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Original Article

Risk association of meningiomas with MTHFR C677T and GSTs polymorphisms: a meta-analysis

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Abstract: Previous studies have shown that the single nucleotide polymorphisms (SNPs) in Methylenetetrahydrofolate reductase (MTHFR) and Glutathione S-transferases (GSTs, including GSTM1, GSTT1) genes play an important role in determining the response of an individual to environmental pathogenesis and significantly relate to incidences of various human tumors, including brain tumors. However, these genes' polymorphisms on meningioma risk remains poorly understood. The relevant inferences from previous studies are hindered by their limited statistical power and conflicting results. The aim of this meta-analysis is to provide a relatively comprehensive account of the association between these polymorphisms and human meningioma risk. A literature search for eligible studies published before January 1, 2014 was conducted in PubMed, Embase, Web of Science, Cochrane Library, and CNKI databases. Pooled odds ratios (OR) with their corresponding 95% confidence intervals (95% CI) were used to evaluate the strength of the association under a fixed or random effect model according to heterogeneity test results. Heterogeneity and publication bias were evaluated. All statistical analyses were conducted by using the software of STATA 12.0 (STATA Corporation, College Station, TX, USA). For MTHFR C677T (dbSNP: rs1801133) (C T) polymorphism, 9 individual case-control studies from six publications with 1,615 cases and 1,909 controls were obtained. For GSTM1 null polymorphism, there were 4 studies with 417 cases and 1,735 controls. For GSTT1 null polymorphism, there were 4 studies with 405 cases and 1,622 controls. The combined results for the MTHFR C677T show that carriers of the CT genotype may be associated with a higher meningioma risk (OR = 1.20, 95% CI 1.05-1.38, P = 0.009). Stratified analyses show that Caucasians have significantly higher risk if they carry the CT genotype of MTHFR (OR = 1.31, 95% CI 1.05-1.63, P = 0.02). Risk of Caucasians carrying TT + CT genotype is also significantly higher (OR = 1.27, 95% CI 1.02-1.58, P = 0.03). Risk of Caucasians carrying TT genotype is not significantly different compared to control population (OR = 0.96, 95% CI 0.69-1.34, P = 0.82). All of the enrolled studies about GSTM1/GSTT1 are on Caucasians. The pooled ORGSTM1 and ORGSTT1 were not significant in Caucasian population. These results indicate SNPs of MTHFR C677T are related to meningioma risk with ethnic differences. Caucasians carrying CT genotype of MTHFR C677T have significantly higher meningioma susceptibility. SNPs of GSTM1/GSTT1 are not related to meningioma risk.

Keywords: MTHFR, GSTM1, GSTT1, meningioma, gene polymorphism, meta-analysis

Introduction

Meningiomas

Meningioma originates from the arachnoid membrane of the brain and is the second most common primary tumor of the central nervous system (CNS) [1]. In its etiologies, multiple genetic and environmental factors have been implicated. Genetic variants and polymorphisms are the main factors that have been proven or assumed to be involved in meningioma formation. According to the histologic features these tumors are classified into three categories: benign/meningioma (WHO grade I), atypical meningioma (WHO grade II) and anaplastic/malignant meningioma (WHO grade III). Meningioma is a slow-growing benign tumor that accounts for approximately 20% of brain tumors, with an incidence of 2.3/100,000 overall and a 2:1 female-to-male ratio according to literatures [2]. Nowadays Meningioma is a very common brain tumor in the US [3] and also in China [4]. Most meningiomas are benign (WHO Grade I), but up to 20% of meningiomas are assigned to the WHO Grades II (atypical menin-

gioma) and III (anaplastic/malignant meningioma) [5]. Despite largely benign histology, these tumors can lead to serious morbidity owing to their intracranial location [6, 7]. The 5-year survival rate of patients with meningiomas could be 81.8% [8]. The etiologies of meningiomas are not well understood. In recent years, multitudinous genes have been identified to be associated with meningiomas [5, 9, 10]. Evidences from prior epidemiologic studies, although inconsistent, suggest a possible association between the incidence of meningioma and some genes polymorphisms [11, 12]. The cryptic genetic background leading to meningiomas includes a great deal of nucleotides mutations, or single nucleotide polymorphisms (SNPs), the latter might be involved in meningiomas development, progression and recurrence. Moreover, more and more genome-wide association studies have suggested genetic polymorphisms as risk factors for brain tumors [13].

MTHFR

Methylenetetrahydrofolate reductase (MTHFR) plays critical roles in the maintenance of DNA normal methylation, de novo synthesis of nucleotide, and DNA repair by modulating the folate metabolism [14, 15]. The human MTHFR gene is located on 1p36.3 containing a total of 11 extrons and 10 introns and encoding a protein of 74.6 kDa [14]. The encoded protein of MTHFR can convert 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the primary circulating form of folate and is an irreversible conversion [16]. Some mutations in the MTHFR gene, such as C (cytosine) > T (thymidine) at nucleotide 677, leading to a conversion of alanine to valine, are associated with lower folate level when compared to the normal genotype [17]. Thus results in decreased thermal stability and enzyme activity of the encoded protein [18-20]. Some academicians found the MTHFR C677T polymorphism is associated with a number of human malignant tumors, such as cervical cancer [21], hepatocellular carcinoma [22], and breast cancer [23]. However, an other study found there is no association between the MTHFR C677T polymorphism and breast cancer [24]. Because of the complicated molecular mechanisms of tumors and the different genetic backgrounds and environmental exposures, relationship between MTHFR C677T polymorphism and tumors is still controversial and ambiguous.

GSTs

Glutathione S-transferases (GSTs) are dimeric phase II metabolic enzymes that catalyze the reactions between reduced glutathione and toxic. The range of potential GST substrates is very large, including occupational and environmental carcinogens such as solvents, pesticides, and polycyclic aromatic hydrocarbons. Four families of cytosolic soluble GSTs α (GSTA), μ (GSTM), Π (GSTP), and θ (GSTT) are known in humans [25].

GSTM1 is one member of GSTM family. Three alleles of GSTM1 gene locus (GSTM1A, GSTM1B and GSTM1 0) have been found in human populations. GSTM1A and GSTM1B differ by a single amino acid but have similar enzyme activity, whereas GSTM1 0 (null allele) produces no catalyzing activity [26]. GSTM1 null genotype frequencies have been reported to be ethnic differences [27]. A deletion polymorphism was reported also at GSTT1locus (22q12) [28]. The GSTT1 null genotype distribution also has ethnic differences [29, 30]. Similar to GSTM1, individuals carrying a homozygous of GSTT1 null genotype encode deficient protein that affects detoxification enzyme activity [26, 31].

The knowledge of the role of the GSTs enzymes in detoxification has led to the hypothesis that if an individual's genotype at GSTs locus encodes a deficient GSTs enzyme it may result in increased risk of tumors. Absent or deficient GSTs enzyme activity may result in increased risk of somatic mutations, subsequently leading to tumor formation [27]. Some epidemiological studies have discovered the association between GSTM1 null genotype and incidences of some tumors, especially oligodendrogliomas [32], myelodysplastic diseases [33], lung cancer [34] and bladder cancers [35]. However, for GSTT1 null polymorphism, no relationship was found with incidence of glioma [36].

The purpose of this study was to examine the effect of folate metabolism gene MTHFR C677T and GSTM1/GSTT1 null polymorphisms on human meningioma risk in total population and the difference in Caucasia and Asian. Although the association of MTHFR C677T and GSTM1/GSTT1 polymorphisms with brain tumor risk

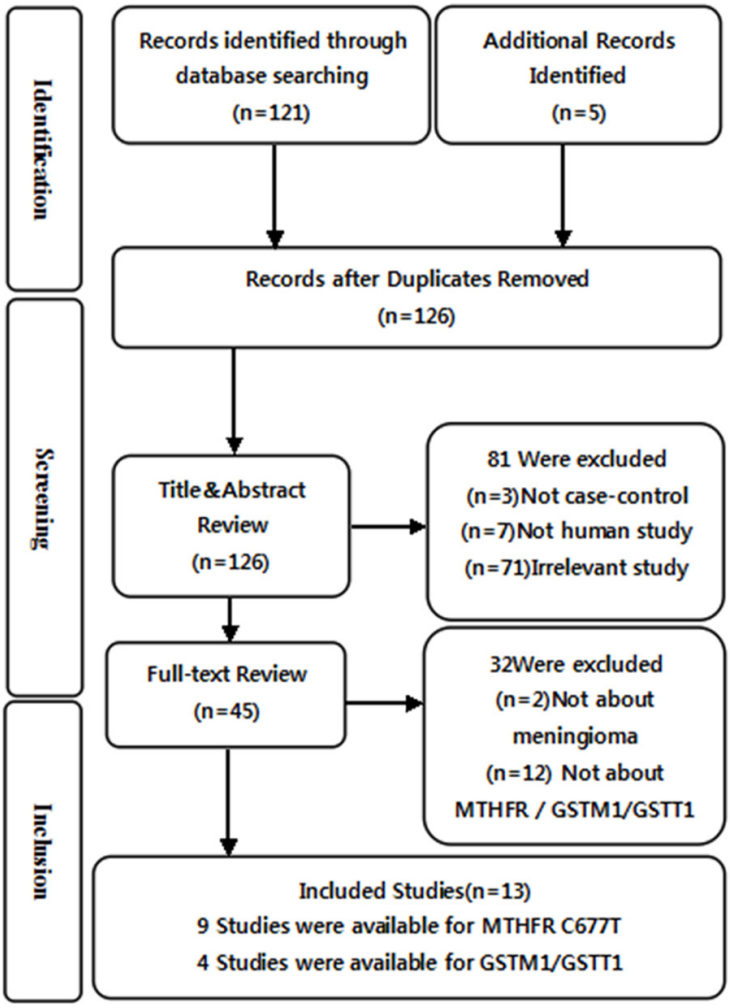

Figure 1. Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

has been widely studied, the role of polymorphic variants as risk factors for meningioma has received comparatively little attention. The previous findings of individual case-control studies are paradoxical, possibly due to the small sample sizes and the differences in the source of controls and methods of classification. Thus, we carried out the current meta-analysis by pooling available data from published studies to elucidate the relationship of meningioma incidence risk with the above gene polymorphisms.

Materials and methods

Literature search strategy

A literature search for eligible studies published before January 1, 2014 was conducted among the following electronic databases: PubMed, Embase, Web of Science, Cochrane Library, and CNKI (China National Knowledge Infrastructure) databases. The following key words search strategy was used: ("meningiomas" or "brain tumor") and ("MTHFR" or "Folate metabolism") and ("GSTs" or "GSTM1" or "GSTT1" or "Glutathione S-transferases") and ("genetic polymorphism" or "SNP" or "gene"). The search was done without any limitation on languages and only included studies conducted with human subjects. The reference lists of reviews and retrieved articles were manually screened by two investigators to identify additional potential sources.

Selection criteria

To be included in the analysis, candidate studies had to meet the following criteria: (1) case-control study focused on the relationship between the MTHFR C677T or GSTM1/GSTT1 null polymorphisms and meningioma risk, (2) all patients met the diagnostic criteria for meningioma, (3) sufficient original data for calculating odds ratios (OR) with corresponding 95% confidence intervals (95% CI) was provided. Major reasons for excluding studies were the following: (1) not case-control study, (2) duplicate publications, (3) no usable data reported, (4) missing ethics board approval. This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [37] with only slight modification to better suit the nature of those studies.

Data extraction

According to the PRISMA guidelines, two independent reviewers checked each full-text report for eligibility and extracted and tabulated the following data from eligible studies: surname of first author, year of publication, country of origin, ethnicity, definition and numbers

Table 1. Main characteristics of all eligible studies

	Author	Year	Country	Racial descent	Sample size		Control source	Genotyping method
					Case	control		
MTHFR C677T (rs1801133)								
	Kafadar [42]	2006	Turkey	Caucasian	35	98	HB	PCR-RFLP
	Ahn [43]	2002	South Korea	Asian	32	254	HB	PCR-RFLP
	Behke FL [44]	2008	Finland	Caucasian	77	77	PB	Illumina
	Bethke DM [44]	2008	Denmark	Caucasian	110	113	PB	Illumina
	Bethke NO-UK [44]	2008	North UK	Caucasian	174	175	PB	Illumina
	Bethke SD [44]	2008	Sweden	Caucasian	149	149	PB	Illumina
	Bethke SE-UK [44]	2008	Southeast UK	Caucasian	121	123	PB	Illumina
	Li [45]	2013	China	Asian	317	320	HB	PCR-RFLP
	Zhang [46]	2013	China	Asian	600	600	PB	PCR-RFLP
GSTM1 Null								
	Jose [47]	1995	UK	Caucasian	49	577	HB	PCR-RFLP
	Pinarbasi [48]	2004	Turkey	Caucasian	23	153	HB	PCR-RFLP
	Roos [49]	2003	USA	Caucasian	169	575	HB	PCR-RFLP
	Schwartzbaum [50]	2007	European	Caucasian	176	430	PB	PCR-RFLP
GSTT1 Null								
	Jose [47]	1995	UK	Caucasian	47	494	HB	PCR-RFLP
	Pinarbasi [48]	2004	Turkey	Caucasian	23	153	HB	PCR-RFLP
	Roos [49]	2003	USA	Caucasian	159	545	HB	PCR-RFLP
	Schwartzbaum [50]	2007	European	Caucasian	176	430	PB	PCR-RFLP

Notes: PCR-RFLP: polymerase chain reaction–restriction fragment length polymorphism; PB: population-based; HB: hospital-based; Behke FL: Finland; Bethke DM: Denmark; Bethke NO-UK: UK-North; Bethke SD: Sweden; Bethke SE-UK: UK-Southeast.

Table 2. Meta-analysis results for the MTHFR C677T, GSTM1/GSTT1 Polymorphism and meningioma risk

	Genotype	Population	Begg's test	Egger's test
			p	p
MTHFR C677T (rs1801133)	T	Total	> 0.466	0.921
		Caucasians	> 0.452	0.465
		Asian	1	0.984
	TT	Total	> 0.602	0.886
		Caucasians	> 0.26	0.47
		Asian	1	0.967
	CT	Total	> 0.602	0.738
		Caucasians	> 0.452	0.577
		Asian	1	0.465
	TT+TC	Total	> 0.348	0.978
		Caucasians	> 0.26	0.135
		Asian	1	0.973
GSTM1	Null	Caucasians	> 0.308	0.337
		Asian	--	--
GSTT1	Null	Caucasians	> 0.734	0.694
		Asian	--	--

of cases and controls, genotyping method. Disagreements were resolved through discussion and subsequent consensus between reviewers.

Statistical analysis

To account for the between-study heterogeneity, a statistical test of Cochran's Q statistic was used. The heterogeneity was indicated by $P < 0.05$ [38]. Heterogeneity was also assessed through the I^2 test, with $I^2 > 50\%$ indicating significant heterogeneity [39]. When no heterogeneity was found ($P > 0.05$ or $I^2 < 50\%$), a fixed-effect model was used to estimate pooled odds ratios (OR) and their corresponding 95% confidence intervals (CI). Otherwise, a random effects model was applied. The significance of the pooled OR was determined

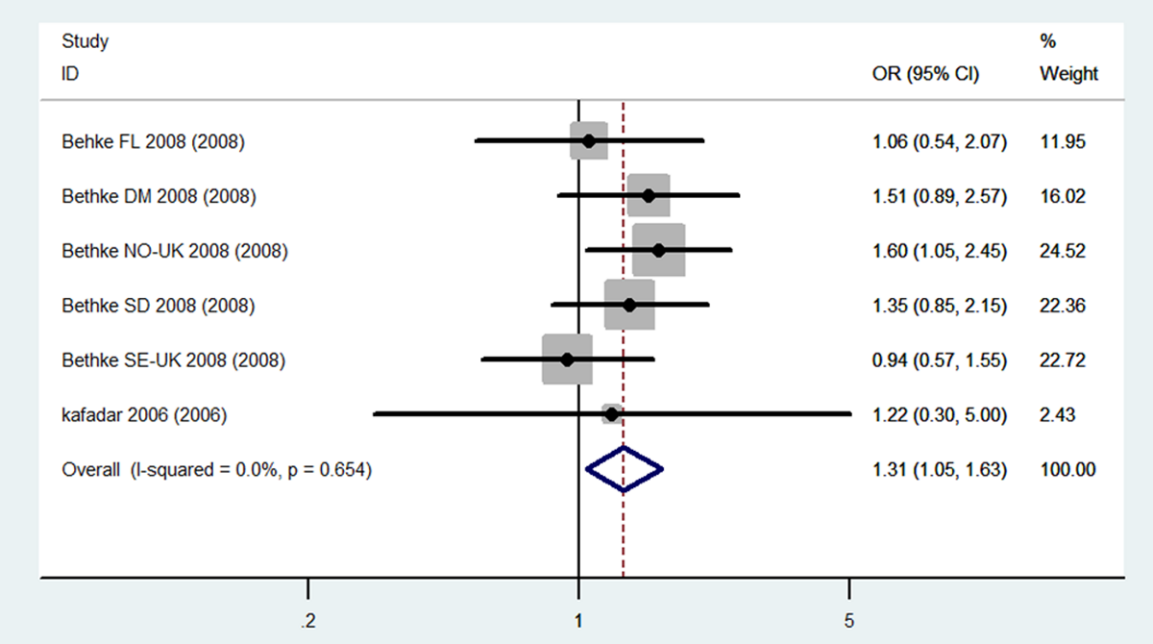

Figure 2. Forest plots for the association between the MTHFR C677T polymorphism and meningioma incidence in CT genotypes among total population.

using the Z test. Stratified analyses were performed in ethnicity subgroups (Caucasians, Asians). Sensitivity analyses were performed to assess the stability of pooled results. Each case-control study was omitted in turn to reflect the influence of individual datasets on the pooled results. Begg's funnel plot and Egger's linear regression test were used to assess the potential for publication bias [40, 41]. All two-tailed $P < 0.05$ were considered as statistical significance. All analyses were performed using STATA software v12.0 (Stata Corp, College Station, TX, USA).

Results

A total of 126 relevant papers were identified using the prespecified search strategy. In accordance with the inclusion criteria, thirteen case-control studies were included from nine publications [42-50], of which nine were on MTHFR C677T (rs1801133) and four were on GSTM1/GSTT1. A flow chart of the selection process and specific reasons for exclusion from this meta-analysis are shown in **Figure 1**. A total of 7,703 individual were included in this meta-analysis, of which 2,437 were meningioma patients and 5,266 were controls. The publication years of included studies ranged from 1995 to 2013. The characteristics and methodology of the included studies are summarized in **Table 1**.

Association between the MATHF C667T polymorphism and meningioma risk

The evaluation of the association between the MTHFR C677T (dbSNP: rs1801133, C>T) polymorphism and meningioma incidence risk is summarized in **Table 2**. It includes nine case-control studies, with a total of 1,615 meningioma cases and 1,909 controls. The combined results indicate that for total population (Caucasians + Asian) carriers of the CT genotype may be associated with a higher risk of meningioma incidence risk than others genotypes carriers (CT Total: OR = 1.20, 95% CI 1.05-1.38, P = 0.009). Stratified analysis shows that for Caucasians population, not only the CT genotype carriers, but also the sum carriers of CT+TT genotype, have significantly higher meningioma risk when compared to the control population (CT Caucasians: OR = 1.31, 95% CI 1.05-1.63, CT+TT Caucasians: OR = 1.27, 95% CI 1.02-1.58, P = 0.03) (**Figures 2**-**4**). No statistical significance was obtained for Asian population in this stratified analysis, indicating there are ethnic differences in meningioma susceptibility.

Association between the GSTM1/GSTT1 null polymorphism and meningioma risk

The evaluation of the association between the GSTM1/GSTT1 null polymorphism and meningioma

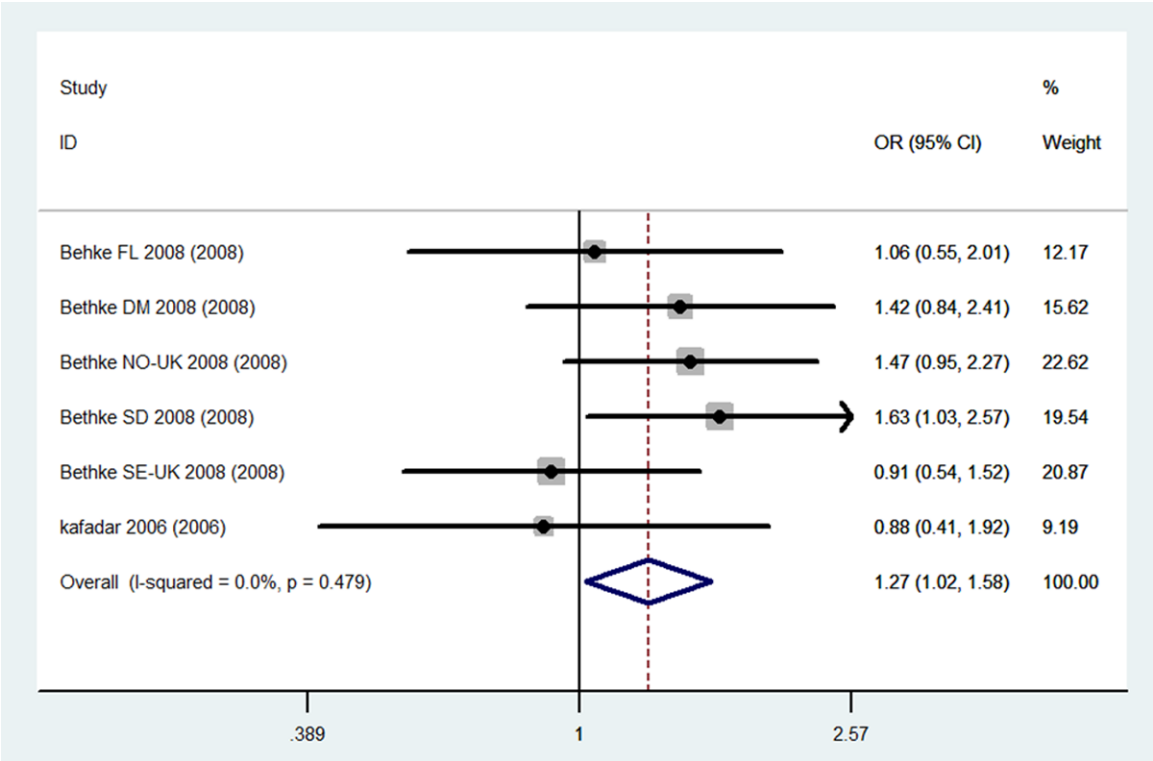

Figure 3. Forest plots for the association between the MTHFR C677T polymorphism and meningioma incidence in CT genotypes among Caucasians.

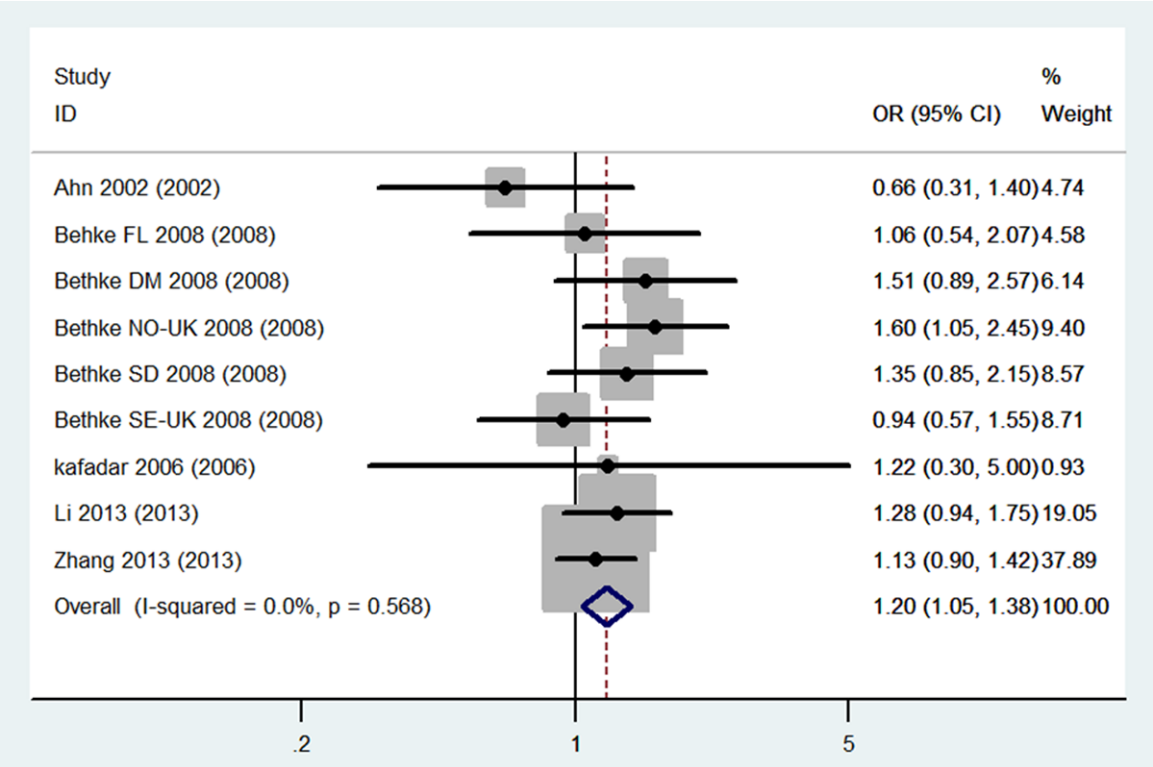

Figure 4. Forest plots for the association between the MTHFR C677T polymorphism and meningioma incidence in CT+TT genotypes among Caucasians.

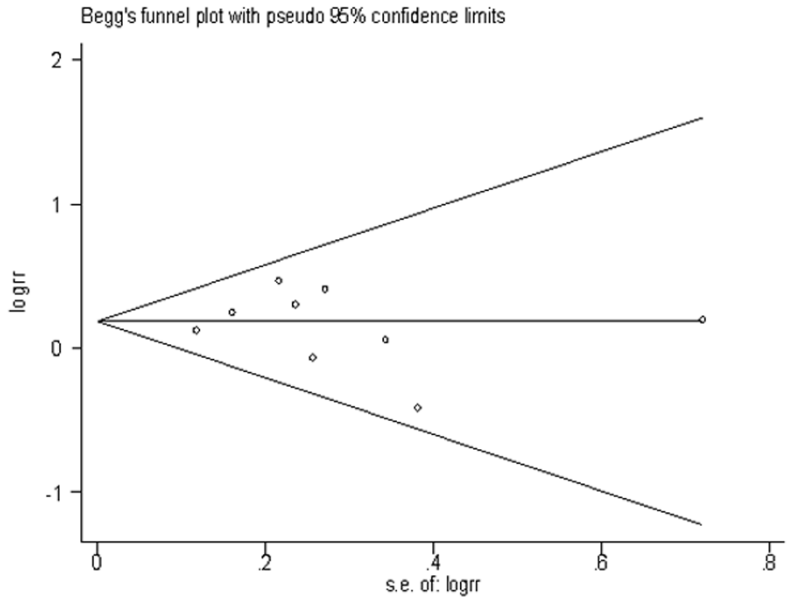

Figure 5. Begg's funnel plots of publication bias for the association between MTHFR C677T CT genotype and risk of meningioma among total population.

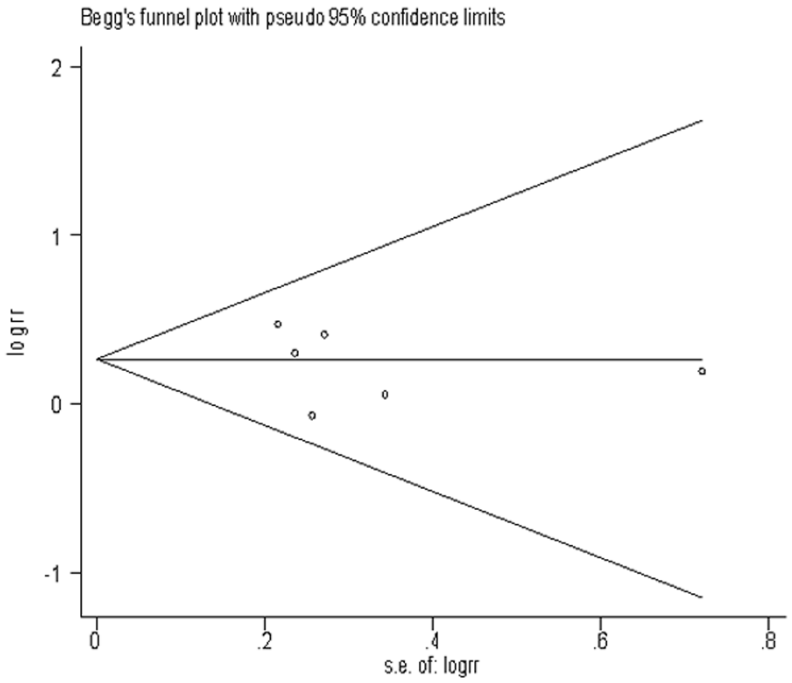

Figure 6. Begg's funnel plots of publication bias for the association between MTHFR C677T CT genotype and risk of meningioma among Caucasians population.

incidence is summarized in **Table 2**. For GSTM1 there were four case-control studies, with a total of 417 meningioma cases and 1,735 controls. For GSTT1 genotypes there were also four case-control studies, but with total 405 meningioma cases and 1,622 controls. The random effect model was conducted since heterogeneity obviously existed both in GSTM1 (P = 0.03 and I^2 = 66%) (**Table 2**) and in GSTT1 (P = 0.01 and I^2 = 73%) (**Table 2**). The combined results indicate that Caucasians carriers of both the GSTM1 null genotype and GSTT1 null genotype do not have statistically different risk of meningioma incidence than other allele genotypes carriers (GSTM1: OR = 1.17, 95% CI 0.77-1.79, P = 0.46; GSTT1: OR = 1.59, 95% CI 0.91-2.78, P = 0.1). Unfortunately, all of the studies were conducted for Caucasians and no study derived from Asian was retrieved. Therefore there was no direct evidence showing the GSTM1/GSTT1 null polymorphism association with meningioma incidence in Asian.

Sensitivity analyses and publication bias

Sensitivity analysis was performed to test the influence of each single study to the pooled OR. The pooled OR was not significantly altered when any individual study was deleted for the MTHFR C677T, GSTM1 and GSTT1 analysis. Begg's test (**Figures 5-7**) and Egger's test were used to assess the publication bias throughout the studies selected for the meta-analysis. Neither of these tests demonstrated any significant publication bias in studies for the MTHFR, GSTM1 or GSTT1 polymorphisms (**Table 3**).

Discussion

The findings from the current meta-analysis supported that MTHFR C677T variant may exert an increased risk effect on meningioma incidence. From this meta-analysis we demon-

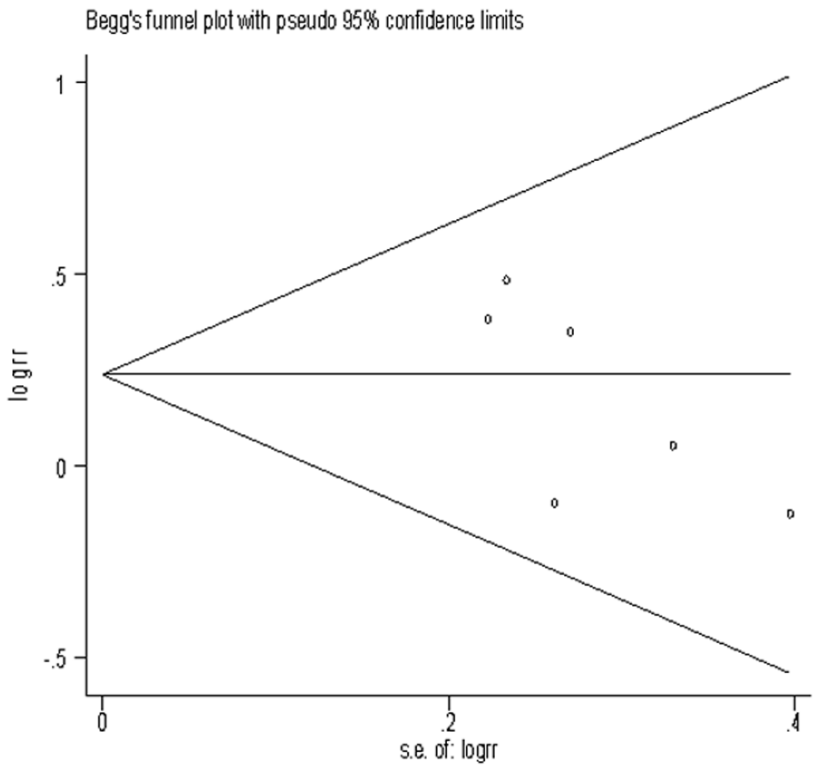

Figure 7. Begg's funnel plots of publication bias for the association between MTHFR C677T CT+TT genotype and risk of meningioma among Caucasians population.

strated that carriers of the CT genotype of MTHFR C677T may associate with a higher meningioma risk. The data also show that Caucasians have significantly higher meningioma risk if they carrying the CT genotype, since both Caucasians carriers of the CT genotype and the sum Caucasians carriers of CT+TT genotype have higher meningioma risk according to the stratified analysis. Therefore, we conclude that detecting the MTHFR C677T polymorphism may become a method of forecasting the meningioma susceptibility of human being, especially for Caucasians. In the data no meningioma risk difference was found for Asian in the MTHFR C677T analysis, which may result from the limited sample sizes in the retrieved studies that conducted for Asian. No studies conducted for other ethnicities were retrieved. Therefore, we think the role of MTHFR C677T mutation in meningioma pathogenesis across diverse ethnicities needs further elucidation by more future studies with large sample sizes.

In this study, we present an intensive analysis for associations between GSTM1/GSTT1 variant genotypes and the risk of meningioma incidence. The association between GSTM1 deletion polymorphism (GSTM1 null genotype) and the meningioma risk did not reach statistical significance in our analysis. However, the statistical data (OR = 1.17, 95% CI 0.77-1.79) reflect a trend of positive association. The same, no positive association was confirmed between the meningioma risk and GSTT1 deletion polymorphism (GSTT1 null genotype) but the statistical data (OR = 1.59, 95% CI 0.91-2.78) reflect a positive trend. Although this meta-analysis for the included studies did not found the association between the GSTM1/GSTT1 polymorphisms and the meningioma risk, we believe that amplifying the sample sizes may obtain a different result, since some previous studies have found a positive association between these polymorphisms and types of brain tumors, including brain meningiomas [32, 47, 49, 51, 52].

In conclusion, our results indicated MTHFR C677T polymorphism is significantly related to meningioma risk. Even the relationship between the GSTM1/GSTT1 null polymorphisms and meningioma risk cannot be demonstrated by this meta-analysis, we believe it might be positively discovered if relevant studies with large sample sizes be performed in the future. However, we think these conclusions should be received with caution, since the meta-analysis in this study was limited by the quality and quantity of included studies. For one hand, although no statistical significance of publication bias was found in this study, the underlying bias may be produced when only English and Chinese publications were included. On the other hand, it is hard to identify precise gene associations in Asians and other mixed population since the included population was too limited. Further studies should be conducted on a

Table 3. *P* values for publication bias tests

MTHFR C677T (rs1801133)	Genotype	Population	N			Test of association			Mode	Test of heterogeneity		
				CASE	CONTROL	OR	95% CI	P		χ^2	P	I^2
	T	Total	9	1101	1242	1.1	[0.85, 1.42]	0.48	R	41.5	0.00001	81%
		Caucasians	6	452	449	1.15	[0.98, 1.35]	0.1	F	3.75	0.59	0%
		Asian	3	649	793	1.06	[0.93, 1.21]	0.38	R	37.22	0.00001	95%
	TT	Total	9	192	251	0.98	[0.61, 1.57]	0.94	R	31.68	0.0001	75%
		Caucasians	6	77	104	0.96	[0.69, 1.34]	0.82	F	2.91	0.71	0%
		Asian	3	115	147	0.96	[0.28, 3.34]	0.95	R	28.77	0.00001	93%
	CT	Total	9	726	771	1.2	[1.05, 1.38]	0.009	F	6.71	0.57	0%
		Caucasians	6	307	272	1.31	[1.05, 1.63]	0.02	F	3.3	0.65	0%
		Asian	3	419	499	1.14	[0.95, 1.37]	0.15	F	2.55	0.28	22%
	TT+TC	Total	9	918	1022	1.18	[0.89, 1.57]	0.26	R	28.13	0.0004	72%
		Caucasians	6	384	376	1.27	[1.02, 1.58]	0.03	F	4.5	0.48	0%
		Asian	3	534	646	1.06	[0.52, 2.17]	0.87	R	22.86	0.0001	91%
GSTM1	Null	Caucasians	4	230	910	1.17	[0.77, 1.79]	0.46	R	8.95	0.03	66%
		Asian	--	--	--	--	--	--	--	--	--	--
GSTT1	Null	Caucasians	4	92	290	1.59	[0.91, 2.78]	0.1	R	10.93	0.01	73%
		Asian	--	--	--	--	--	--	--	--	--	--

broader scale in order to investigate these gene variants in different ethnicities especially in Asian and to achieve more comprehensively understanding the associations between MTHFR C677T, GSTM1/GSTT1 genes and the risk of meningioma.

Disclosure of conflict of interest

None.

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