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META-ANALYSIS

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Methylenetetrahydrofolate Reductase 677TT Genotype may be Associated with an Increased Lung Cancer Risk in North China: An Updated Meta

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Although many epidemiology studies have investigated the methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and their associations with lung cancer (LC), definite conclusions cannot be drawn. To clarify the effects of MTHFR polymorphisms on the risk of LC, we performed a meta-analysis in Chinese populations.

Material/Methods: Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) until 16 February 2014. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations.

Results: A total of 11 studies with 2487 LC cases and 3228 controls were included in this meta-analysis. Overall, no significant association was found between MTHFR C677T polymorphism and LC risk when all studies in Chinese populations were pooled into this meta-analysis. In subgroup analyses stratified by geographical location and source of controls, significantly increased risk was found in North China (T *vs.* C: OR=1.28, 95% CI: 1.14–1.44; TT *vs.* CC: OR=1.67, 95% CI: 1.33–2.10; TT + CT *vs.* CC, OR=1.39, 95% CI=1.15–1.69; TT *vs.* CC + CT: OR=1.46, 95% CI: 1.03–2.06) and in population-based studies (TT *vs.* CC: OR=1.37, 95% CI: 1.14–1.65; TT *vs.* CC + CT: OR=1.25, 95% CI: 1.07–1.45).

Conclusions: This meta-analysis provides evidence that MTHFR C677T polymorphism may contribute to LC development in North China. Studies with larger sample sizes and wider spectrum of populations are warranted to verify this finding.

MeSH Keywords: 5,10-Methylenetetrahydrofolate Reductase (FADH2) • Lung Neoplasms • Meta-Analysis

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Background

Lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer death in males globally, with 1.6 million newly confirmed cases and 1.4 million deaths from lung cancer annually [1]. The incidence of lung cancer is increasing significantly and constantly [2]. Although tobacco smoking has been established as the most important cause of lung cancer, not all lung cancers are due to smoking, and increasing evidence for the association between genetic factors and lung cancer risk has been identified by hundreds of studies [3,4], suggesting that genetic factors may play a very important role in the development of lung cancer.

Epidemiologic studies have provided evidence that high consumption of vegetables and fruits is associated with a reduced risk of lung cancer [5–7], and dietary folate may be one of the micronutrients that provide protection against lung carcinogenesis [8]. Biological functions of folate in so-called 'one-carbon metabolism' are to facilitate *de-novo* deoxynucleoside triphosphate synthesis and to provide methyl groups required for intracellular methylation reactions. Methylenetetrahydrofolate reductase (MTHFR) is a central regulatory enzyme in folate metabolism that catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulating form of folate. Hence, MTHFR acts as a critical juncture in folate metabolism by directing folate metabolites toward the DNA methylation pathway and away from the DNA synthesis pathway. Two common functional polymorphisms of the MTHFR gene, C677T and A1298C, have been identified, and the variant genotypes are associated with low plasma folate levels and significantly diminish the MTHFR activity of individuals [9–11]. Therefore, polymorphisms in the MTHFR gene may contribute to genetic susceptibility to lung and other cancers [12].

A series of studies have investigated the association between the MTHFR gene polymorphisms and lung cancer susceptibility, but provided controversial or inconclusive results. To lessen the impact of different genetic background, we performed this meta-analysis to assess the relationship of MTHFR gene polymorphisms with risk of lung cancer in Chinese populations.

Material and Methods

Materials

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 16 February 2014, using the following MeSH terms: ("Lung Neoplasms " [MeSH] or "lung cancer" or "lung tumor" or "lung carcinoma" or "carcinoma of lung") and ("MTHFR" or "methylenetetrahydrofolate reductase"). We limited the languages to English and Chinese. References from retrieved articles were also searched.

Inclusion/exclusion criteria

Studies included in this meta-analysis had to meet the following criteria: (1) case-control study or cohort study on associations between 2 functional polymorphisms (C677T and A1298C) in MTHFR gene and lung cancer susceptibility; (2) all patients with the diagnosis of lung cancer confirmed by pathological or histological examination; (3) sufficient published data about sample size, ORs, and their 95% CIs; (4) published in English or Chinese language; (5) the distribution of the genotypes in control groups was in the Hardy–Weinberg equilibrium; (6) all participants were Chinese. Studies were excluded when they were: (1) not case–control study or cohort study; (2) duplicate of a previous publication; (3) based on incomplete data; (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Data were independently extracted by 2 reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved, the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following information was collected from each study: authors, journal and year of publication, study design, sample size, geographical location, ethnicity of subjects, source of controls, numbers of cases and controls, and genotype frequencies of MTHFR C677T and A1298C.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX). The distributions of genotypes in controls were tested by Hardy-Weinberg equilibrium using the chi-square test. The association of polymorphisms of MTHFR and lung cancer risk was estimated by ORs with 95% CIs. The heterogeneity was tested by the Q-statistics with *P*-values <0.1, and its possible sources of heterogeneity were assessed by subgroup analysis. Dependent on the results of heterogeneity test among individual studies, the fixed-effects model (Mantel–Haenszel) or random effects model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. The significance of the pooled ORs was determined by the z test. Publication bias was investigated with the funnel plot, in which the standard error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by Egger's linear

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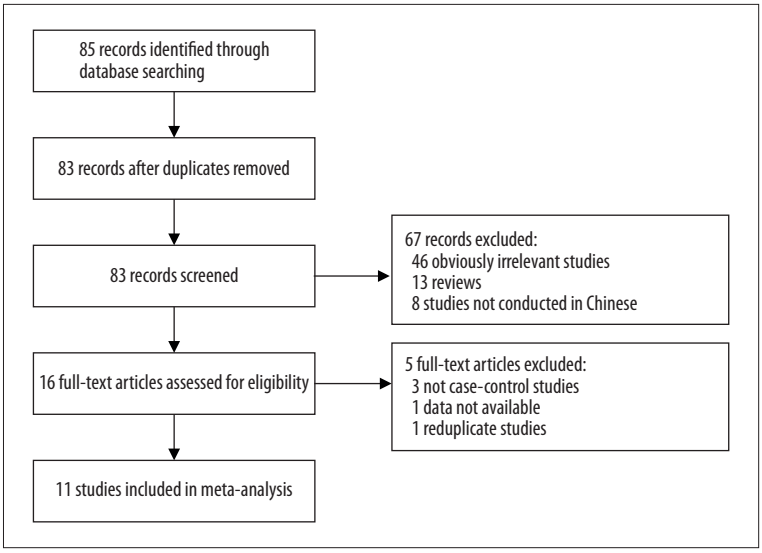

Figure 1. Flow diagram of the literature search.

regression test. All the *P* values were 2-sided. *P* value less than 0.05 was considered statistically significant.

Results

Eligible studies

According to the inclusion criteria, 11 case-control studies [13–23] were included and 74 articles were excluded. The publication year of involved studies ranged from 2003 to 2012. The flow chart of study selection is shown in Figure 1. In total, 2487 lung cancer cases and 3228 healthy controls were involved in this meta-analysis, which evaluated the relationship between MTHFR polymorphism and lung cancer risk. The source of controls was mainly based on a healthy population. Ten of these studies were conducted for MTHFR C677T polymorphisms and 5 studies for MTHFR A1298C polymorphisms. The characteristics of the included studies are summarized in Table 1.

Quantitative synthesis

The main results of this meta-analysis and the heterogeneity test were shown in Tables 2 and 3. With respect to C677T polymorphism, no significantly elevated lung cancer risk was found in overall analyses (Table 2). In the subgroup analysis by geographical locations, significantly increased risk was found in the population from North China (T *vs.* C: OR=1.28, 95% CI: 1.14–1.44; TT *vs.* CC: OR=1.67, 95% CI: 1.33–2.10; TT + CT *vs.* CC, OR=1.39, 95% CI=1.15–1.69; TT *vs.* CC + CT: OR=1.46, 95% CI: 1.03–2.06), was not found in the South. In the subgroup analysis by ethnicity, significantly increased risk was not found in Han populations. In the subgroup analysis by source of controls, significant association was found in population-based studies (TT *vs.* CC: OR=1.37, 95% CI: 1.14–1.65; TT *vs.* CC + CT: OR=1.25, 95% CI: 1.07–1.45). With respect to A1298C polymorphism, no significant association with lung cancer risk was demonstrated among overall analyses and subgroup analyses by ethnicity, geographical locations, and source of controls.

Sensitive analysis and bias diagnosis

To compare the difference and evaluate the sensitivity of the meta-analyses, we used both models (the fixed effects model and random effects model) to evaluate the stability of the meta-analysis. None of the results were materially altered (data not shown). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal obvious asymmetry (Figures not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there was no obvious publication bias for MTHFR C677T in North China (T *vs.* C, t=0.12, *p*=0.925; TT *vs.* CC, t=–0.77, *p*=0.583; TT + CT *vs.* CC, t=–2.14, *p*=0.278; TT *vs.* CC + CT, t=1.21, *p*=0.441).

Discussion

Although many studies analyzing the research results about the MTHFR polymorphisms and their associations with lung cancer, definite conclusions cannot be drawn. Therefore, we did this updated meta-analysis to estimate the relationships between MTHFR polymorphisms and susceptibility to lung cancer among Chinese populations only, in order to lessen the impact of different genetic background. The meta-analysis involved 11 articles, of which 10 related to C677T polymorphism and

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Table 1. Characteristics of studies included in the meta-analysis.

Authors	year	Source of controls	Area	Ethnicity	Genotype	C677T						A1298C					
						Cases			Controls			Cases			Controls		
						CC	CT	TT	CC	CT	TT	AA	AC	CC	AA	AC	CC
Jeng et al.	2003	PB	Taiwan	Mixed**	C677T	36	22	1	123	95	14						
Zhang et al.	2005	PB	Beijing	Not stated	C677T, A1298C	120	230	155	160	231	109	355	141	9	345	150	5
Shen et al.	2005	PB	Yunnan	Not stated	C677T, A1298C	33	65	18	53	42	16	71	41	2	69	34	6
Jin et al. *	2007	PB	Guangzhou	Not stated	C677T, A1298C							70	28	2	68	30	2
Liu et al.	2008	HB	Nanjing	Han	C677T, A1298C	157	245	98	149	265	103	341	141	18	364	142	11
Liu et al.	2009	PB	Taiwan	Not stated	C677T, A1298C	205	124	29	362	291	63	228	115	15	467	226	23
Yao et al.	2010	PB	Hubei	Not stated	C677T	27	46	20	36	51	19						
Yang et al.	2010	PB	Jiangxi	Han	C677T	49	52	19	62	75	28						
Cui et al.	2011	PB	Shandong	Not stated	C677T	58	240	140	121	325	195						
Cheng et al.	2011	PB	Henan	Han	C677T	49	58	71	47	88	45						
Ma et al.	2012	HB	Yunnan	Han	C677T	20	54	46	22	28	10						

PB – population-based; HB – hospital-based. * Study excluded from the meta-analysis of MTHFR C677T; not in Hardy-Weinberg equilibrium; ** Including Fukien Taiwanese, Hakka Taiwanese and Mainland Chinese.

5 related to A1298C polymorphism. The results of this meta-analysis show that the variant genotypes of the MTHFRC677T polymorphisms were significantly associated with lung cancer risk in North China.

To the best of our knowledge, there are 6 published meta-analyses of MTHFR polymorphisms and lung cancer risk. Of these, 4 meta-analyses reported that there was no association between MTHFR polymorphisms (C677T and A1298C) and lung cancer risk [24–27]. Two found that MTHFR 677TT variant genotype was associated with an increased lung cancer risk [28,29], especially in Asians [28]. Furthermore, in the meta-analysis by et al. [29], stratified analysis by ethnicity indicated that there was no significant association observed in any genetic model of the MTHFR C677T polymorphism among Chinese populations, which is consistent with our results in overall analysis.

When we performed the subgroup analyses by ethnicity, source of controls, and geographical locations, significant association with susceptibility for the development of lung was found in North China and population-based studies, and this may be explained by several factors. First, the relationship between genes and lung cancer might vary by ethnicity. In addition, gene-environmental interaction might play an important role in susceptibility to lung cancer. Most importantly, according to the previous studies, there exist seasonal and sex differences in folate status among Chinese people [30,31]. People living in North China have a higher prevalence folate concentration deficiency [30]. Therefore, these results support the hypothesis that concomitant inadequate folate intake and impaired MTHFR activity might be important susceptibility factors for lung cancer.

Our meta-analysis has several strengths. First, we strictly followed the inclusion and exclusion criteria to reduce possible selection bias. Second, a funnel plot and Egger's linear regression test were used to assess publication bias. Third, our inclusion of non-English-language reports was important in minimizing a major potential threat to the validity of any meta-analysis-publication bias and the related threat of a language bias. Fourth, the sensitivity analysis was performed to confirm the reliability and stability of this meta-analysis. Most importantly, the impact of different genetic backgrounds was minimized by including the studies performed in Chinese populations only, and the test of Hardy-Weinberg equilibrium for distribution of the genotypes in control groups suggested that there was no significantly different genetic background among the subjects. Therefore, the 11 studies would appear to be comparable in all respects relevant to our meta-analysis.

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Table 2. Summary ORs and 95% CI of MTHFR C677T polymorphism and lung cancer risk.

Analysis model	Ethnicity	OR	95% CI (P value)		P[a]
T *vs.* C	Overall	1.15[b]	0.97–1.37	(0.109)	0.000
	Han	1.20[b]	0.65–2.22	(0.566)	0.000
	Not stated	1.18[b]	0.95–1.47	(0.143)	0.002
TT *vs.* CC	Overall	1.35[b]	0.99–1.83	(0.058)	0.002
	Han	1.43[b]	0.77–2.67	(0.259)	0.004
	Not stated	**1.42**	**1.02–1.97**	**(0.036)**	**0.076**
TT + CT *vs.* CC	Overall	1.18[b]	0.91–1.53	(0.205)	0.000
	Han	1.10[b]	073–1.65	(0.648)	0.021
	Not stated	1.35[b]	0.92–1.98	(0.128)	0.000
TT *vs.* CC + CT	Overall	1.25[b]	0.99–1.57	(0.060)	0.014
	Han	1.47[b]	0.87–2.47	(0.148)	0.005
	Not stated	**1.22**	**1.03–1.44**	**(0.021)**	**0.212**
Source of controls					
Population-based					
T *vs.* C	–	1.12[b]	0.93–1.33	(0.225)	0.001
TT *vs.* CC	**–**	**1.37**	**1.14–1.65**	**(0.001)**	**0.063**
TT + CT vs. CC	–	1.14[b]	0.86–1.52	(0.349)	0.000
TT *vs.* CC + CT	**–**	**1.25**	**1.07–1.45**	**(0.004)**	**0.070**
Hospital-based					
T *vs.* C	–	1.45[b]	0.60–3.50	(0.414)	0.000
TT *vs.* CC	–	0.49[b]	0.09–2.66	(0.412)	0.001
TT + CT *vs.* CC	–	1.53[b]	0.48–4.86	(0.475)	0.002
TT *vs.* CC + CT	–	1.65[b]	0.53–5.09	(0.384)	0.006
Subgroup by area					
South China*					
T *vs.* C	–	1.09[b]	0.86–1.39	(0.481)	0.000
TT *vs.* CC	–	1.20[b]	0.77–1.89	(0.422)	0.007
TT + CT *vs.* CC	–	1.13[b]	0.81–1.57	(0.487)	0.000
TT *vs.* CC + CT	–	1.06	0.87–1.30	(0.552)	0.115
North China**					
T *vs.* C	**–**	**1.28**	**1.14–1.44**	**(0.000)**	**0.293**
TT *vs.* CC	**–**	**1.67**	**1.33–2.10**	**(0.000)**	**0.615**
TT + CT *vs.* CC	**–**	**1.39**	**1.15–1.69**	**(0.001)**	**0.178**
TT *vs.* CC + CT	**–**	**1.46[b]**	**1.03–2.06**	**(0.034)**	**0.031**

[a] P value for heterogeneity; [b] Estimates for random effects model. * South China including Taiwan, Yunnan, Guangzhou, Nanjing, Hubei and Jiangxi; ** North China including Beijing, Shandong and Henan.

The limitations of this meta-analysis should be acknowledged. The key limitation of this study is the lack of an assessment of folate status. However, considering stratification by geographical locations, the folate status may have limited influence on the association between MTHFR polymorphisms and lung cancer susceptibility. Another potential limitation was that our results were based on unadjusted estimates. More precise analyses can be conducted if individual data were available, which

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Table 3. Summary ORs and 95% CI of MTHFR A1298C polymorphism and lung cancer risk.

Analysis model	Ethnicity	OR	95% CI (P value)		P[a]
C *vs.* A	Overall	1.05	0.92–1.19	(0.461)	0.845
	Not stated	1.01	0.87–1.17	(0.868)	0.878
CC *vs.* AA	Overall	1.33	0.87–2.02	(0.187)	0.449
	Not stated	1.17	0.70–1.95	(0.547)	0.381
CC + AC *vs.* AA	Overall	1.03	0.89–1.19	(0.682)	0.913
	Not stated	1.00	0.84–1.19	(0.998)	0.904
CC *vs.* AA + AC	Overall	1.31	0.86–1.99	(0.202)	0.412
	Not stated	1.16	0.70–1.92	(0.565)	0.340
Source of controls					
Population-based					
C *vs.* A	–	1.01	087–1.17	(0.868)	0.878
CC *vs.* AA	–	1.17	0.70–1.95	(0.547)	0.381
CC + AC *vs.* AA	–	1.07	0.90–1.27	(0.442)	0.949
CC *vs.* AA + AC	–	1.16	0.70–1.92	(0.565)	0.340
Subgroup by area					
South China*					
C *vs.* A	–	1.07	0.93–1.24	(0.336)	0.805
CC *vs.* AA	–	1.26	0.80–2.00	(0.317)	0.328
CC + AC *vs.* AA	–	1.07	0.90–1.27	(0.442)	0.949
CC *vs.* AA + AC	–	1.24	0.79–1.95	(0.352)	0.304

[a] P value for heterogeneity. * South China including Taiwan, Yunnan, Guangzhou, Nanjing, Hubei and Jiangxi.

would allow for the adjustment by other covariates, including age, sex, location, race, and other factors. Thirdly, the conclusions drawn from subgroup analyses might be limited because of the small sample size.

Conclusions

Our meta-analysis results support that MTHFR C677T polymorphism might contribute to individual susceptibility to lung cancer in North China. Concerning lung cancer with multifactorial etiology, to further evaluate gene–gene and gene–environment interactions on MTHFR polymorphisms and lung cancer, larger studies in selected populations with different environmental background or other risk factors are required. Such studies taking these factors into account may eventually lead to a better and more comprehensive understanding of the association between the MTHFR polymorphism and lung cancer risk.

Conflicts of interest

None.

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