

RESEARCH COMMUNICATION

Methylenetetrahydrofolate Reductase C677T Polymorphism and Cervical Cancer Risk: a Meta-Analysis

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Abstract

Background: Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of folate, and the role of MTHFR C677T polymorphism in cervical carcinogenesis is still controversial. **Method:** We performed a meta-analysis of all relevant case-control studies that examined any association between the C677T polymorphism and cervical cancer risk. We estimated summary odds ratios (ORs) with their confidence intervals (CIs) to assess links. **Results:** Finally, 10 studies with a total of 2113 cervical cancer cases and 2804 controls were included. Results from this meta-analysis showed that significantly elevated cervical cancer risk was associated with the MTHFR T allele in the Asian population under conditions of two genetic comparison models (for TT vs. CC, OR = 1.37, 95% CI 1.00-1.87, P = 0.050; for TT vs. TC+CC: OR = 1.34, 95% CI 1.01-1.77, P = 0.039). However, there was no obvious association between the MTHFR C677T polymorphism and cervical cancer risk in the other populations. **Conclusion:** The MTHFR C677T polymorphism is associated with cervical cancer risk in Asians, while any possible link in the Caucasian population needs further studies.

Keywords: Methylenetetrahydrofolate reductase - genetic polymorphism - cervical cancer - meta-analysis

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Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in the females worldwide, accounting for 9% (529,800 cases) of the total new cancer cases and 8% (275,100 deaths) of the total cancer deaths among females in 2008 (Jemal et al., 2011). More than 85% of these cases and deaths occur in developing countries (Jemal et al., 2011, Li et al., 2011). Epidemiological studies have confirmed that oncogenic subtypes of the human papilloma virus (HPV) are a crucial etiological factor of cervical tumorigenesis (Walboomers et al., 1999; Munoz et al., 2003). However, this virus is cleared by the immune system in the majority of HPV infected women and only stays in the few individuals, with the oncogenic subtypes resulting in cervical cancer (Munger et al., 2004; Mun et al., 2011). Thus, this information suggests a remarkable interaction between the virus and the host's genetic factors, which may increase the host's susceptibility to cervical cancer (Magnusson et al., 1999; Baseman and Koutsky, 2005).

The 5, 10-methylenetetrahydrofolate reductase gene (MTHFR) maps to chromosome 1p36.3, and MTHFR plays a central role in folate metabolism, together with other enzymes by irreversibly catalyzing the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulating form of folate and a cosubstrate for homocysteine methylation to methionine (Goyette et al., 1994; Goyette et al., 1998). Many rare mutations of

the MTHFR gene have been described in individuals, resulting in very low enzymatic activity, whereas the most common polymorphism is a C to T mutation in exon 4 at nucleotide 677, leading to Ala222Val and presenting in healthy individuals with lower enzyme activity (Frosst et al., 1995; Goyette et al., 1998). This MTHFR genetic polymorphism can lead to abnormal DNA methylation and DNA synthesis, possibly leading to an altered risk for cervical cancer (Frosst et al., 1995; Goyette et al., 1998). Recent studies have shown that the MTHFR 677 TT genotype is associated with an increased risk of cancer risk, suggesting an important role of folate levels and subsequent impaired chromosomal DNA synthesis and aberrant DNA methylation in carcinogenesis (Dong et al., 2008; Zhang et al., 2010). There are also many published studies investigating the association between C677T polymorphism and cervical cancer risk, but the effect of MTHFR C677T polymorphism on cervical cancer risk remains controversial (Shekari et al., 2008; Kohaar et al., 2010; Mostowska et al., 2011; Prasad and Wilkhoo, 2011; Tong et al., 2011; von Keyserling et al., 2011). With the present meta-analyses, we aimed to assess the overall effect of the MTHFR C677T polymorphism on cervical cancer by including all available published papers.

Materials and Methods

Study identification and selection criteria

We searched PubMed, Embase and CNKI database

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using the following search strategy: ('cervical carcinoma' or 'cervical cancer') and ('Methylenetetrahydrofolate reductase' or 'MTHFR' or 'C677T') and ('polymorphism' or 'polymorphisms' or 'mutation' or 'mutations') for papers published (last search was done on November 12, 2011). The language of the papers was not restricted. All searched studies were retrieved, and their bibliographies were checked for other relevant publications. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis. The following criteria were used to select the eligible studies: (1) case-control studies; (2) evaluation of the MTHFR C677T polymorphism and cervical cancer risk; (3) identification of cervical cancer was confirmed histologically or pathologically; (4) sufficient reported genotypic frequencies in both case and control populations for estimating an odds ratio (OR) with a 95% confidence interval (CI); (5) the genotype distribution among the control population was consistent with Hardy-Weinberg Equilibrium (HWE). The major reasons for exclusion of studies were: (1) case only studies; (2) review papers; (3) containing overlapping data.

Data extraction

Data retrieved from the articles included the following: first author's name, publication year, country of origin, racial descent of the study population (categorized as Caucasian population, Asian population and others), the frequency for MTHFR C677T genotypes and the allele frequency of MTHFR C677T. Disagreements were resolved by reaching a consensus among all reviewers.

Statistical analysis

For the control group of each study, the distribution of genotypes was tested for HWE using the Chi-square test. If controls of studies were found not to be in HWE, sensitivity analyses were performed with and without these studies to test the robustness of the findings. The strength of association between MTHFR C677T polymorphism and cervical cancer risk was estimated by Odds ratios (ORs) with 95% confidence intervals (CIs). Five different comparison models of ORs were calculated: the allele model (T vs. C), the Homozygote comparison model (TT versus CC), the Heterozygote comparison model (CT versus CC), the Recessive genetic comparison model (TT versus T/C+CC), and the Dominant genetic comparison model (TT+T/C versus CC). The χ^2 -based Q statistic was used to investigate the degree of heterogeneity between the studies, and a P value < 0.05 was interpreted as significant heterogeneity among the studies (Cochran, 1954). To calculate the proportion of total variability attributed to between-study heterogeneity, the I^2 statistic was calculated, which statistic was useful when deciding whether there was too much heterogeneity to combine the studies and derive a pooled estimate (Higgins et al., 2003). I^2 values of 25%, 50%, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively. If heterogeneity existed, the random effects model (the DerSimonian and Laird method) (DerSimonian and Laird, 1986), which yields

wider confidence intervals, was adopted to calculate the overall OR value. Otherwise, the fixed effects model (the Mantel-Haenszel method) was used (Mantel and Haenszel, 1959). In order to assess the stability of the results, sensitivity analyses were performed by reanalyzing the significance of ORs after omitting each study in turn. An estimate of potential publication bias was carried out by the Begg's funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggested a possible publication bias. Besides, the funnel plot asymmetry was further assessed by the method of Egger's linear regression test, a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR (Egger et al., 1997). The significance of the intercept was determined with the t-test suggested by Egger (P < 0.05 was considered representative of statistically significant publication bias). We also calculated separate pooled estimates for different ethnic groups (Caucasian population, Asian population and the others). The analysis was conducted using STATA (version 9.2; Stata Corp, College Station, TX). All P values were two-sided and a P value of less than 0.05 was deemed statistically significant.

Results

Characteristics of included studies

34 unique references were initially identified by the search. After discarding those which clearly did not meet the criteria, 19 studies were further assessed for eligibility (Piyathilake et al., 2000; Goodman et al., 2001; Gerhard et al., 2003; Lambropoulos et al., 2003; Sull et al., 2004; Kang et al., 2005; Zoodsma et al., 2005; Delgado-Enciso et al., 2006; Rao et al., 2006; Piyathilake et al., 2007; Nandan et al., 2008; Shekari et al., 2008; Agodi et al., 2010; Kohaar et al., 2010; Tong et al., 2010; Mostowska et al., 2011; Prasad and Wilkhoo, 2011; Tong et al., 2011; von Keyserling et al., 2011). After reviewing each original paper and extracting data, nine studies were excluded including five studies focusing on cervical intraepithelial neoplasia (Piyathilake et al., 2000; Goodman et al., 2001; Lambropoulos et al., 2003; Piyathilake et al., 2007; Agodi et al., 2010), three studies for not specifying genotypic frequencies of CC, CT, and TT (Gerhard et al., 2003; Nandan et al., 2008; Rao et al., 2006) and one study for overlapping data (Tong et al., 2010). Finally, 10 case-control studies with a total of 2113 cervical cancer cases and 2804 controls were included into this meta-analysis (Sull et al., 2004; Kang et al., 2005; Zoodsma et al., 2005; Delgado-Enciso et al., 2006; Shekari et al., 2008; Kohaar et al., 2010; Mostowska et al., 2011; Prasad and Wilkhoo, 2011; Tong et al., 2011; von Keyserling et al., 2011). The detailed characteristics of these studies are summarized in Table 1. There were three case-control studies from Caucasian population, four studies were from Asian population, four studies from Indians and one study from Latino (Table 1). Besides, the distributions of genotypes were all consistent with HWE in the control groups of these 11 studies (All P_{HWE} were more than 0.05, Table 1).

Meta-analysis results

Table 1. Description of the studies included in the meta-analyses of the MTHFR C677T polymorphism and cervical cancer risk

First author	Year	Study	Ethnicity (Country)	MTHFR C677T genotype distribution*	MTHFR C677T genotype distribution*			P _{HWE}
					TT	CT	CC	
Prasad VV	2011	Case-control	Indian(India)	Case	0	5	57	0.07
				Control	1	12	228	
von Keyserling H	2011	Case-control	Caucasian (Germany)	Case	34	188	164	0.9
				Control	27	136	165	
Mostowska A	2011	Case-control	Caucasian (Poland)	Case	9	59	56	0.43
				Control	18	81	69	
Tong SY	2011	Case-control	East Asian	Case	28	65	53	0.37
				Control	77	198	152	
Kohaar I	2010	Case-control	Indian	Case	4	47	113	0.6
				Control	5	65	161	
Shekari M	2008	Case-control	Indian	Case	2	28	170	0.54
				Control	7	68	125	
Delgado-Enciso I	2006	Case-control	Latino (Mexico)	Case	18	34	18	0.34
				Control	20	49	20	
Zoodsma M	2005	Case-control	Caucasian (Netherlands)	Case	49	230	357	0.61
				Control	57	262	273	
Kang S	2005	Case-control	East Asian (Korea)	Case	20	32	27	0.49
				Control	12	32	30	
Sull JW	2004	Case-control	East Asian (Korea)	Case	58	115	73	0.99
				Control	80	221	153	

*MTHFR, methylenetetrahydrofolate reductase gene; #P_{HWE}, the P value for Hardy-Weinberg equilibrium in the control group

Table 2. Meta-Analysis of the Association Between the MTHFR C677T Polymorphism And Cervical Cancer Risk

Comparison Model		No. of studies	OR(95%CI)	POR	Model	I ² (%)	PH*
All studies	T vs. C	10	0.94(0.76-1.17)	0.587	Random	78.90%	<0.001
	TC vs. CC	10	0.92(0.70-1.20)	0.525	Random	73.10%	<0.001
	TT vs. CC	10	1.12(0.79-1.59)	0.528	Random	58.00%	0.008
	TT vs. TC+CC	10	1.15(0.96-1.38)	0.136	Fixed	43.70%	0.059
	TT+ TC vs. CC	10	0.96(0.72-1.27)	0.769	Random	78.50%	<0.001
Caucasian	T vs. C	3	0.92(0.66-1.27)	0.6	Random	82.30%	0.003
	TC vs. CC	3	0.94(0.57-1.54)	0.802	Random	85.10%	0.001
	TT vs. CC	3	0.80(0.59-1.09)	0.161	Fixed	48.70%	0.142
	TT vs. TC+CC	3	0.85(0.63-1.34)	0.268	Fixed	0.00%	0.518
	TT+ TC vs. CC	3	0.92(0.56-1.49)	0.728	Random	86.00%	0.001
East Asian	T vs. C	3	1.16(0.99-1.36)	0.068	Fixed	0.00%	0.409
	TC vs. CC	3	1.04(0.80-1.34)	0.787	Fixed	0.00%	0.854
	TT vs. CC	3	1.37(1.00-1.87)	0.05	Fixed	0.00%	0.435
	TT vs. TC+CC	3	1.34(1.01-1.77)	0.039	Fixed	0.00%	0.507
	TT+ TC vs. CC	3	1.13(0.89-1.43)	0.33	Fixed	0.00%	0.63

*PH, the P value of heterogeneity analysis

Table 2 listed the main results of this meta-analysis. Overall, there was no association between the MTHFR C677T polymorphism and cervical cancer risk (All P values were more than 0.05, Table 2). A single study involved in the meta-analysis was deleted each time to define the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered, indicating that our results were statistically robust.

In the subgroup analyses by ethnicity, significantly elevated cervical cancer risk was associated with MTHFR T allele in the Asian population under two genetic comparison models (for TT vs. CC, OR = 1.37, 95%CI 1.00-1.87, P = 0.050; for TT vs. TC+CC: OR = 1.34, 95%CI 1.01-1.77, P = 0.039) (Table 2). However, there was no obvious association between the MTHFR C677T polymorphism and cervical cancer risk in the other

population (Table 2).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures in this meta-analysis. The shape of the funnel plot did not reveal any evidence of obvious asymmetry, and the outcome of Egger's test provided statistical evidence for the symmetry of Begg's funnel plot ($t_{\text{Egger test}} = -0.30, 95\%CI -2.46 \sim 1.88, P_{\text{Egger test}} = 0.771$). Thus, there was no obvious publication bias of literatures in this meta-analysis.

Discussion

MTHFR regulates the metabolism of folate and it is an important factor in DNA methylation and synthesis (Goyette et al., 1998). A base change from C to T at

nucleotide position 677 of the MTHFR gene results in coding for valine instead of alanine (Frosst et al., 1995). Both heterozygous and homozygous variants have reduced MTHFR enzyme activity compared with the homozygous normal wild-type genotype (Frosst et al., 1995). This common polymorphism of the MTHFR gene can lead to abnormal DNA methylation and DNA synthesis, possibly leading to an altered risk for cervical cancer. For almost a decade, many case-control studies investigating the association between MTHFR C677T polymorphism and cervical cancer risk have been published, but this association is still controversial (Sull et al., 2004; Kang et al., 2005; Zoodma et al., 2005; Delgado-Enciso et al., 2006; Shekari et al., 2008; Kohaar et al., 2010; Mostowska et al., 2011; Prasad and Wilkoo, 2011; Tong et al., 2011; von Keyserling et al., 2011). Thus, to establish a comprehensive picture of the relationship between MTHFR C677T polymorphism and cervical cancer risk, we performed this meta-analysis, and it is the first meta-analysis to investigate the association between MTHFR C677T polymorphism and cervical cancer risk up to now. Finally, eleven studies with a total of 2224 cervical cancer cases and 2915 controls were included into this meta-analysis. Results from this meta-analysis showed that significantly elevated cervical cancer risk was associated with the MTHFR T allele in the Asian population under three genetic comparison models (T vs. C: OR = 1.24, 95%CI 1.07-1.44, P = 0.004; TT vs. CC: OR=1.56, 95%CI 1.17-2.08, P = 0.003; TT vs. TC+CC: OR = 1.51, 95%CI 1.17-1.94, P = 0.001) (Table 2). Sensitivity analyses were performed by reanalyzing the significance of ORs after omitting each study in turn, and the outcomes showed this result was statistically robust. However, there was no obvious association between the MTHFR C677T polymorphism and cervical cancer risk in the other population. Thus, the MTHFR C677T polymorphism is associated with cervical cancer risk in the Asian population, while this possible association in the Caucasian population needs further study. Besides, in the subgroup analysis based on ethnicities, significant associations were found in the Asian population but not for the Caucasians, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they live in (Hirschhorn et al., 2002).

This finding above is biologically plausible. Individuals with the MTHFR 677TT genotype have been shown to have only 30% of in vitro MTHFR enzyme activity compared with the wild type, whereas those with the heterozygous CT genotype have 60% of wild-type MTHFR enzyme activity (Frosst et al., 1995). Reduction of the MTHFR enzyme activity can increase the pool of 5, 10-methylene-THF at the expense of the pool of 5-methyl-THF and impair the DNA methylation. Because the DNA methylation plays a critical role in regulation of gene expression and maintenance of genomic stability, the aberrations in normal methylation patterns have been associated with the development of cancer by impairing the DNA methylation (Cheng et al., 1997). More importantly, the homozygous variant genotype MTHFR 677TT has been associated with risk for many different types of cancer, including colorectal cancer, gastric cancer

and breast cancer (Taioli et al., 2009; Dong et al., 2010; Zacho et al., 2011).

Some limitations of this meta-analysis should be acknowledged. Firstly, the controls were not uniformly defined. The controls in some studies were selected mainly from healthy populations, while the others were selected mainly from individuals having benign diseases, such as cervical intraepithelial neoplasia, or non-cancer individuals. Secondly, potential cervical cases were possible because some studies may have included the control groups selected mainly from non-symptom populations. Thirdly, our results were based on unadjusted estimates, while a more precise analysis should be conducted if all individual data were available, which would allow for the adjustment by other co-variants including smoking status, environmental factors, and HPV infection status (Chansaenroj et al., 2012). Thus, further large sample size studies with gene-gene and gene-environment interactions need performing to identify this association more comprehensive.

In conclusion, this meta-analysis suggests that the MTHFR C677T polymorphism is associated with cervical cancer risk in the Asian population, while this possible association in the Caucasian population needs further study. Moreover, gene-gene and gene-environment interactions should also be considered in this association, and such studies taking these factors into account may eventually lead to our better and comprehensive understanding of the association between the MTHFR C677T polymorphism and cervical cancer risk.

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