

## RESEARCH COMMUNICATION

# Methylenetetrahydrofolate Reductase Gene C677T Polymorphism and Lung Cancer: an Updated Meta-analysis

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### Abstract

**Objective:** Methylenetetrahydrofolate reductase (MTHFR) catalyzes the metabolism of folate and nucleotides needed for DNA synthesis and repair. Variations in MTHFR functions likely play roles in the etiology of lung cancer (LC). So far, several studies between MTHFR C677T polymorphism and LC provide controversial or inconclusive results. **Methods:** To better assess the purported relationship, we performed a meta-analysis of 14 publications. Eligible studies were identified by searching the Pubmed, Embase, Web of Science and Google Scholar databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association. **Results:** Overall, no significant association was detected between the MTHFR C677T polymorphism and LC risk, the same as in race subgroup. However, in the stratified analysis by histological type, significantly increased non-small-cell lung cancer (NSCLC) risk was indicated (T-allele vs. C-allele: OR = 1.11, 95% CI = 1.03-1.19; TT vs. CC: OR = 1.24, 95% CI = 1.09-1.41; TC vs. CC: OR = 1.11, 95% CI = 1.03-1.20 and TT+TC vs. CC: OR = 1.09, 95% CI = 1.03-1.15). At the same time, ever-smokers who carried T-allele (TT+TC) had a 10% decreased LC risk compared with CC genotype carriers. **Conclusions:** Our study provided evidence that the MTHFR 677T null genotype may increase NSCLC risk, however, it may protect ever-smokers against LC risk. Future studies with large sample sizes are warranted to further evaluate this association in more detail.

**Keywords:** MTHFR - lung cancer - polymorphism - meta-analysis

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### Introduction

Lung cancer (LC) was the most commonly diagnosed cancer as well as the leading cause death in males in 2008 globally. Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death (Jemal et al., 2011). Although it is well known that smoking is the primary risk factor for LC (Xiao et al., 2011), LC develops in less than 20% of people who smoke throughout their life (Shields, 2002). Moreover, LC is a multi-cellular and multistage process involving a number of genetic changes in oncogenes, suggesting that genetic factors may play an important role in its development (Mattson et al., 1987; Shields et al., 2000; Spitz et al., 2003).

Numerous epidemiological studies have pointed out that low dietary folate intake is important factor in development of cancer including lung (Shen et al., 2003), breast (Shrubsole et al., 2004), bladder (Schabath et al., 2005) and prostate (Muslumanoglu et al., 2009). Folate is involved in DNA methylation, synthesis and repair (Xu et al., 2007). In all of these events, folate serves as one carbon donor and its metabolic product provides methyl group for both synthesis of methionine and DNA methylation (Heijmans et al., 2003).

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism and catalyzes 5,10-MTHF to 5-MTHF. The importance of MTHFR in cancer susceptibility arises from its involvement in two pathways of folate metabolism: reduced activity of MTHFR may decrease the methylation of homocysteine to methionine and in turn the level of S-adenosyl-methionine (SAM), resulting in DNA hypomethylation; a reduced level of MTHFR substrate could lead to uracil misincorporation into DNA, diminished DNA repair and increased frequency of chromosomal breaks and damage (Krajinovic et al., 2004).

A common mutation of the MTHFR gene is the C to T transition at nucleotide 677, which converts alanine to valine, results a decreased activity enzyme (Jacques et al., 2003). The low enzymatic activity is associated with DNA hypomethylation, which may induce genomic instability or the derepression of proto-oncogenes.

A number of studies indicated that this polymorphism was involved in the etiology of LC. However, the results from those studies remain conflicting rather than conclusive. Previous, two meta-analyses (Mao et al., 2008; Boccia et al., 2009) both didn't show any significantly association between MTHFR C677T polymorphism and LC risk. In the last two years, some new articles have been

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published. Considering the important role of MTHFR gene in LC carcinogenesis, we performed an update analysis on all eligible case-control studies (Shen et al., 2001; Heijmans et al., 2003; Jeng et al., 2003; Siemianowicz et al., 2003; Shen et al., 2005; Shi et al., 2005; Zhang et al., 2005; Hung et al., 2007; Suzuki et al., 2007; Liu et al., 2008; Liu et al., 2009; Arslan et al., 2011; Cui et al., 2011; Cui et al., 2011) estimate the LC risk associated with this polymorphism.

## Materials and Methods

### Identification of eligible studies

A literature search of the Pubmed, Embase, Web of science and Google Scholar databases (updated on June 30, 2011) were conducted using combinations of the following keywords 'polymorphism' or 'variant' or 'mutation', 'lung cancer' or 'carcinoma' and 'MTHFR' or 'methylenetetrahydrofolate reductase'. Only English language papers were adopted. All studies that evaluated the associations between MTHFR C677T polymorphism and LC risk were retrieved. Studies that were included in our meta-analysis had to meet all of the following criteria: (1) evaluation of MTHFR C677T polymorphisms and LC risk; (2) case-control design; (3) genotype frequency was available; (4) only the full-text manuscripts were included and (5) genotype distributions of control consistent with Hardy-Weinberg equilibrium (HWE). Meanwhile, the following exclusion criteria are also used: HWE of controls were less than 0.05.

### Data extraction

Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria listed above. The following data were collected from each study: first author's last name, year of publication, race of origin, sample size (cases/controls), number of genotype frequency in cases/controls, study design and HWE of controls.

### Statistical analysis

Odds ratios (ORS) with 95% confidence intervals (CIS) were used to measure the strength of the association

between MTHFR C677T polymorphism and LC based on the genotype frequencies in cases and controls. Subgroup analysis stratified by race was performed first. Race was categorized as European and Asian. LC was performed on two classifications based on pathology: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Because smoking is the major cause of LC, we included this factor in our analysis.

The statistical significance of the summary OR was determined with the Z-test. Heterogeneity assumption was evaluated with a chi-square-based Q test among the studies. A P value of more than 0.05 for the Q-test indicated a lack of heterogeneity among the studies. In case significant heterogeneity was detected, the random effects model was used, however, the fixed effects model was chosen (Mantel et al., 1959; DerSimonian et al., 1989). For MTHFR C677T, we investigated the relationship between genetic variants and LC risk in four different models (T-allele vs. C-allele, TT vs. CC, TC vs. CC and TT+TC vs. CC).

Publication bias was assessed with Egger's test,  $P < 0.05$  was considered statistically significant (Egger et al., 1997). The departure of frequencies of MTHFR polymorphism from expectation under HWE was assessed by  $\chi^2$  test in controls using the Pearson chi-square test,  $P < 0.05$  was considered significant. All statistical tests for this meta-analysis were performed with Stata software (version 10.0; StataCorp LP, College Station, TX).

### Genotyping methods

Genotyping for SNP of MTHFR gene polymorphisms was conducted using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan, DNA sequence, real-time PCR, TaqMan and Illumina genotyping facility.

## Results

### Study selection and characteristics in our meta-analysis

We established a database according to the extracted information from each article. All essential information was listed in Table 1. Table 1 showed first author, publishing year, race, the numbers of cases and controls, HWE and

**Table 1. Characteristics of Studies of MTHFR C677T Polymorphism Included in This Meta-analysis**

First author	Year	Origin	Ethnicity	Case/ Control	Case			Control			Design	
					TT	TC	CC	TT	TC	CC		HWE
Cui	2011	China	Asian	438/641	140	240	58	195	325	121	0.483	HB
Arslan	2011	Turkey	European	64/61	7	27	30	3	29	29	0.206	PB
Cui	2011	Korean	Asian	3938/1700	668	1909	1361	298	862	540	0.148	HB
Liu	2009	China (Taiwan)	Asian	358/716	29	124	205	63	291	362	0.679	PB
Liu	2008	China	Asian	500/517	98	245	157	103	265	149	0.449	HB
Hung	2007	France	European	2169/2803	231	929	1009	259	1147	1397	0.288	HB
Suzuki	2007	Japan	Asian	515/1030	77	256	182	177	474	379	0.17	HB
Shi	2005	USA	European	1051/1141	100	468	483	124	519	498	0.516	PB
Zhang	2005	China	Asian	505/500	155	230	120	109	231	160	0.138	PB
Shen	2005	China	Asian	116/111	18	65	33	16	42	53	0.117	HB
Siemianowicz	2003	Poland	European	146/44	48	60	38	6	20	18	0.906	PB
Jeng	2003	China (Taiwan)	Asian	59/232	1	22	36	14	95	123	0.438	HB
Heijmans	2003	Netherlands	European	44/793	4	17	23	65	329	399	0.806	PB
Shen	2001	USA	European	550/554	57	252	241	57	252	245	0.508	PB

HB, hospital-based; PB, population-based

**Table 2. Stratified Analyses of the MTHFR C677T Polymorphism on LC Risk**

Variables	N	Case/Control	T-allele vs. C-allele		TT vs. CC		TC vs. CC		TT+TC vs. CC	
			OR(95%CI)	Ph	OR(95%CI)	Ph	OR(95%CI)	Ph	OR(95%CI)	Ph
Total	14	10453/10843	1.05(0.96-1.15)	0.000	1.12(0.93-1.35)	0.000	1.04(0.93-1.18)	0.001	1.07(0.94-1.21)	0.000
Race										
Asian	8	6429/5447	1.04(0.91-1.19)	0.000	1.10(0.85-1.43)	0.001	1.08(0.88-1.33)	0.000	1.09(0.88-1.34)	0.000
European	6	4024/5396	1.07(0.93-1.23)	0.021	1.16(0.86-1.57)	0.041	1.03(0.98-1.07)	0.534	1.03(0.99-1.07)	0.188
Histological type										
NSCLC	3	593/746	1.11(1.03-1.19)	0.060	1.24(1.09-1.41)	0.121	1.11(1.03-1.20)	0.976	1.09(1.03-1.15)	0.393
SCLC	2	55/105	1.07(0.77-1.49)	0.110	1.51(0.68-3.37)	0.472	0.93(0.65-1.35)	0.113	0.99(0.73-1.34)	0.087

frequency of T allele in the control, genotype numbers in cases/controls and study design. Overall, 14 case-control studies with 10453 LC cases and 10843 controls were retrieved based on the search criteria for LC susceptibility related to the MTHFR C677T polymorphism. So in our study, there are six European case-control studies, eight Asian case-control studies. Three studies involved NSCLC and two of SCLC. Five publications analyzed this relationship among ever-smokers and never-smokers. The T frequency in Asians was 40.59%, higher than Europeans (34.23%), which did not exist statistically significant ( $P = 0.235$ ). The distribution of genotypes in all the controls was in agreement with HWE.

#### Quantitative data synthesis

Table 2 showed that the summary odds ratios of MTHFR on the basis of 10453 LC cases and 10843 matched controls, we did not observe any association between the MTHFR C677T polymorphism and LC in total population. Given the pathology differences in LC, we evaluated the effect of MTHFR C677T polymorphism in SCLC and NSCLC risk, respectively. We found T null genotype was a risk factor for NSCLC (T-allele vs. C-allele: OR = 1.11, 95%CI = 1.03-1.19, Pheterogeneity = 0.060, TT vs. CC: OR = 1.24, 95%CI = 1.09-1.41, Pheterogeneity = 0.121, TC vs. CC: OR = 1.11, 95%CI = 1.03-1.20, Pheterogeneity = 0.976 and TT+TC vs. CC: OR = 1.09, 95%CI = 1.03-1.15, Pheterogeneity = 0.393, Table 2). In contrast, in the smoking status, T-allele (TT+TC) played a pooled protective role in ever-smokers (TT+TC vs. CC, OR = 0.90, 95%CI = 0.84-0.98, Pheterogeneity = 0.334, Table 3).

#### Publication bias

The Begg's funnel plot and Egger's test were performed to access the publication bias of literature. The shape of the funnel plots seemed asymmetrical in allele comparison for MTHFR C677T polymorphism, suggesting the presence of publication bias. Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. Finally, no obvious evidence of publication bias was detected in overall analysis (data not shown).

## Discussion

All over the world, LC has become one of the most common malignancies. Despite rapid advances in treatment over recent decades, the prognosis has not greatly improved. Therefore, effects toward primary prevention in addition to early detection have come

**Table 3. Relationship Between C677T Polymorphism in MTHFR Gene and LC Risk in Ever-smokers**

Smoking	Genotype	Case	Control	Ph	Egger's test
Ever-smoker	CC	450	760		
	TT+TC	455	1009	0.334	t = 0.09, p = 0.928

under the spotlight. On the one hand, several meta-analyses involving associations between LC risk and gene polymorphisms have been published: SULT1A1 Arg213His polymorphism and LC (Liao et al., 2012); cyclooxygenase 8473 T/C polymorphism and LC (Pan et al., 2011); hOGG1 Ser326Cys polymorphism and LC (Guan et al., 2011). On the other hand, epidemiologic studies have provided evidence that high consumption of vegetable and fruits are associated with a reduced risk of LC, and dietary folate may be one of the micronutrients that provide protection against lung carcinogenesis (Bandera et al., 1997; Voorrips et al., 2000; Shen et al., 2003). MTHFR is an important enzyme in folate metabolism, which contains a common polymorphism (C677T).

Some studies have reported conflicting findings on the association of MTHFR C677T polymorphism with the risk and prognosis of LC: Shen et al. (2001) first studied the role of this SNP in a subtype of LC, suggesting that the MTHFR C677T polymorphism did not play an important role in the etiology of LC, the same as the previous two meta-analyses; Arslan et al. (2011) provided the evidence that individuals carried TT genotype was 2.4-fold higher of LC risk, compared with CC genotype carriers. However, in a recently study, Cui et al. (2011) found that the T-allele provided a weak protective association with LC risk. Small sample size, various ethnic group, diet, environment and methodologies might be responsible for the discrepancy.

Although two meta-analyses have been published two years ago (Mao et al., 2008; Boccia et al., 2009), considering the small subjects, they both did not detect any significant association, although Boccia et al. (2009) reported that low folate intake was an increased risk factor for LC (OR = 1.28, 95%CI = 0.97-1.68). In the past four years, several novel studies have been published (Liu et al., 2008; Liu et al., 2009; Arslan et al., 2011; Cui et al., 2011). It is necessary to perform an updated analysis to indicate the relationship between MTHFR C677T polymorphism and LC risk. We performed a meta-analysis involving 10453 LC cases and 10843 controls. We found T null genotype was a risk factor for NSCLC. In the smoking status, decreased relationship was observed between 677T allele and LC risk in ever-smokers. Although it is well known that cigarette smoking is the major cause

of LC, only 10-20% of lifetime smokers are known to develop LC. The role of MTHFR C677T polymorphism in modulating cancer risk is associated with folate status. Under adequate folate conditions, the protective effect of the 677TT genotype turns to a situation of elevated risk of LC among MTHFR 677TT genotype with low folate intakes. The MTHFR enzyme plays a pivotal role in folate metabolism, catalyzing the irreversible conversion of 5,10-MTHF to 5-MTHF. In one hand, 5-MTHF is the methyl group donor for the remethylation of homocysteine to methionine, which is subsequently used for DNA methylation, abnormalities of which are also known to play a role in carcinogenesis (Krajinovic et al., 2004). In the other hand, the heterozygote and homozygous variant of C677T were shown to have 65% to 30% of the enzyme activity, respectively (Frosst et al., 1995). Reduced MTHFR activity would result in increased 5,10-MTHF for DNA synthesis and decreased 5-MTHF for DNA methylation, finally can increase the anticancer effect of 5-FU. Thus, the effects of MTHFR on carcinogenesis are complex, exerting either an adverse effect on DNA methylation or an advantageous influence on nucleotide synthesis in determining cancer risk, which can explain our results.

Some limitations in our meta-analysis should be mentioned. First of all, the number of published studies included in our meta-analysis remained not sufficiently large for a comprehensive analysis, especially the numbers for NSCLC and SCLC. Second, our meta-analysis was based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, family history, environmental factors (dietary folate intake), cancer stage and lifestyle. Third, the cases were not from the same pathology, we considered them as a whole to calculate the summary OR.

In spite of these, our meta-analysis also had three advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Second, the quality of case-control studies included in the current meta-analysis was satisfactory based on our selection criteria. Third, publication bias was not detected in all genetic models, suggesting that the results were relatively stable and powerful.

In present, our meta-analysis showed the evidence that MTHFR 677T null genotype was associated with increased NSCLC risk, moreover, T-allele (TT+TC) may play a pooled protective factor in ever-smokers. Therefore, further well designed large studies, particularly referring to gene-gene and gene-environment interactions are warranted. These future studies should lead to better and comprehensive understanding of the association between the MTHFR C677T polymorphism and development of LC risk.

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