The association of MTHFR A1298C polymorphism with cervical cancer: An Updated Meta-Analysis Involving 2835 Subjects

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Abstract

Background Published data have reported the relationships between MTHFR A1298C polymorphisms and cervical cancer susceptibility. However, the conclusions of these findings lack consistency.

Methods A comprehensive literature search was performed using Web of Science, PubMed, EMBASE, Cochrane library, Wan Fang and CNKI databases. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the correlation of MTHFR A1298C polymorphism and cervical cancer risk. Fixed-effects or random effects models was adopted according to heterogeneity test.

Results A total of nine studies (1145 cases and 1690 controls) were included in this meta-analysis. Pooled data revealed that MTHFR A1298C polymorphism was significantly associated with an increased risk of cervical cancer in the allele model (P=0.028); the recessive model (P=0.028); and the heterozygous model (P=0.031).

Conclusions Our results revealed that MTHFR A1298C polymorphism was associated with risk of cervical cancer.

Background

Cervical cancer is a worldwide public health problem. In spite of being preventable, this disease is still the fourth most common type of cancer among women and the seventh among the general population [1]. Several certain factors appeared to be related with an increased risk of developing cervical cancer are early start of sexual life, multiple pregnancies, diet, smoking, and infection with human papilloma viruses (HPV), among which HPV infection was prominent [2, 3]. High-risk subtypes of the human papillomavirus (HPV) cause almost all cervix cancers [4]. However, this does not mean that all HPV infection ultimately cause cervix cancer. It was reported that a single same type HPV infection can only lead to cell immortalization and cannot induce malignant transformation of epithelial cells. HPV infection, with host internal and external environment factors, such as genetic polymorphism leading to susceptibility, the interaction of these factors causes an accumulation of cell damage that eventually leads to cancer.

Folic acid, as a water-soluble B vitamin [5], is essential for proper cellular function. Some studies have identified that levels of folate, play a role in cervical carcinogenesis [6, 7]. Folic acid is considered to be critical for the biosynthesis of purines and thymidylates which are key factors for normal DNA replication and repair as well as DNA methylation [8]. Once deficiency, it would impair cellular physiology and increase the risk of cervical cancer if it was accompanied by a persistent HPV infection. In addition to exogenous supplements, one of the most vital enzymes as intrinsic factor, named methylenetetrahydrofolate reductase (MTHFR), affect the level of folic acid. MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate acid into 5-methyltetrahydrofolate acid which is a major circulating form of folate acid. However, the activity of the enzyme was affected by gene polymorphism which was associated with reduced enzyme activity and folate deficiency [9]. There are 2 common types: one is a C-to-T transition at nucleotide 677 (677 C/T) in exon 4, resulting in an alanine-to-valine substitution that affects the catalytic domain of the enzyme, leading to reduced enzyme activity; another is an A-to-C transversion at position 1298 in exon 7 (1298A /C), resulting in

a substitution of glutamate with alanine at codon 429 [10]. The later will also lead to low activity to a lesser extent, but the summary is lacking. Therefore, to address this gap, in this study, we assessed and explored the association between MTHFR 1298 A/C with the susceptibility of cervical cancer. Elucidation of an association, if any, might be informative regarding the hypothesis that impaired folate metabolism due to MTHFR polymorphism, resulting in low folate concentration, plays an intensified role in the occurrence of cervical cancer with HPV infection.

Methods

Search strategy

The meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. Two authors independently searched electronic databases (Web of Science, PubMed, Embase, Cochrane library, WanFang and CNKI from inception to May 2019) for identify relevant articles. Electronic databases were searched using the keywords: “MTHFR”, “A1298C”, “rs1801131”, “polymorphism”, “SNP”, “variant” and “cervical cancer”. The reference lists of the retrieved articles were also searched carefully to identified other relevant publications.

Inclusion and exclusion criteria

Inclusion criteria: (1) case-control or cohort studies; (2) evaluated the association between MTHFR A1298C polymorphism and cervical cancer; (3) provided the sufficient data of allelic or genotypic frequencies of MTHFR A1298C; (4) the control group genotype followed Hardy–Weinberg equilibrium (HWE). Exclusion criteria: (1) reviews, duplication, case reports or animal studies; (2) incomplete data; (3) not case-control study.

Data extraction

Two authors independently extracted the necessary data from each eligible article, and disagreements were reconciled by third author. The following data form each study were extracted: first author’s name, year of publication year, country, ethnicity of population, genotyping methods, number of cases and control, genotyping data, Hardy–Weinberg equilibrium (HWE) in controls.

Quality assessment

The Newcastle–Ottawa Quality Scale (NOS) was used by two authors to evaluate the quality of the studies [12].

Statistical analysis

All statistical analyses were performed Stata 12.0 software (StataCorp, College Station, TX, USA). Five allelic models as allelic model (A vs. C), heterozygote model (AA vs. AC), homozygote model (AA vs. CC), recessive (AA vs. AC+CC), and dominant (CC vs. AA+AC) model were used to estimate the association between MTHFR A1298C polymorphism and cervical cancer. HWE of the control populations was calculated with Chi-square test and the significance level was defined as $p<0.05$. The pooled ORs with 95% confidence intervals (CIs)

were used to evaluate the correlation of MTHFR A1298C polymorphism and cervical cancer risk. P value < 0.05 was considered statistically significant. Heterogeneity across studies was assessed by the Q and I^2 tests. If heterogeneity was detected (P <0.05, I^2 > 50%), the random-effects model was be used to pool ORs. Otherwise, the fixed-effects model was adopted. Publication bias was assessed by Begg's funnel plots and Egger's regression test. The sensitivity analysis was performed to evaluate the stability of the pooled results. Subgroup analyses were performed according to the ethnicity.

Results

Characteristics of Studies

After initial search, a total of 132 articles were identified, of which 40 were excluded as duplicates. Of these, 62 records were excluded after screening titles and abstracts. 21 irrelevant studies were excluded after reading full papers. Ultimately, nine articles [13-21] were included in this meta-analysis according to inclusion criteria. The literature screening process was shown in Figure 1. Characteristics of the included studies in this meta-analysis are presented in Table 1. Among these studies, 6 studies were performed in Asian populations, 3 studies were conducted in Caucasian populations. The articles were published from 2006 to 2018. Two case-control studies were deviated from the HWE [20, 21].

Quantitative Synthesis

The results revealed that MTHFR A1298C polymorphism was significantly associated with cervical cancer susceptibility in the whole population under allelic (OR: 1.99, 95% CI: 1.08~3.67), recessive (OR: 0.48, 95% CI: 0.25~0.92) and heterozygous genetic models (OR: 1.75, 95% CI: 1.05~2.92). No significant association was found between them under dominant (OR: 2.91, 95% CI: 0.93~9.12) and homozygous genetic models (OR: 3.76, 95% CI: 0.92~15.40) (Figures 2-6; Table 2). In the subgroup analysis by ethnicity, no significant results were found for Caucasian and Asian population under all five genetic models (Table 3). There was also significant heterogeneity under the all the genetic models. Meta-regression was performed to explore the source of heterogeneity under these genetic models. The confounding factors included the publication year, ethnicity. However, these confounding factors couldn't explain the heterogeneity (P>0.05)

Sensitivity Analysis and Bias Diagnostics

In the current meta-analysis, there was high heterogeneity under recessive, dominant, homozygous and allelic genetic models. Thus, sensitivity analysis was performed by removing one study and re-calculated the pooled ORs and CIs to evaluate stability of the result. After the Gong et al. was removed from the current meta-analysis, the heterogeneity was significance decreased while still providing results consistent with our initial findings (Figure 7). However, removal of any other studies did not change the results from the original analysis. Therefore, the study of Gong et al. was the high sensitivity study on the pooled OR. Begg's and Egger's test implied that there was no publication bias in the current analysis (Figure 8; Table 2)

Discussion

Infection by HPV is not exclusive to cause cervical cancer. Genetic polymorphism is also important in inducing cervicogenesis collectively. Moreover, in distinct populations, the relationship between the risk of cervical tumorigenesis and gene polymorphism was almost various. In our analysis, 1145 cases and 1690 controls from nine publications were involved. The meta-analysis results showed that MTHFR A1298C is a risk factor for cervical cancer, especially in Asian population. As to MTHFR A1298C polymorphism, in previous study, Zhuo et al. [22] published the first meta-analysis assess the association between MTHFR A1298C gene polymorphisms and cervical cancer risk and did not find significant associations. In contrast, recent meta-analysis by Yi et al. [23], including five studies, suggested that the significant associations between MTHFR A1298C polymorphism and cervical cancer were found among Asians. However, these studies were limited to small sample sizes and high heterogeneity. Therefore, we performed a comprehensive large-scale meta-analysis to investigate these associations. We performed a more comprehensive large-scale meta-analysis (nine studies involving 2835 individuals) to accurately assess these associations.

Folate was indicated a protective effect on cervical epithelial cell [24]. In addition, multiple clinical evidences have reported that evaluated level folate level was inversely related with the risk of cervical cancer [19, 25, 26]. As the introduction described, folate metabolism is very important for protection of cervical epithelial cell through maintain the methylation, repair, and synthesis of DNA [27]. In physically, folates appear to be essential for cell growth and cell cycle. Once folate deficiency induces lower proliferation rates by increased apoptosis and cell cycle arrest[28]. Thus, this is very negative for normal cell survival, which would promote cell transformation into cancer cells. Some study has shown that low level of serum folate may increase the risk of cervical cancer. Furthermore, it could be potential synergy with HPV infection, promoting cervical cancer development [29]. In our study, we set up the relation of MTHFR, as a key enzyme involving the chemical reaction of vitamin folate, A1298C polymorphism and cervical cancer susceptibility. It is this polymorphism that affects the activity of the enzyme and leads to low folate concentration in serum. To be more specific, the activity was decreased when a substitution of glutamate with alanine occurred.

In basic research, carriers of variant alleles for MTHFR1298 exhibit genome-wide DNA hypomethylation, which is a characteristic of genome instability [30]. When the activity of MTHFR was decreased or lose, it would lead to relaxation of heterochromatin, a decrease of H3K9me3 levels that often associates with heterochromatin at the centromeric and telomeric regions, and an increase of certain transcripts at the centromeric region. In summary, it would destroy heterochromatin or whole genome stability [31]. Thus, it was not hard to speculate the hazardous of MTHFR A1298C. It has reported that the MTHFR 1298C allele frequency is approximately 20- 70% in Asia, 24-46% in Europe, and 0-15% in America [32], which may explain why Asians are strong association. This could give us an appropriate reminder that Asians with carriers of variant alleles for MTHFR1298 may probably more likely to get cervical cancer, if they are infected HPV simultaneously.

In our study, there are still some limitations as follows. Firstly, the sample size was relatively small and may not have provided sufficient statistical power. More studies with a larger sample size are required. Meanwhile, it is hoped that the exploration was expanded on the association of MTHFR A1298C polymorphism and tumors of the female reproductive system, including ovarian cancer, which will make the study more broad-spectrum and meaningful. Secondly, the subgroup analyses according to age, histological types and other

elements were not performed owing to insufficient relevant data. Thus, it is suggested that future study could combine environmental factors, age and genetic polymorphism together to explore the interaction. Thirdly, given that the MTHFR has two types of polymorphisms, whether there is an interaction is unknown.

Conclusions

Our meta-analysis suggested that MTHFR A1298C was associated with cervical cancer development, especially in Asian population. In the future, well-designed and larger-scale studies are necessary to explore the roles of tumor stage, smoking, histology, or gene–gene/gene–environment interactions in the pathogenesis of cervical cancer.

Abbreviations

MTHFR: methylenetetrahydrofolate reductase; HPV: human papilloma viruses; 677 C/T: C-to-T transition at nucleotide 677; 1298A/C: A-to-C transversion at position 1298 in exon 7; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HWE: Hardy–Weinberg equilibrium; NOS: Newcastle–Ottawa Quality Scale; OR: odds ratio; CI: confidence intervals.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Avaliability of date and meterials

All data are included in this article.

Competing interests

The authors declare that they have no conflicts of interests.

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Authors ' contributions

TL and PM conceived and designed this study. CM and ZW collected literatures, extracted and analyzed the date and wrote this article. YW and YL took part in controversial articles selection. BG and TL participated in quality assessment. All authors read the manuscript and favored submission.

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Tables

Table 1. Characteristics of the investigated studies of the association between the MTHFR A1298C polymorphism and cervical cancer.

First author	Year	Country	Ethnicity	Genotyping method	Sample size (cases/controls)	Case			Controls			HWE (control)	Quality score
						AA	AC	CC	AA	AC	CC		
Kang	2005	Korea	Asian	PCR-RFLP	79/84	55	22	2	58	25	1	0.344	7
Tong	2011	Korea	Asian	Taqman	148/428	89	57	2	278	132	18	0.643	7
Kohaar	2010	India	Caucasian	SNaPShot	164/231	58	83	23	85	119	27	0.130	7
Delgodo-Ensico	2006	Russia	Caucasian	PCR-RFLP	70/89	44	24	2	64	23	2	0.969	8
Hajiesmaeil	2016	Iran	Caucasian	PCR-RFLP	22/100	2	7	13	35	53	12	0.233	8
Gong	2018	China	Asian	TaqMan	146/115	26	64	56	85	27	3	0.631	8
Xie	2016	China	Asian	PCR-RFLP	230/230	106	63	61	136	53	41	0.000	8
Fan	2014	China	Asian	PCR-RFLP	129/214	68	53	8	148	63	3	0.195	8
Yang	2011	China	Asian	PCR-RFLP	157/199	89	67	1	132	54	13	0.029	8

HWE, Hardy–Weinberg equilibrium

Table 2. Summary of meta-analysis of association of MTHFR A1298C polymorphism and cervical cancer in the whole population.

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	Z-score	p-value	I^2 (%)	*p*-value	Begg's test	Egger's test
recessive genetic mode	7	0.48(0.25,0.92)	2.20	0.028	89.8	0.000	0.176	0.415
dominant genetic model	7	2.91(0.93,9.12)	1.83	0.067	83.1	0.000	0.881	0.691
homozygous genetic model	7	3.76(0.92,15.40)	1.84	0.066	86.7	0.000	0.881	0.536
heterozygous genetic model	7	1.75(1.05,2.92)	2.15	0.031	81.3	0.000	0.453	0.556
allelic genetic	7	1.99(1.08,3.67)	2.20	0.028	92.9	0.000	0.176	0.375

OR, odds ratio; CI, confidence interval.

Table 3 Results of the association between MTHFR A1298C polymorphism and cervical cancer risk by different ethnicities.

Comparison	Studies	Overall effect			Heterogeneity	
		OR (95% CI)	Z-score	p-value	I^2 (%)	*p*-value
Asian						
recessive genetic mode	4	0.42(0.15,1.18)	1.64	0.101	93.9	0.000
dominant genetic model	4	3.06(0.43,21.92)	1.11	0.266	85.1	0.000
homozygous genetic model	4	4.21(0.40,44.71)	1,19	0.234	89.4	0.000
heterozygous genetic model	4	2.04(0.94,4.43)	1.80	0.072	88.6	0.000
allelic genetic	4	2.09(0.79,5.52)	1.49	0.138	95.4	0.000
Caucasian						
recessive genetic mode	3	0.66(0.35,1.25)	1.28	0.200	55.8	0.104
dominant genetic model	3	2.66(0.55,12.91)	1.22	0.224	84.1	0.000
homozygous genetic model	3	3.07(0.53,17.63)	1.26	0.209	76.9	0.000
heterozygous genetic model	3	1.18(0.83,1.70)	0.92	0.356	0	0.453
allelic genetic	3	1.54(0.60,3.90)	1.50	0.133	85.2	0.001

OR, odds ratio; CI, confidence interval.

Figures

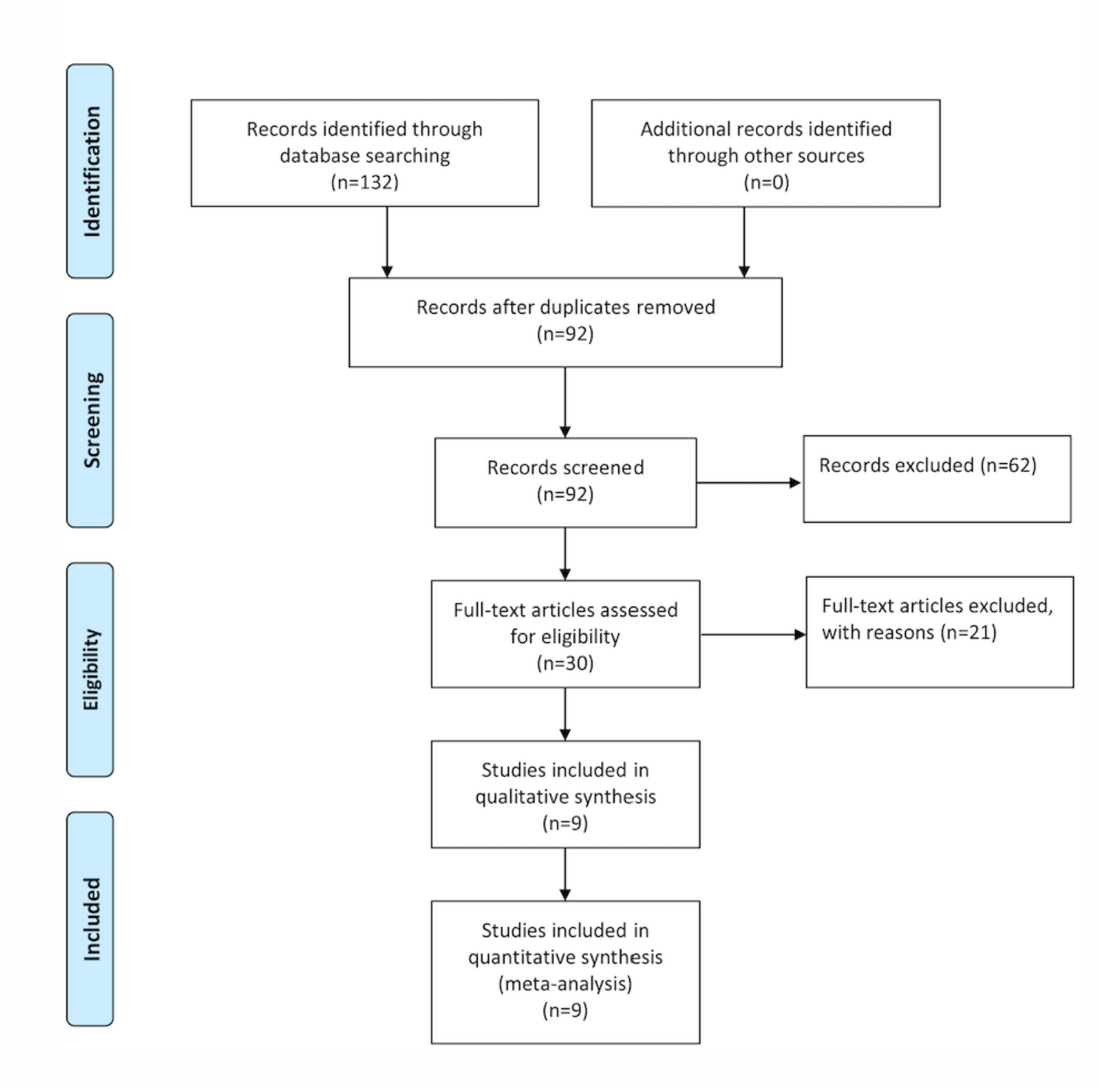

Figure 1

Flow diagram of literature screening and selection

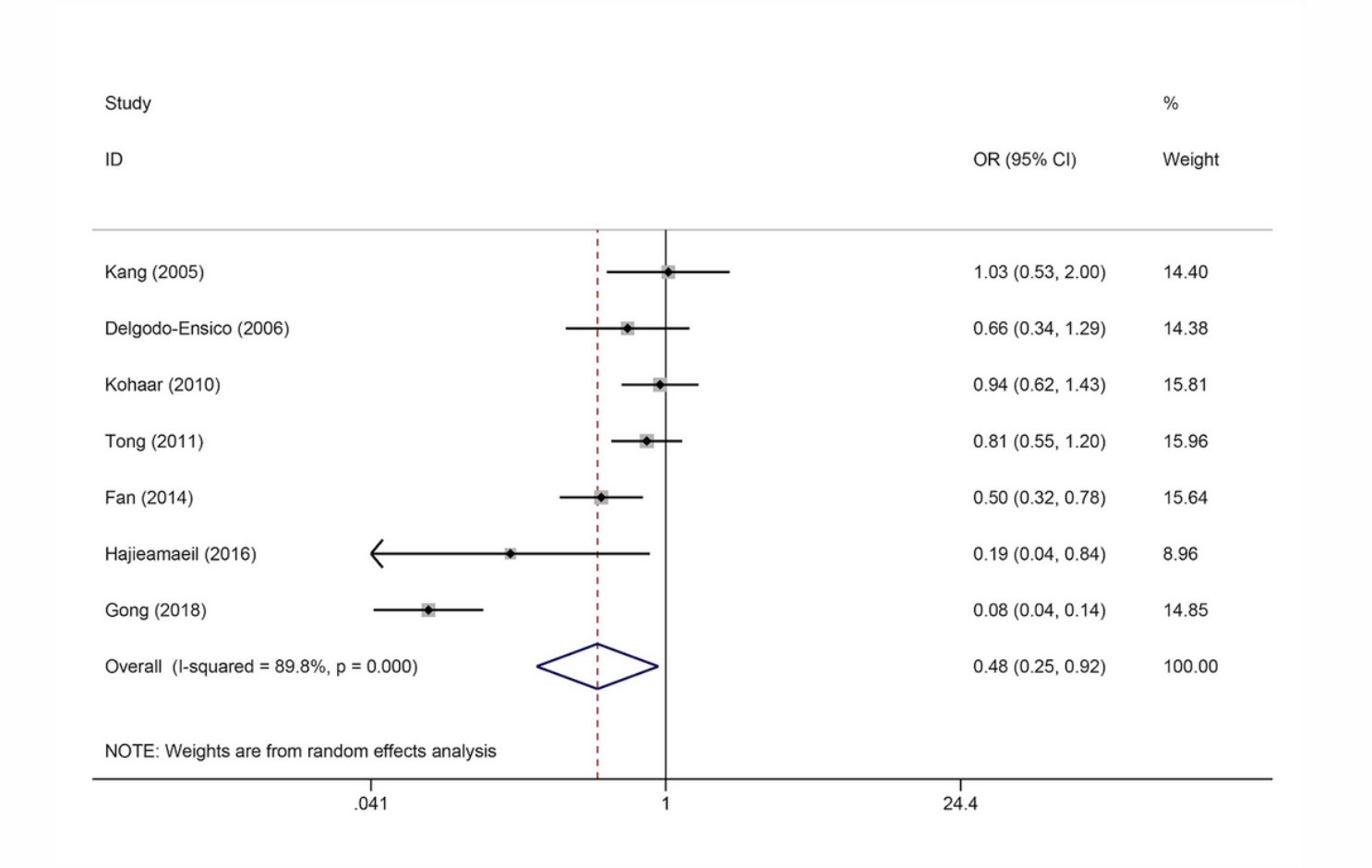

Figure 2

Forest plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under recessive genetic model (AA vs. AC + CC).

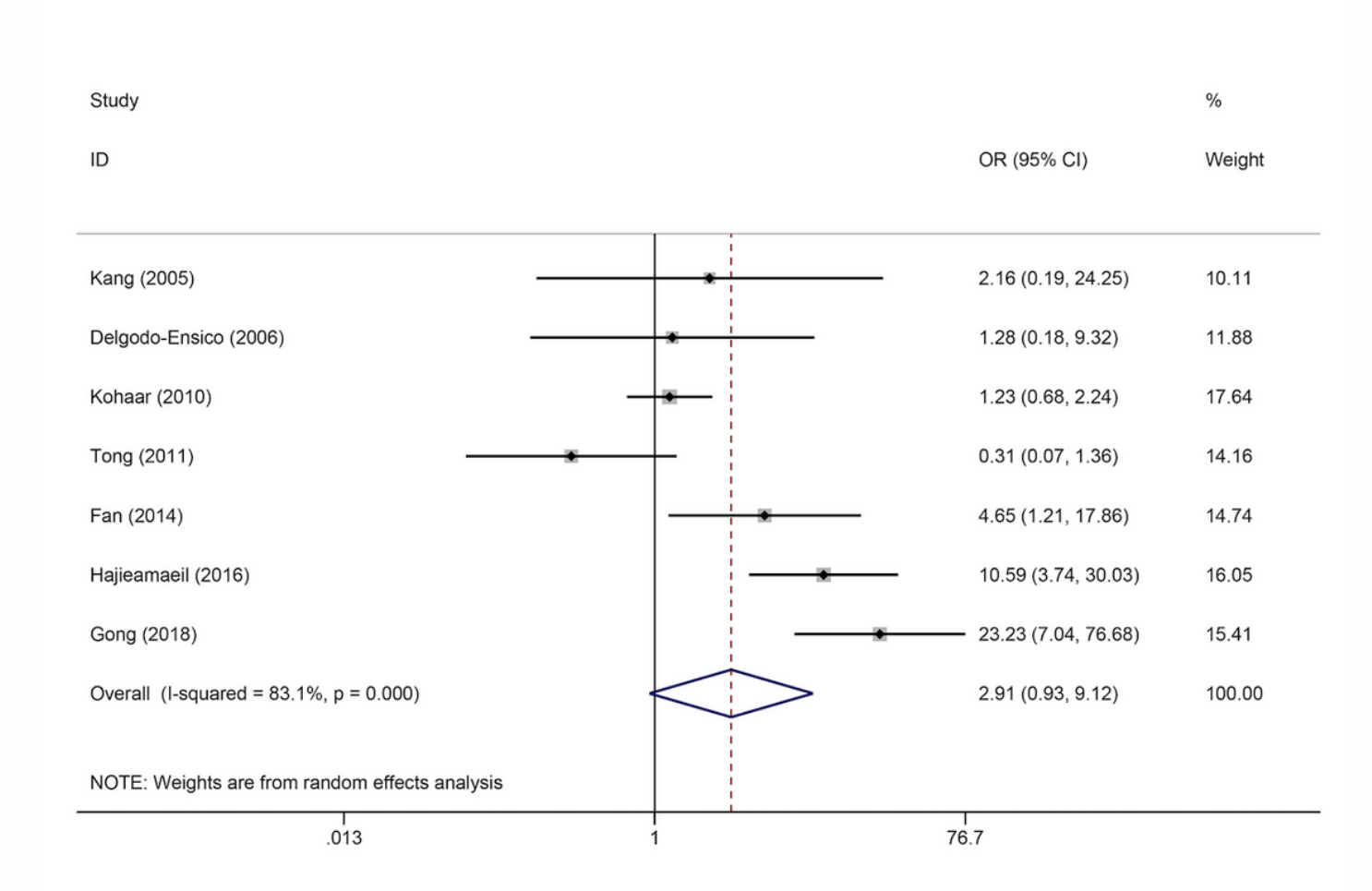

Figure 3

Forest plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under dominant genetic model (CC vs. AA + AC).

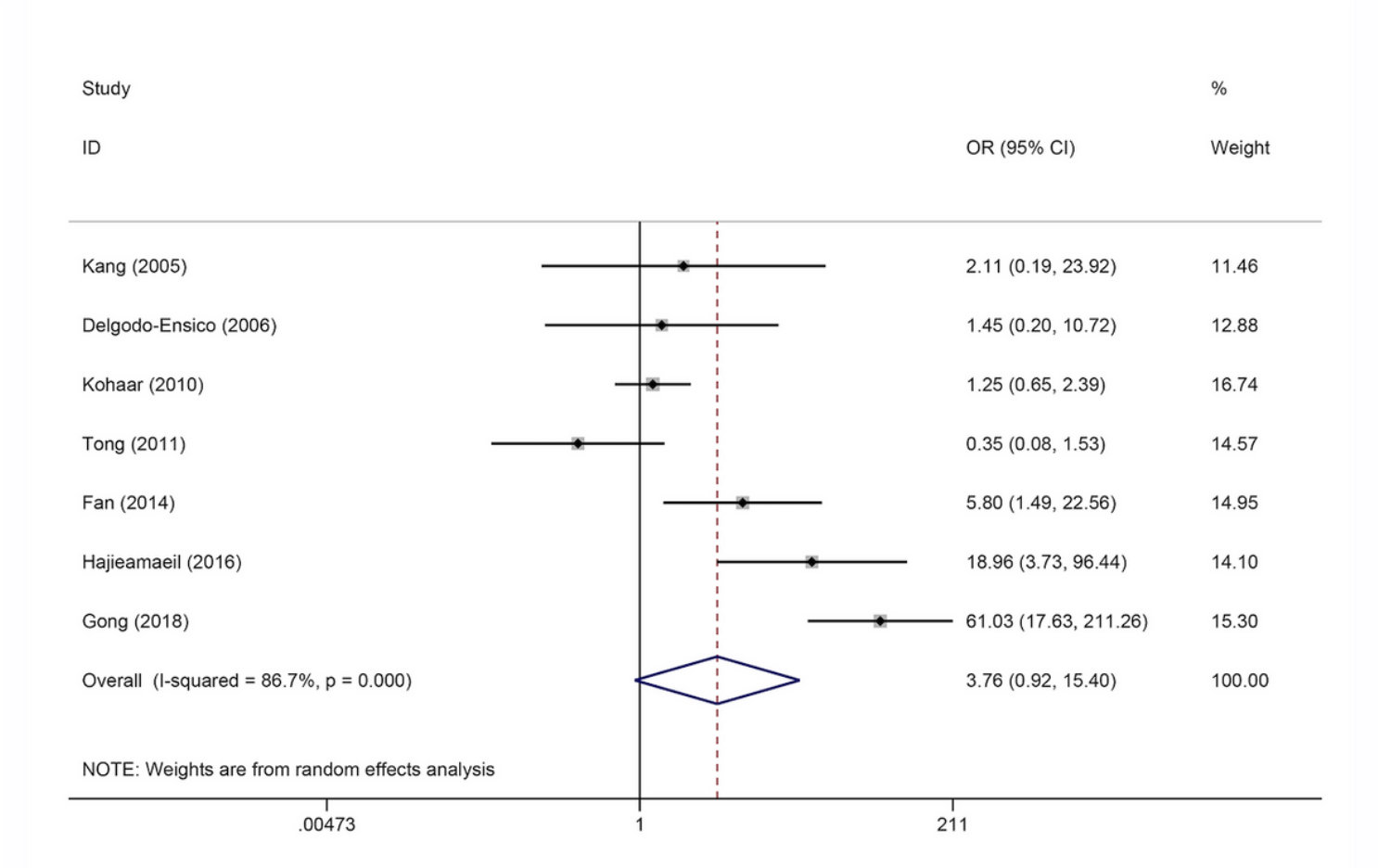

Figure 4

Forest plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under homozygous model (CC vs. AA).

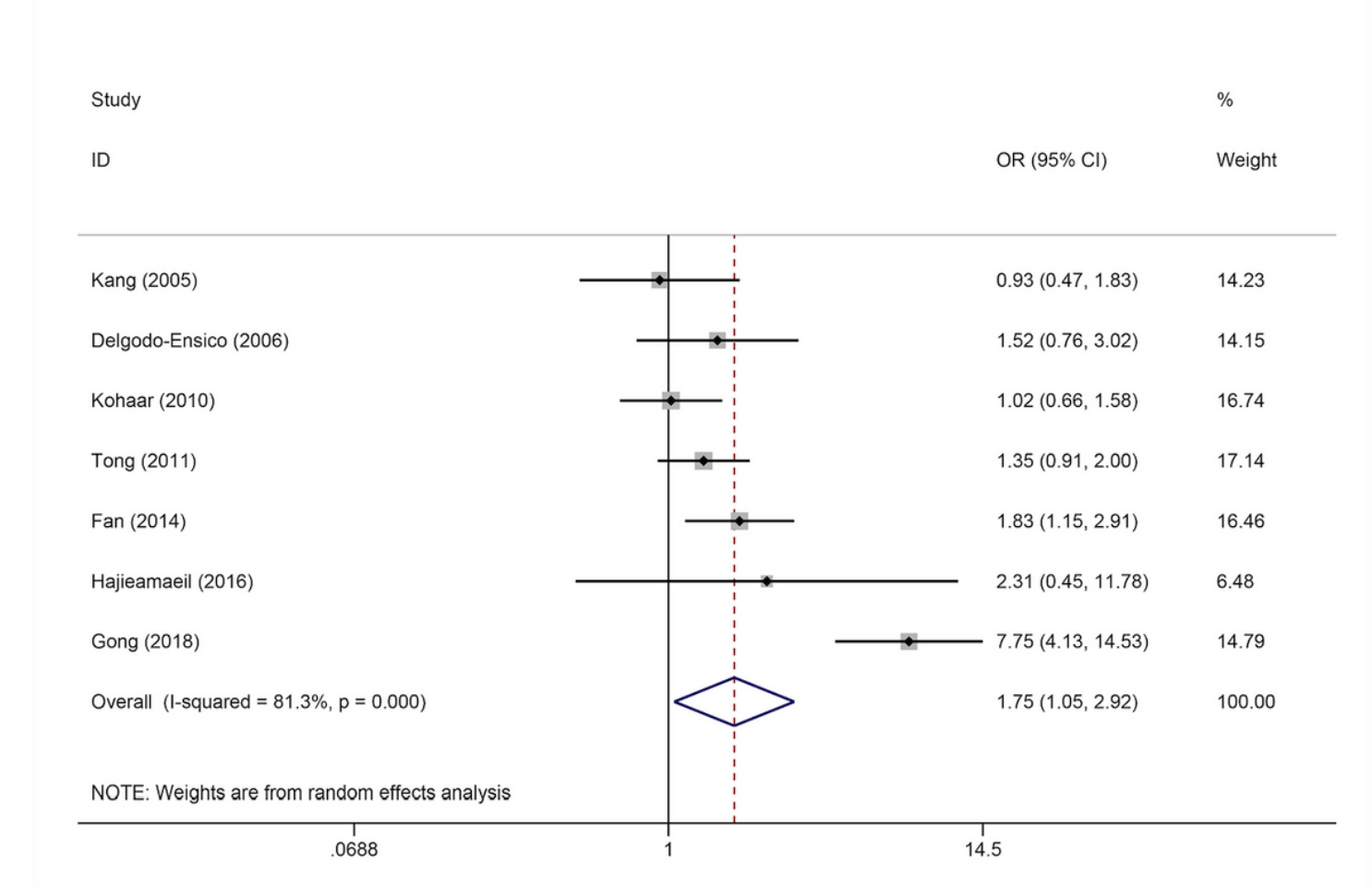

Figure 5

Forest plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under heterozygous model (AC vs. AA).

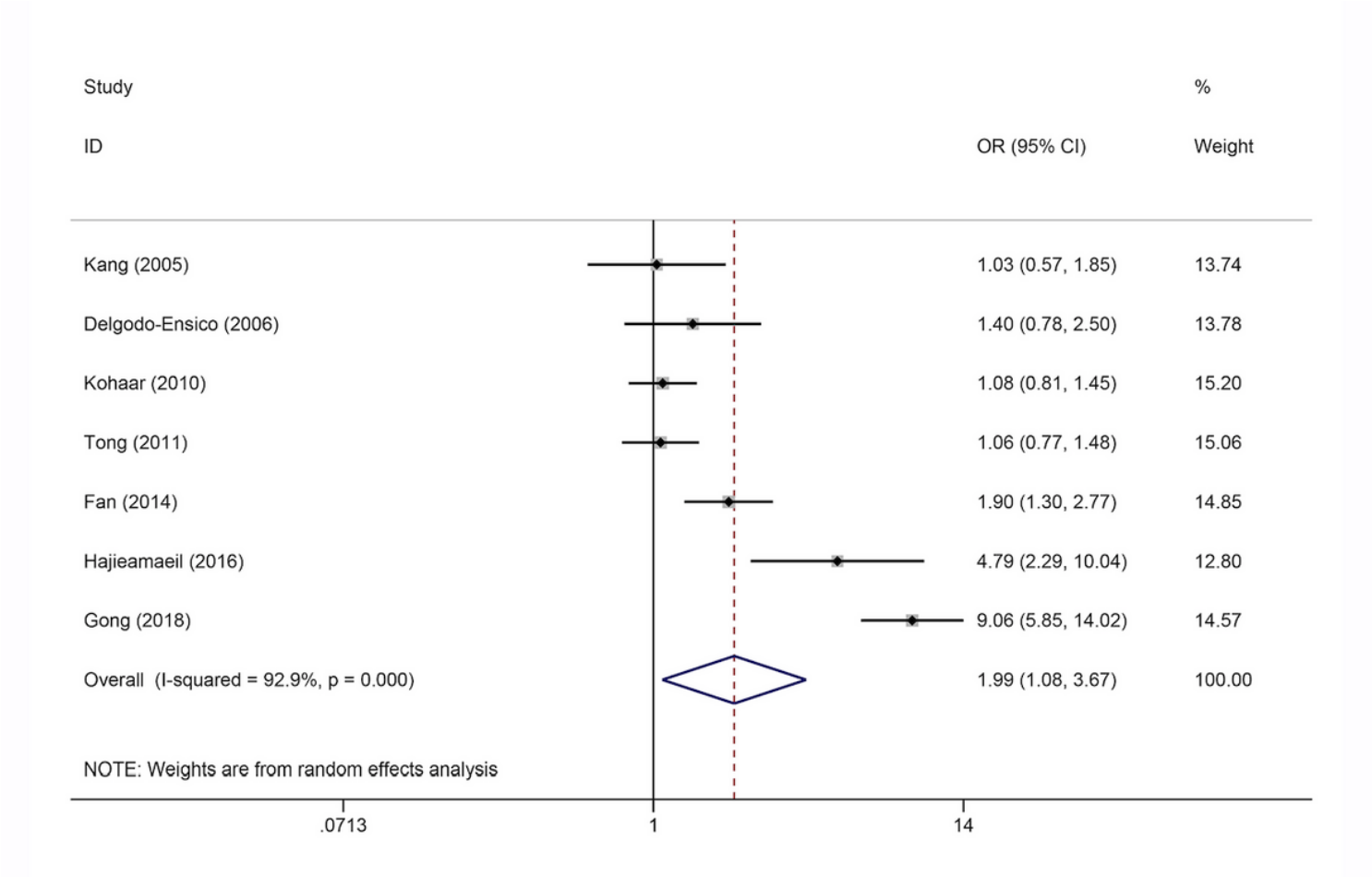

Figure 6

Forest plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under allelic genetic model (C vs. A).

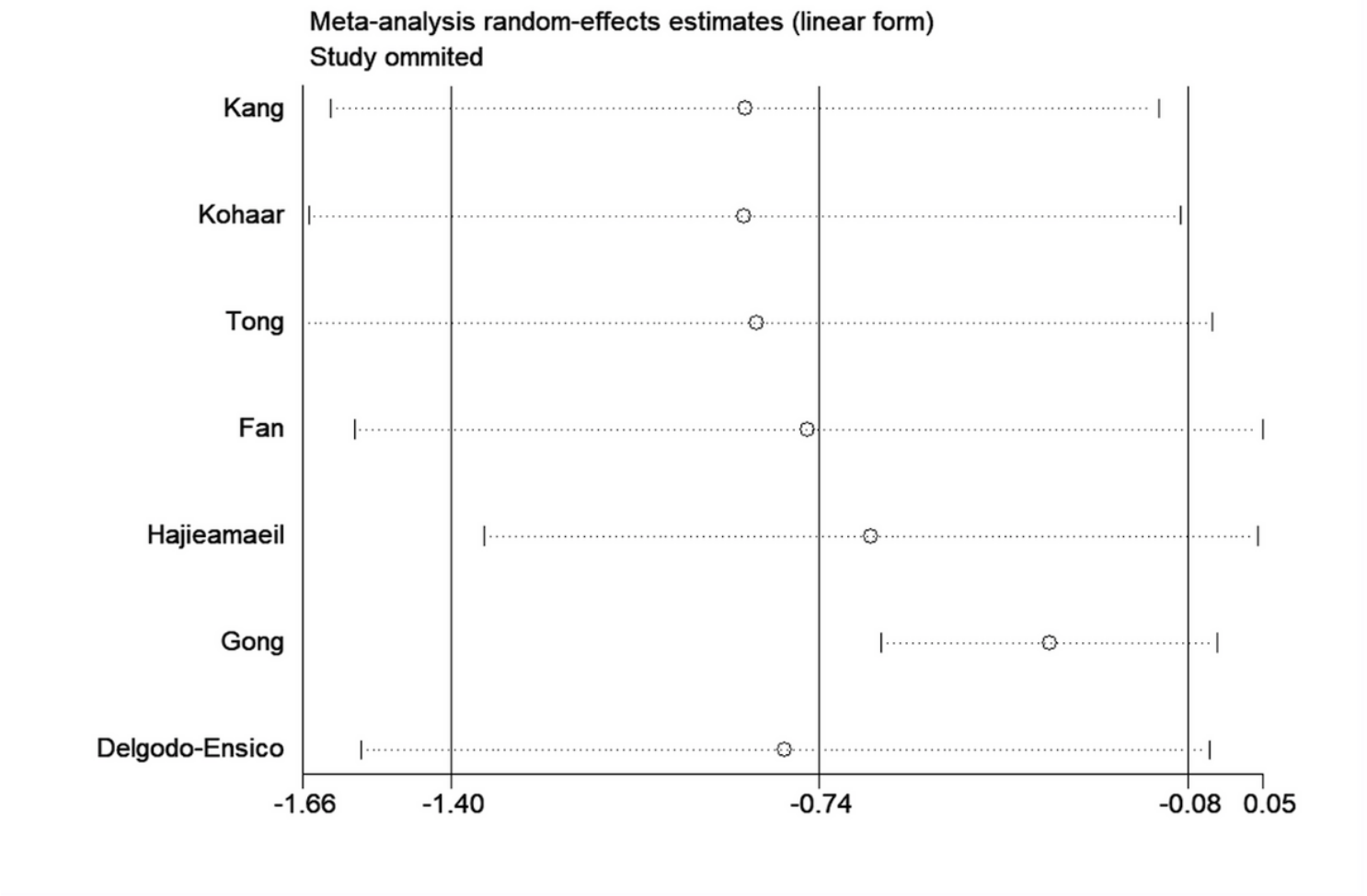

Figure 7

The sensitivity analysis results under recessive genetic model (AA vs. AC + CC).

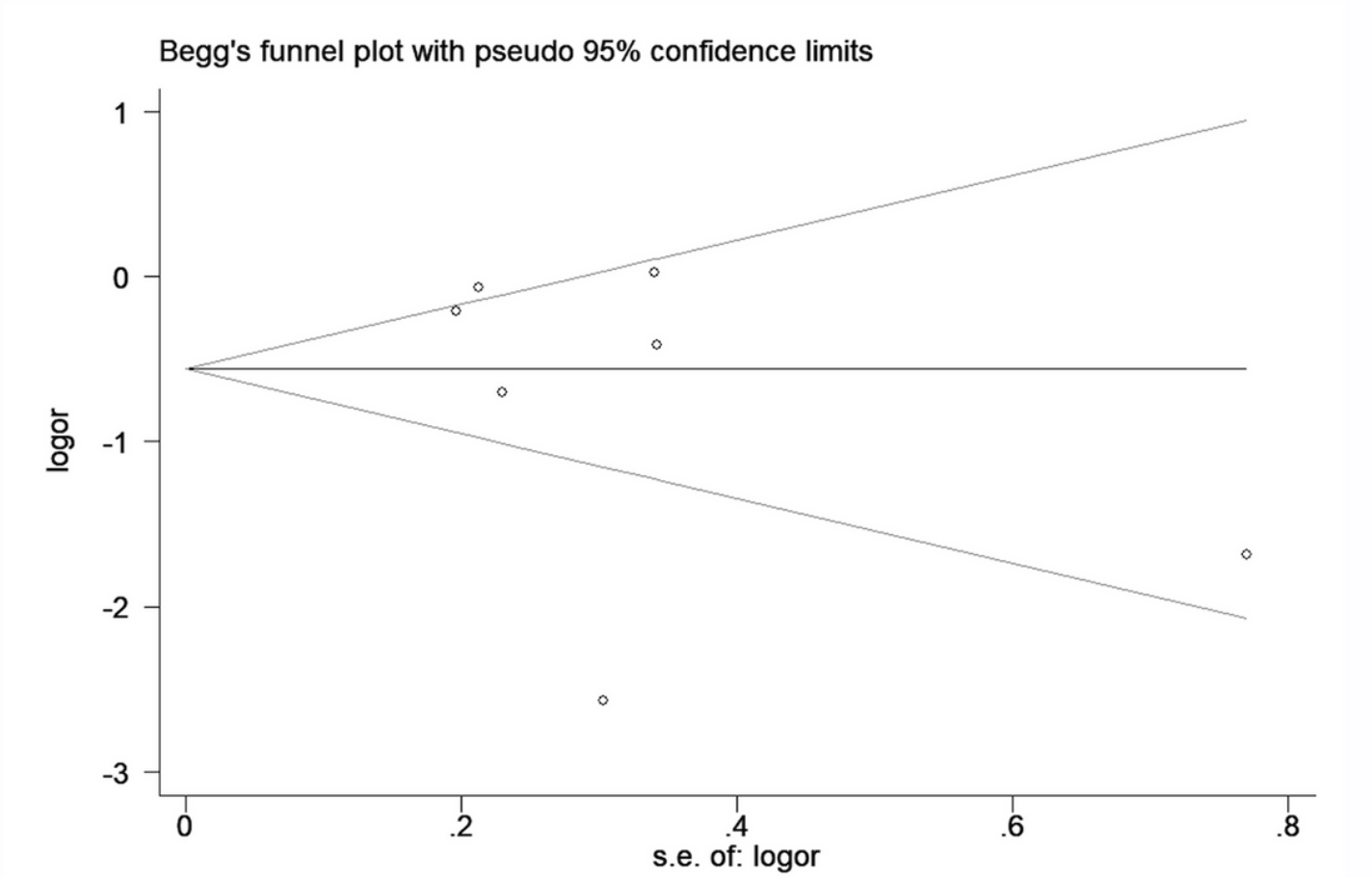

Figure 8

Funnel plots for the association between MTHFR A1298C polymorphism and cervical cancer risk under recessive genetic model (AA vs. AC + CC).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009Checklist20200618.doc
- PRISMA2009FlowDiagramMSWord20200618.doc