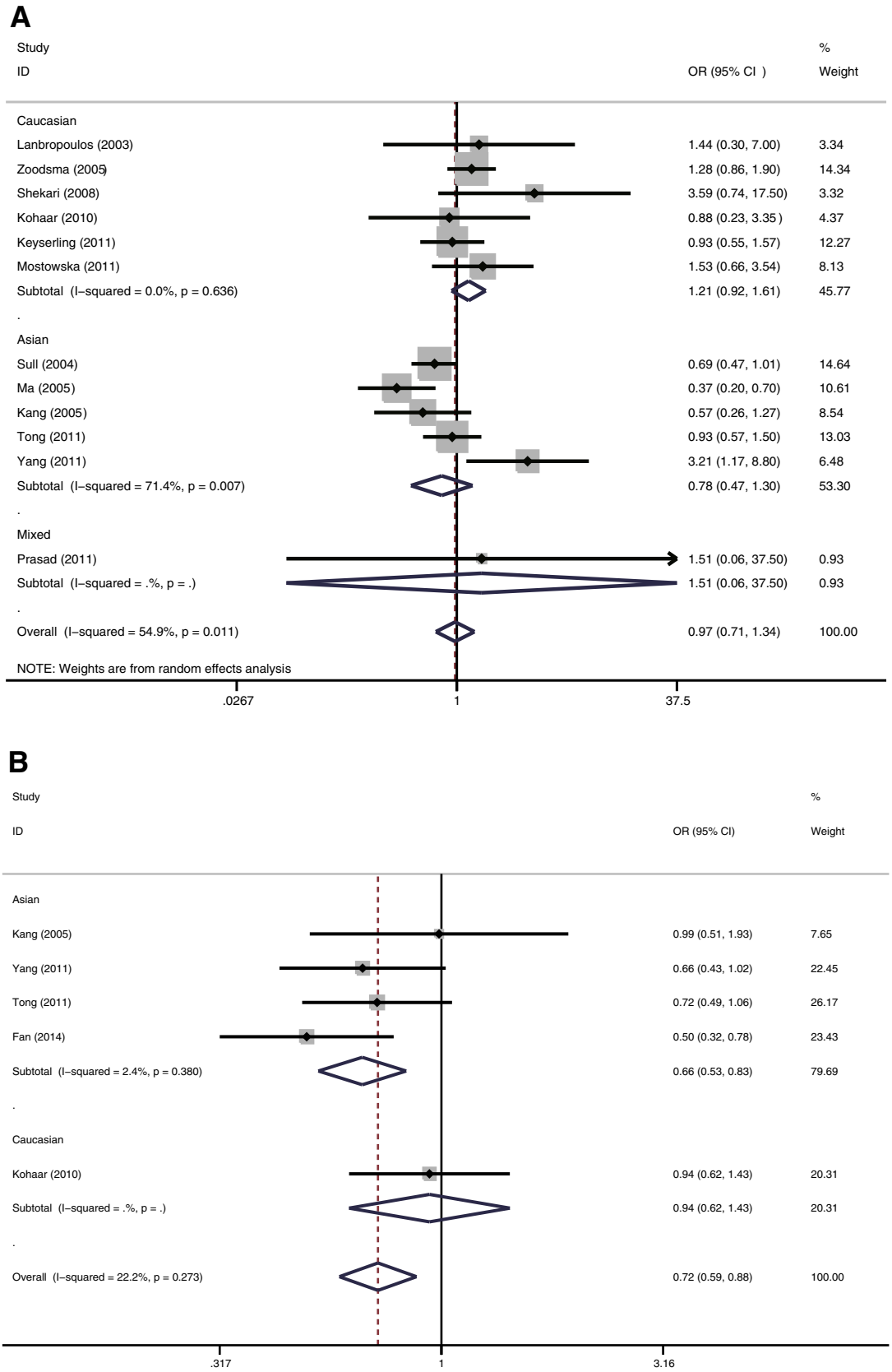

Fig. 1 **a** Forest plot for C677T polymorphism (CC+CT vs. TT) and cervical cancer; **b** forest plot for A1298C polymorphism (AA vs. AC+CC)

Table 3 Quantitative analyses of the MTHFR A1298C polymorphism on the cervical cancer risk

Genetic model			Allele contrast		Homozygote		Heterozygote		Dominant model		Recessive model	
Variables	Sample size		A vs. C		AA vs. CC		AA vs. AC		AA vs. AC+CC		AA+AC vs. CC	
	N^a	Case/control	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}	OR (95 % CI)	P^b_{value}
Total	5	677/1191	0.84 (0.71, 0.98)	0.131	2.02 (0.75, 5.41)	0.011	0.72 (0.59, 0.89)	0.189	0.72 (0.59,0.88)	0.273	2.37 (0.79, 7.09)	0.002
Ethnicity												
Asian	4	513/960	0.80 (0.66, 0.97)	0.092	3.21 (0.53, 6.71)	0.331	0.66 (0.52, 0.83)	0.297	0.66 (0.53,0.83)	0.380	3.99 (2.01, 7.94)	0.357
Caucasian	1	164/231	0.92 (0.69, 1.24)	–	0.80 (0.42, 1.53)		0.98 (0.63, 1.51)	–	0.94 (0.62,1.43)	–	0.81 (0.45, 1.47)	–
Source of control												
PCC	4	529/763	0.81 (0.67, 0.97)	0.092	1.87 (0.56, 6.21)	0.006	0.71 (0.56, 0.91)	0.106	0.72 (0.57, 0.91)	0.162	2.23 (0.59, 8.41)	0.001
HCC	1	148/428	0.94 (0.68, 1.31)	–	2.88 (0.67, 12.66)		0.74 (0.50, 1.10)	–	0.71 (0.49, 1.06)	–	3.21 (0.74, 13.98)	–

HCC hospital-based case–control, *PCC* population-based case–control

[a] Number of comparisons

[b] *P* value of *Q* test for heterogeneity test. Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used

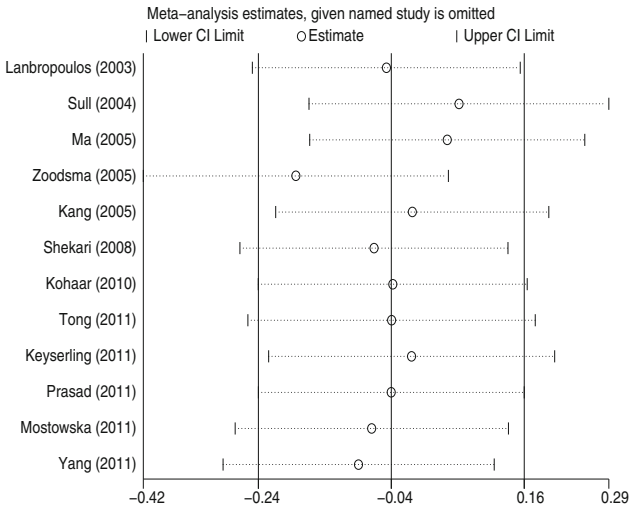

Fig. 2 Sensitivity analysis for C677T polymorphism

examined models, which may be explained by obvious heterogeneity among the included trials. When studies contributing to heterogeneity were excluded, the result did not change. In addition, the subgroup analyses were performed by ethnicity and source of controls; however, we still found no significant association in any subgroup.

As for MTHFR A1298C polymorphism, significantly increased cervical cancer risk was found in allele contrast, dominant model and heterozygote comparison. When stratified for ethnicity and source of controls, significantly increased cervical cancer risk was found among Asian descent and among PCC studies in allele contrast, heterozygote comparison and dominant model. The null result of Caucasian descent may be due to the limited number of studies. Since only one study was from Caucasian descent, a high risk of reporting bias for the association of the MTHFR A1298C polymorphism and cervical cancer risk in Caucasian descent should be considered.

Interestingly, we found a significantly increased cervical cancer risk with MTHFR A1298C polymorphism in heterozygote comparison, but not in homozygotes comparison. Although the reason for the increased association only observed in heterozygote comparison remains unknown, it is probable that the heterozygous genotype may be in LD with other susceptibility loci. Another possible explanation is that these heterozygotes may have deficient function due to the potential imbalance of the protein structure. Similar phenomenon was reported by Ma et al., who studied the association between breast cancer risk and polymorphisms of CDKN1A and CDKN1B [29]. They observed a significantly elevated breast cancer risk only with CDKN1B C-79T heterozygotes, but not the homozygotes.

The results implicating C677T polymorphism are partly consistent with previous studies. Yu et al. performed a

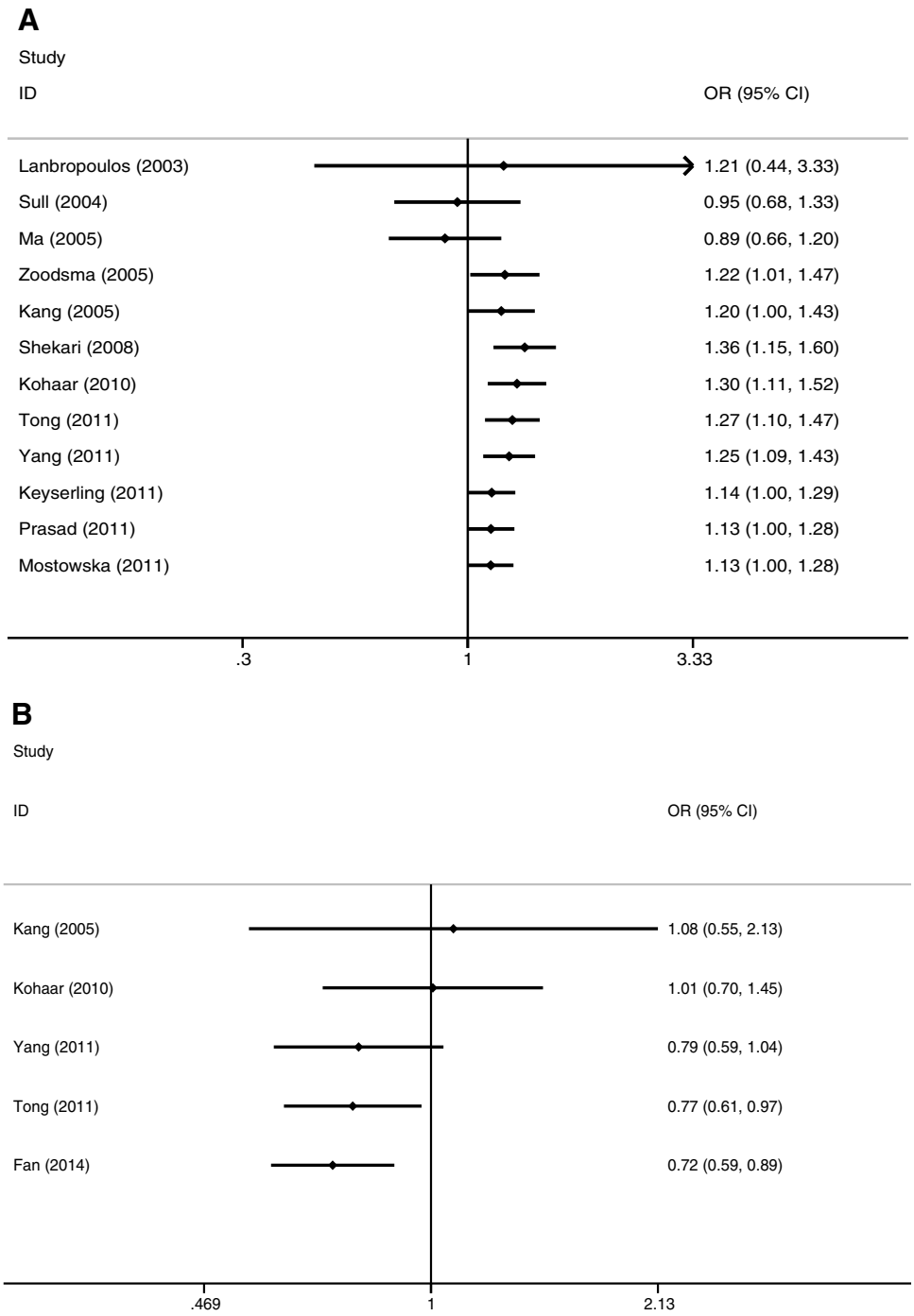

Fig. 3 **a** Cumulative meta-analysis for C677T polymorphism and cervical cancer in chronologic order. **b** Cumulative meta-analysis for A1298C polymorphism

system review and did not find any association between cervical cancer risk and MTHFR C677T polymorphism except for recessive model [30]. And yet, another meta-analysis reported the association between cervical cancer risk and MTHFR C677T polymorphism was only observed in a complete over-dominant model [31]. The diversity of results may be explained by different ethnic composition: various meta-analyses included diverse original trials which were conducted in different ethnic groups and the ethnic composition in a variety of meta-analyses may be discrepancy. And some diversity of researching methods, such as inclusion/exclusion criteria, sample size of study, quality of original studies and selection bias, also can contribute to the difference. Regarding MTHFR A1298C polymorphism, an association with increased cervical cancer risk emerged at allele contrast, heterozygote comparison and dominant model. Present study was based on five case–control trials (677 cases and 1191 controls) and

the result is not consistent with a previous meta analysis [32]. The possible explanation is that the previous study had a relatively small sample size [meta-analysis of Wu et al. only included three studies (391 cases and 734 controls) for MTHFR A1298C polymorphism and cervical cancer risk] and may lead to a rough risk estimate.

Several risk factors including smoking, pregnancy, multiple sexual partners and infection of HPV were identified to be correlated to the progression of cervical cancer. However, the majority of data is lacking stratification by age, smoking status, stage of disease and the infection of HPV; specifically, only one included study presented separate reporting about the association between HPV infection and MTHFR polymorphism, and found a null result [13]. We failed to obtain data of HPV-infection status from authors, thus, the subgroup analysis stratified by HPV-infection status could not be actualized.

One important issue for any meta-analysis is the degree of heterogeneity because studies of non-homogeneous may generate misleading results. In current meta analysis, the I^2 statistics and Q test were performed to evaluate the significance of heterogeneity. Obvious heterogeneity among the including studies was found in all models of MTHFR C677T polymorphism. A Galbraith plot was drawn to find the sources of heterogeneity, and several studies were found to be the main contributor for the heterogeneity of MTHFR C677T polymorphism. The heterogeneity was significantly decreased and the conclusion maintained unchanged after removal of the outlier study. Another major concern in the meta-analysis is publication bias by the reason of the potential selective publication of reports. In present meta analysis, Begg's funnel plot and Egger's test were conducted to assess the publication bias. Both statistical results and the shape of funnel plots exhibited no sign of publication bias. It is worth to mention that the results held when the sensitivity analysis was carried out, which implies that the results are robust and reliable. Also, cumulative meta-analyses were conducted by sorting of the included studies according to the publication time and the result of the MTHFR C677T revealed that the pooled OR trend was stable and no significant associations were found with each accumulation of more data over time. The odds ratios (OR) of MTHFR C677T polymorphism reached 1.13 and 95 % confident intervals (95 % CI) was (1.00, 1.28) in 2011, when the last study (Mostowska et al.) was added into the cumulative meta-analyses, the value of OR and 95 % CI was still 1.13 (1.00, 1.28), which indicates that the results are stable and precise [12].

Several limitations of present study should be noted: (1) the number of subjects in the studies and the number of studies included in the meta-analysis of MTHFR A1298C polymorphism were relatively small, the results may be not enough to explore the real associations statistically; (2) the current study was based on unadjusted OR estimates for the reason that not all included trials presented adjusted ORs or when they did, the ORs were not adjusted by the same factors, such as race, age and smoking status; (3) obvious heterogeneity among studies of MTHFR C677T polymorphism was found in all models, and the genotype distribution of one included study in control group was not consistent with HWE [22]. (4) Lacking of the combinative data of the two-SNP limited further pooled analysis of the potential interactions between the two single-SNPs.

In conclusion, our meta-analysis suggests that the polymorphism of MTHFR C677T may be not associated with cervical cancer risk, while the polymorphism of MTHFR A1298C may have a increased risk associated with cervical cancer among Asian descent. Since only one study of MTHFR A1298C polymorphism was from an Caucasian population, it is critical that well-designed and larger multicenter studies based on Caucasian patients should be carried out to re-evaluate the association.

Compliance with ethical standards

Conflict of interest We declare no potential conflicts of interest involved in this study.

Ethical standards The manuscript was a review article, which included studies of ethical approval.

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