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Original Article

Genetic polymorphism of MTHFR C677T contributes to the risk of ovarian cancer: a meta-analysis

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Abstract: The goal of this study was to evaluate the association between genetic polymorphism of methylenetetrahydrofolate reductase (MTHFR) in exon 4 codon 677 (C/T) and the susceptibility to ovarian cancer. A comprehensive review and a meta-analysis of 12 studies involving 7876 controls and 5057 cases was performed to evaluate the association between ovarian cancer risk and genetic polymorphism of MTHFR C677T. Use the odds ratio (OR) the degree of possible correlation with the 95% confidence interval (95% CI) was determined. Overall, in all genetic models, our study showed that MTHFR C677T polymorphism didn't contribute to the risk of ovarian cancer. Results of subgroup analysis based on ethnicity showed no significant association between genetic polymorphism of MTHFR C677T and ovarian cancer risk in the Caucasian group, while MTHFR C677T polymorphism in the Asian group, as a risk factor, contributes to a significantly increased risk of ovarian cancer. No publication bias was found in our study. This meta-analysis included all eligible studies showing that MTHFR C677T polymorphism conferred an increased risk to ovarian cancer in Asians although there was no association observed in Caucasian group or a pooled group of both.

Keywords: Ovarian cancer, MTHFR C677T, polymorphism, risk, meta-analysis

Introduction

Ovarian cancer, as the major reason of gynecologic malignant cancer death has 5-year survival rates of only five percent to thirty percent in women [1]. Although various therapies have been used, the impact on patients' health and life all over the world required study. The cacoethes prognosis is due to the lack of available and confident biomarkers to diagnose the ovarian cancer patient on early stages of this disease [2]. Therefore, significant clinical value of credible biomarkers that could diagnose and predict the outcome of ovarian cancer patients has been rising with time. Some studies have shown that genetic factors play a crucial role in the tumorigenesis and development of ovarian cancer [3-5].

Folate has been assumed to have a significant association with physiologic and pathologic processes, including tumorigenesis and metabolism [6]. The important role played in folate metabolism makes it focus by researchers. MTHFR is a key enzyme that catalyzes the conversion of 5-methyltetrahydrofolate, which is the primary circulating configuration of folate, form 5,10-methylenetetrahydrofolate irreversibly. The later involves transfer of uracil deoxyribonucleotide to deoxyuridine monophosphate (dUMP) as the methy donor, which reactions with DNA synthesis, and the former can enter the methionine metabolism cycle, and offer methyl for DNA methylation. If the activity of MTHFR decreased, the amount of methyl and 5-methyltetrahydrofolate product would be reduced, and the homocysteine (Hcy) and Tunmethylated dUMP would be increased in the cycle [7]. In the MTHFR gene, the functional single nucleotide polymorphism (SNPs), 677C > T, is associated with decreased the activity of enzyme [8-9]. Reducing the activity of MTHFR enzymes may increase the risk of cancer by impinging on DNA repair synthesis and destruc-

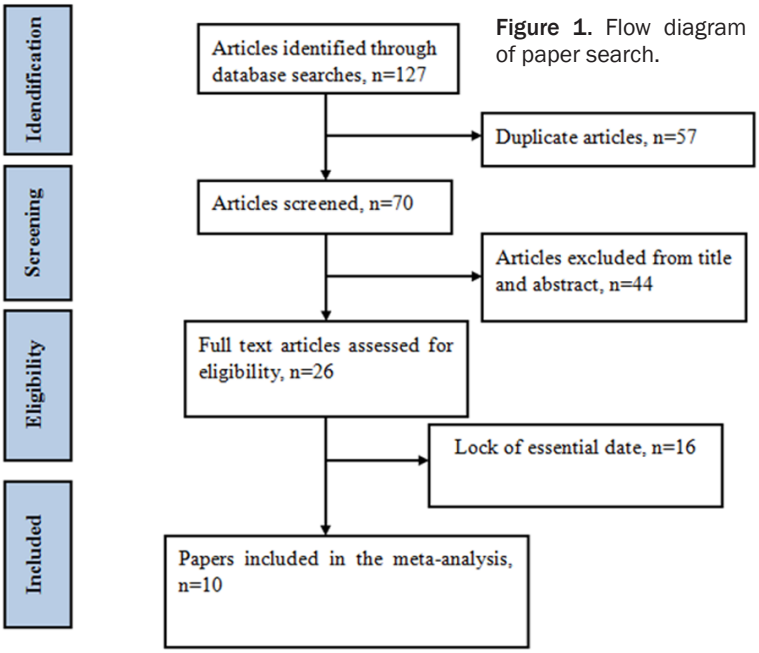


Figure 1. Flow diagram of paper search.

tion of DNA methylation. Therefore, MTHFR C677T polymorphism is a potential risk factor for cancer.

Multiple groups have studied the relationship between MTHFR C677T polymorphism and ovarian cancer risk [10-19], but the conclusions are still inconsistent. Therefore, in order to determine the strength MTHFR C677T polymorphism's contribution to ovarian cancer risk, meta-analysis was performed.

Methods

Identification of eligible studies

A comprehensive publication search in the China National Knowledge Infrastructure (CNKI), Embase, and PubMed was performed by two independent persons with computer, used the key words "MTHFR C677T" or "MTHFR T/C", or "rs1801133 T/C", "Polymorphism", "Ovarian cancer" and "risk" as well as their combinations (from 2000 to 2018). All investigators were trained in literature retrieval. All studies that met the inclusion criteria were saved for further exploration and data extraction.

The studies of Inclusion and exclusion criteria

Data inclusion criteria: (1) Papers should include ovarian cancer risk and MTHFR gene C677T polymorphisms; (2) Cohort studies or case-control studies; (3) Competent data to calculate the odds ratio (OR) and 95% confidence interval (95% CI). For overlapping or repeated studies, the original date from the initial studies was adopted. Accordingly, papers lacking essential information, like review, letter, meta -analysis were excluded. Two investigators (Li and Zhu) independently extracted qualified studies according to the inclusion criteria, and the controversies between the two investigators were consulted with third investigator (Zeng) until a consensus was reached.

Data extraction

Data included in the study was extracted by two investigators (Li and Zhu) respectively using standard data collection tables from all eligible papers. The date collected includes: first author's name, year of publication detail, country and ethnicity. In each study, digital data included the number and genotype frequency of cases and controls, Hardy-Winberg equilibrium (HWE). Different ethnicity was divided into Asian and Caucasian groups. The two investigators were required to agree on all items.

Statistics analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to estimate the degree of association between ovarian cancer risk and MTHFR C677T polymorphism. ORs of five varying comparison models were calculated: included (TT versus CC) the Homozygote comparison model, (TC versus CC) the Heterozygote comparison model, (T versus C) the allele model, (TT versus TC+CC) the Recessive genetic comparison model, and (TT+T/C versus CC) the Dominant genetic comparison model. To assess heterogeneity among studies by used the Cochrane Q statistics test. According to the results of heterogeneity test, a fixed-effect model or a random-effect model was used to estimate the combined effects [20]. The fixed-effects model was used while the effects are assumed to be homogenous, otherwise the

Table 1. Characteristics of studies included

Author	Year	Country	Ethnicity	Genotype						P for HWE
				Control			Case			
				CC	TC	TT	CC	TC	TT	
Wu	2007	China	Asians	32	35	13	17	40	24	0.52
Terry1	2010	USA	Caucasians	499	488	138	427	492	140	0.27
Terry2	2010	USA	Caucasians	210	217	55	71	72	10	0.93
Terry3	2010	USA	Caucasians	193	168	51	164	167	33	0.13
Webb	2011	Australian	Caucasians	571	568	139	744	709	185	0.9
Prasad	2011	India	Asians	116	8	1	72	3	5	0.06
Pawlik	2011	Poland	Caucasians	62	79	18	67	55	13	0.36
Jakubowska	2012	Poland	Caucasians	1447	1481	422	423	446	116	0.16
Zhang	2012	China	Asians	115	92	11	102	94	19	0.17
Gao	2012	China	Asians	232	178	22	97	100	27	0.1
Song	2012	China	Asians	93	88	19	91	83	26	0.78
Singh A	2015	India	Caucasians	10	5	0	19	6	0	0.79

random-effects model was applied. Begg's test was applied to assess the publication bias [21]. To check whether the genotype frequencies of the controls were in agreement with Hardy-Weinberg equilibrium (HWE) or not, the χ^2 test was applied. By removing one study at a time for a sensitivity analysis. All of the statistical analyses were performed by using STATA11.0 software package (Stata Corporation, College Station, TX, USA). Statistical significance was determined to be less than 0.05 as a 2-sided *P*-value.

Results

Characteristics of contained studies

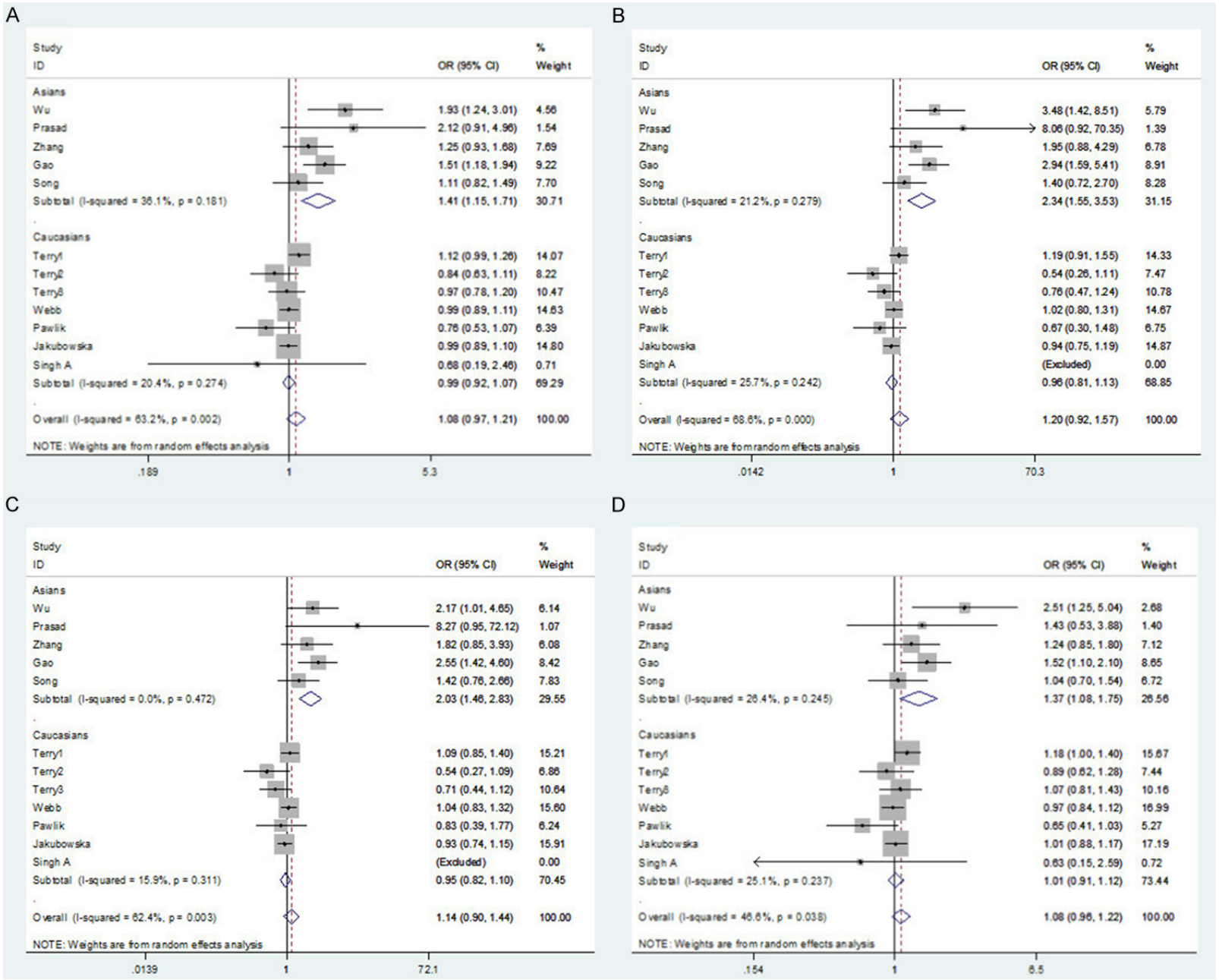
Up to 127 articles including 129 studies were extracted from there databases by the original search. After screen the paper's title and abstract carefully, a total of 101 articles were excluded because of lack of relevance obviously. Then a carefully full text proofing was done to the remaining articles based on the inclusive criteria, 16 articles were excluded, the reasons for which is shown in the flow diagram presented in **Figure 1**. Finally, 10 eligible articles including 12 studies were contained for this meta-analysis. The characteristics of each study is presented in **Table 1** including first author's name, year of publication detail, country and ethnicity. In each study, digital date such like the number and genotype frequency of cases and controls, Hardy-Winberg equilibrium (HWE) is also necessary.

Meta-analysis results

In meta-analysis, MTHFR C677T polymorphism was not observed to contribute to the risk of ovarian cancer under any genetic model. The Allele model OR (T versus C) = 1.08, 95% CI (0.97-1.12); the Homozygote comparison model OR (TT versus CC) = 1.20, 95% CI (0.92-1.57); the Heterozygote comparison model OR (TC versus CC) = 1.05, 95% CI (0.97-1.44); the Recessive genetic comparison model OR (TT versus TC+CC) = 1.1405, 95% CI (0.90-1.44); the Dominant genetic comparison model OR (TT+TC versus CC) = 1.06, 95% CI (0.98-1.44). Subgroup analysis by ethnicity suggested that no significant link between the MTHFR C677T polymorphic and ovarian cancer among Caucasians, but the MTHFR C677T polymorphic increased the risk of ovarian cancer in Asians by variant T. In subgroup analysis performed by ethnicity, in all genetic models in Caucasians, the pooled ORs were not significant. In Asians, the pooled ORs were significant under four genetic models (**Figure 2**), the Allele model OR (T versus C) = 1.41, 95% CI (1.15-1.71); the Homozygote comparison model OR (TT versus CC) = 2.34, 95% CI (1.55-3.53); the Recessive genetic comparison model OR (TT versus TC+CC) = 2.03, 95% CI (1.46-2.83); the Dominant genetic comparison model OR (TT+TC versus CC) = 1.37, 95% CI (1.08-1.75).

Heterogeneity

The P value from Cochran's Q test, which used to examine the inter-heterogeneity of the genet-


A
Study
ID
OR (95% CI)
%
Weight
Asians
Wu 1.93 (1.24, 3.01) 4.56
Prasad 2.12 (0.91, 4.96) 1.54
Zhang 1.25 (0.93, 1.68) 7.69
Gao 1.51 (1.18, 1.94) 9.22
Song 1.11 (0.82, 1.49) 7.70
Subtotal (I-squared = 36.1%, p = 0.181) 1.41 (1.15, 1.71) 30.71
Caucasians
Terry1 1.12 (0.99, 1.26) 14.07
Terry2 0.84 (0.63, 1.11) 8.22
Terry3 0.97 (0.78, 1.20) 10.47
Webb 0.99 (0.89, 1.11) 14.63
Pawlik 0.76 (0.53, 1.07) 6.39
Jakubowska 0.99 (0.89, 1.10) 14.80
Singh A 0.68 (0.19, 2.46) 0.71
Subtotal (I-squared = 20.4%, p = 0.274) 0.99 (0.92, 1.07) 69.29
Overall (I-squared = 63.2%, p = 0.002) 1.08 (0.97, 1.21) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
%
Weight
Asians
Wu 3.48 (1.42, 8.51) 5.79
Prasad 8.06 (0.92, 70.35) 1.39
Zhang 1.95 (0.88, 4.29) 6.78
Gao 2.94 (1.59, 5.41) 8.91
Song 1.40 (0.72, 2.70) 8.28
Subtotal (I-squared = 21.2%, p = 0.279) 2.34 (1.55, 3.53) 31.15
Caucasians
Terry1 1.19 (0.91, 1.55) 14.33
Terry2 0.54 (0.26, 1.11) 7.47
Terry3 0.76 (0.47, 1.24) 10.78
Webb 1.02 (0.80, 1.31) 14.67
Pawlik 0.67 (0.30, 1.48) 6.75
Jakubowska 0.94 (0.75, 1.19) 14.87
Singh A (Excluded) 0.00
Subtotal (I-squared = 25.7%, p = 0.242) 0.96 (0.81, 1.13) 68.85
Overall (I-squared = 68.6%, p = 0.000) 1.20 (0.92, 1.57) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
%
Weight
Asians
Wu 2.17 (1.01, 4.65) 6.14
Prasad 8.27 (0.95, 72.12) 1.07
Zhang 1.82 (0.85, 3.93) 6.08
Gao 2.55 (1.42, 4.60) 8.42
Song 1.42 (0.76, 2.66) 7.83
Subtotal (I-squared = 0.0%, p = 0.472) 2.03 (1.46, 2.83) 29.55
Caucasians
Terry1 1.09 (0.85, 1.40) 15.21
Terry2 0.54 (0.27, 1.09) 6.86
Terry3 0.71 (0.44, 1.12) 10.64
Webb 1.04 (0.83, 1.32) 15.60
Pawlik 0.83 (0.39, 1.77) 6.24
Jakubowska 0.93 (0.74, 1.15) 15.91
Singh A (Excluded) 0.00
Subtotal (I-squared = 15.9%, p = 0.311) 0.95 (0.82, 1.10) 70.45
Overall (I-squared = 62.4%, p = 0.003) 1.14 (0.90, 1.44) 100.00
NOTE: Weights are from random effects analysis
.0139
1
72.1
D
Study
ID
OR (95% CI)
%
Weight
Asians
Wu 2.51 (1.25, 5.04) 2.68
Prasad 1.43 (0.53, 3.88) 1.40
Zhang 1.24 (0.85, 1.80) 7.12
Gao 1.52 (1.10, 2.10) 8.65
Song 1.04 (0.70, 1.54) 6.72
Subtotal (I-squared = 26.4%, p = 0.245) 1.37 (1.08, 1.75) 26.56
Caucasians
Terry1 1.18 (1.00, 1.40) 15.67
Terry2 0.89 (0.62, 1.28) 7.44
Terry3 1.07 (0.81, 1.43) 10.16
Webb 0.97 (0.84, 1.12) 16.99
Pawlik 0.65 (0.41, 1.03) 5.27
Jakubowska 1.01 (0.88, 1.17) 17.19
Singh A 0.63 (0.15, 2.59) 0.72
Subtotal (I-squared = 25.1%, p = 0.237) 1.01 (0.91, 1.12) 73.44
Overall (I-squared = 46.6%, p = 0.038) 1.08 (0.96, 1.22) 100.00
NOTE: Weights are from random effects analysis
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6.5

Figure 2. The pooled Ors were significant under four genetic models in Asians. A: Forest plot on the association between MTHFR C677T polymorphism and ovarian cancer risk in Allele model in Asians. B: Forest plot on the association between MTHFR C677T polymorphism and ovarian cancer risk in Homozygote comparison model in Asians. C: Forest plot on the association between MTHFR C677T polymorphism and ovarian cancer risk in Recessive genetic comparison model in Asians. D: Forest plot on the association between MTHFR C677T polymorphism and ovarian cancer risk in Dominant genetic comparison model in Asians.

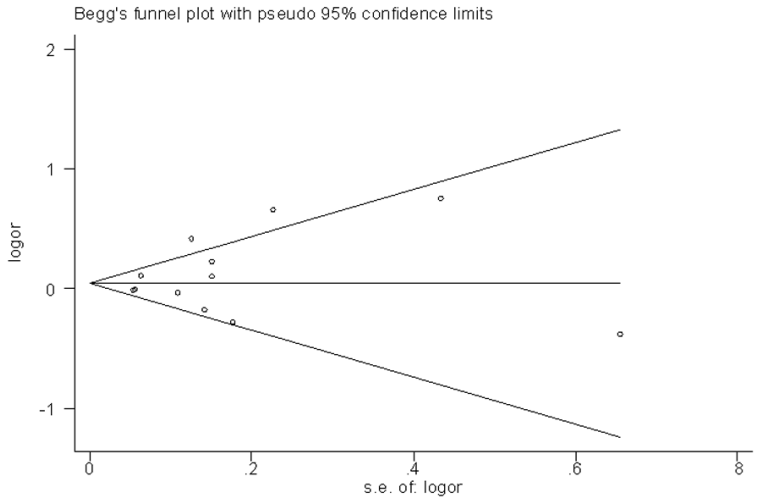

Figure 3. Begg's funnel plot for publication bias.

ic comparison models. When p (heterogeneity) < 0.05 and I-squared > 50%, a random effects model was applied, else, a fixed effects model was applied. As shown in the study, obvious heterogeneities existed in overall Meta-analysis about the Ovarian Cancer Risk and MTHFR C677T Polymorphism. Heterogeneity played an important role in the meta-analysis, and was very considerable [22]. In order to explore potential sources of heterogeneity, subgroup analysis was conducted (consequences not shown). Through subgroup analysis, ethnicity was found to be the major source of heterogeneity in this meta-analysis.

Sensitivity analysis

The effect of the individual paper on the pooled OR is using a sensitivity analysis was estimated by continuously deleted each eligible study from pooled analysis. The results showed that no substantial change was found which suggested that no individual study majorly influenced the pooled OR under any genetic model.

Publication bias

The publication bias was assessed by using Begg's funnel plots to estimate. The shape of funnel plot (**Figure 3**) was symmetric and didn't show distinct publication bias in all the studies. The result implied that no publication bias existed in our study.

Discussion

Ovarian cancer is a representation of eccentric genetic variants and abnormal changes of epigenetic. Disturbance of one-carbon metabolism process may be crucial in etiology alterations of OC, which fosters the cross-effect between genetic variants and epigenetic processes, thus playing an important role in both DNA synthesis and DNA methylation [6]. The association between OC risk and MTHFR C677T polymorphism results was conflicting. Some studies [10, 14, 17-19] suggested that MTHFR C677T polymorphism has a significant contribution to increase the risk of OC, some others [12, 13, 15, 16] didn't agree. These contradictory results are possibly by reasons that a slight impact of the polymorphism contribute to OC risk, or lack of sufficient statistical data of the fore published studies. Maybe both? Because of it, a measurable method for pooling the data of various studies with the one topic was needed, and assessing the link with them and explaining their multiplicity was important. The meta-analysis reported here checked the MTHFR C677T polymorphism contribute to the risk of OC involved 12 studies with 5057 cases and 7876 controls. In summary, MTHFR C677T polymorphism is not associated with an increased risk to ovarian cancer in all genetic models. The results from the Caucasian group was the same as the overall analysis, but the results differ in Asian group, which indicated the MTHFR C677T polymorphism were significant association in Asian group under four genetic models., OR (TT versus CC) = 2.34, 95% CI (1.55-3.53); OR (TT ver-

sus TC+CC) = 2.03, 95% CI (1.46-2.83); OR (T versus C) = 1.41, 95% CI (1.15-1.71); OR (TT+TC versus CC) = 1.37, 95% CI (1.08-1.75).

Genetic and environmental risk factors may have an intricate relationship. Previous studies reported that MTHFR gene is a significant risk factor in the susceptibility to develop a variety of cancer, such as esophageal cancer [23, 24], ovary cancer [25-27] and cervical cancer [28, 29]. In the MTHFR enzyme, at position 677 (C677T), the substitution of C to T results in the substitution of alanine to valine, that sequelae impaired folate binding as well as reduced activity of the MTHFR enzyme. It is likely that C677T mutation of MTHFR renders the enzyme thermolabile with 50% reduced activity that leads to an increase in plasma homocysteine concentrations [30]. Hence, variants of the MTHFR gene can alter the activity of MTHFR, which may lead to an increase in the susceptibility to develop cancers. Even though the heterogeneity between MTHFR C667T polymorphism and ovarian cancer was significant in Asian group, this was not significantly different from the Caucasians group. This suggests that the Asian and Caucasian groups were not homogenous. Additional analysis of the subgroup analysis showed a significant different between ovarian cancer and C677T in four genetic models in two groups defined by ethnicity. To identify the major source of heterogeneity in the meta-regression analysis, ethnicity was analyzed ($P < 0.05$) in our study. Heterogeneity is a potential problem when interpreting the results of all meta-analyses [31, 32]. To check the potential sources for the heterogeneity in our meta-analysis, subgroup analysis was divided by ethnicity. Through subgroup analysis in our meta-analysis, the main source of heterogeneity was race, which could be interpreted as a racially specific influence of MTHFR C677T polymorphism contribute to ovarian cancer susceptibility. However, in this meta-analysis, race did not account for all of the heterogeneity, other potential heterogeneity sources were not found.

Our research has several limitations to consider. First, there were 12 studies, adding up to 5057 cases and 7876 controls included only. More large volume sample and carefully designed studies are required to strictly determine this possible association. Second, due to the void of adjusted estimates, the meta-analysis was based on unadjusted estimates. Whereas, if estimates are adjusted across all studies, more accurate analysis can be performed. In addition, this meta-analysis also revealed significant differences in research design and control selection. Therefore, in order to analyze this association more precisely, more studies on adjustment estimates are asked for. Third, OC have kinds of histologic type differently, such like epithelial OC, endometrioid OC, etc. [33]. The relationship between MTHFR C677T polymorphisms and ovarian cancer may be influenced by different histologic types of ovarian cancer. Whereas, with no data being represented in these papers, and no subgroup analysis being performed by different histological types, more studies are required. Finally, due to the lack of sufficient data, the gene-folic acid factor interactions were not completely reached in our meta-analysis. The relationship between ovarian cancer and MTHFR C677T polymorphism may be affected by the status of folic acid in human body [14, 16]. Future researches may further evaluate the possible gene-folic acid interactions between ovarian cancer risk and MTHFR C677T polymorphism.

In summary, although there are several limitations, our meta-analysis results showed that in Caucasians, MTHFR C677T polymorphism has nothing to do with the risk of ovarian cancer, but the MTHFR polymorphism variant T may increase the risk of ovarian cancer in Asians. Nevertheless, larger and better-designed research studies are needed to that will help us better understanding the link between this MTHFR polymorphism and ovarian cancer.

Disclosure of conflict of interest

None.

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