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Short Communication

Methylenetetrahydrofolate reductase 677TT genotype might be associated with an increased lung cancer risk in Asians

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ABSTRACT

Background: The association between methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and lung cancer risk has been studied in various populations with conflicting results. The aim of this study was to assess the association strength by a meta-analysis of published studies.
Methods: We searched PubMed and Chinese Biomedical (CBM) databases for relevant literatures published by July 18, 2012. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the strength of the association.
Results: A total of 20 studies comprising 11,653 cases and 12,032 controls were included in the final meta-analysis. Using the random effect model, we found that MTHFR 677TT variant genotype was associated with an increased lung cancer risk (OR = 1.26, 95% CI = 1.05–1.50, P = 0.011 for TT vs. CC; OR = 1.19, 95% CI = 1.03–1.37, P<0.001 for TT vs. CC + CT; OR = 1.11, 95% CI = 1.02–1.22, P = 0.017 for T allele vs. C allele). In the further stratified analyses, the increased lung cancer risk was found in Asian subjects (OR = 1.31, 95% CI = 1.01–1.71, P = 0.045 for TT vs. CC; OR = 1.17, 95% CI = 1.00–1.38, P = 0.048 for TT vs. CC + CT). There were no evidences for obvious publication bias in the overall meta-analysis and Asian subjects.
Conclusions: MTHFR 677TT genotype might increase the susceptibility of lung cancer, especially in Asians.

1. Introduction

Lung cancer remains the leading cause of cancer-related death worldwide. The etiology and mechanism of lung carcinogenesis have not yet been ascertained completely. It has been well known that smoking is a major cause of lung cancer; however, not all smokers develop lung cancer (Wang et al., 2011). This observation suggests that other factors such as genetic susceptibility (Crawford et al., 2012) or dietary habit (Khan et al., 2010) may result in the variations in individual lung cancer risk.

Some epidemiological studies have indicated that high consumption of fruits and vegetables lowers the risk of lung cancer (Büchner et al., 2010; Key, 2011). As one of the constituents in fruits and vegetables, dietary folate intake provided the strongest and most consistent protection against lung cancer (Lee et al., 2012). Folate is a crucial mediator of the transfer of one-carbon moieties in both DNA methylation and nucleotide synthesis (Wani et al., 2008). Folate deficiency is thought to induce and accelerate carcinogenesis, the underlying mechanisms of which is DNA damage, impaired repair and chromosomal aberrations (Duthie, 2011; Wei et al., 2003).

Methylenetetrahydrofolate reductase (MTHFR) is a crucial enzyme in folate metabolism, which can catalyze 5, 10-methylene tetrahydrofolate to 5-methyl-tetrahydrofolate. It thus plays a pivotal role in the carcinogenesis process of DNA hypomethylation (La Merrill et al., 2012). As a common polymorphism, MTHFR C677T polymorphism may influence the enzyme activity and the metabolism of folate, thereby increasing homocysteine levels and cancer risk (Vineis et al., 2007). The MTHFR 677C>T variant is associated with a significant decrease of plasma folate levels (Kim et al., 2011). This functional polymorphism of increased T allele dose may elevate the grade of total homocysteine in the mild–moderate range, and associated with low dietary folate consumption in individuals (Imanishi et al., 2007). There are several studies suggesting that MTHFR polymorphisms were associated with increased lung cancer risk, however, other studies have failed to reveal any association. The previous meta-analyses suggested that there was no association between MTHFR C677T polymorphisms and lung cancer risk (Boccia et al., 2009; Mao et al., 2008; Zhang et al., 2012). Nevertheless, some studies published recently relevant to this issue were not included in the previous meta-analyses. To comprehensively clarify the association

Abbreviations: CI, confidence interval; HWE, Hardy–Weinberg equilibrium; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT-PCR, reverse transcription-polymerase chain reaction.

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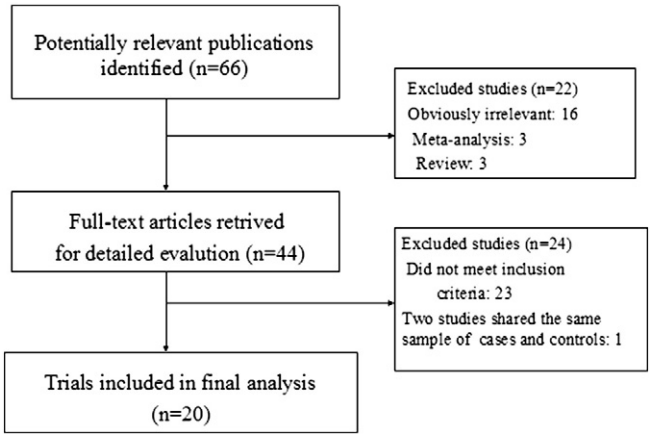

Fig. 1. Flow chart of studies identification with criteria for inclusion and exclusion.

between MTHFR 677C>T polymorphism and lung cancer risk, therefore, an updated meta-analysis involving a larger sample size was warranted. Based on relevant case–control studies published, the aim of this study was to assess the strength of association between MTHFR 677C>T polymorphism and lung cancer risk by a meta-analysis.

2. Materials and methods

2.1. Publication search

We searched relevant studies in PubMed and Chinese Biomedical (CBM) databases. The last search was updated on July 18, 2012. The searching terms were used as follows: "MTHFR" (/"methylene tetrahydrofolate reductase") AND "polymorphism" (/"variant") AND "lung cancer" (/"lung carcinoma"). Moreover, the references of the retrieved articles were also screened by hand-search for original studies that have possibly been missed in the initial search. The search was conducted without language limitation.

2.2. Inclusion criteria

The following eligibility criteria of the publications were used in the present meta-analysis: (1) the study should evaluate MTHFR 677C>T polymorphism and lung cancer risk; (2) the study was a case–control design; (3) the study should contain enough information to calculate the odds ratio (OR) with 95% confidence interval (CI); (4) when some duplicate articles were published by the same authors or group from the same sample of cases and controls, only the most recent or complete study was selected in the present meta-analysis.

2.3. Data extraction

Data were extracted carefully from all the eligible studies by two independent investigators with the criteria stated above. Potential disagreements were resolved by consensus. The following items were collected from each study: the first author's family name, year of publication, ethnicity, genotyping method, and the number of cases and controls, respectively.

2.4. Statistical analysis

The pooled OR with 95% CI was calculated to assess the strength of association between MTHFR 677C>T polymorphism and lung cancer risk. Hardy–Weinberg equilibrium (HWE) was assessed for checking significance of deviation among controls for each of MTHFR 677C>T polymorphism by the chi-square test, and P value below 0.05 were considered significant. Heterogeneity among the studies was measured using the chi-square based Q statistic (Liu et al., 2010). Heterogeneity was quantified using the I^2 metric, which measured the severe degree of variation among the studies in our meta-analysis (I^2<25%, no heterogeneity; values of about 50%, moderate; and I^2>75%, large heterogeneity) (Higgins et al., 2003). P value below 0.05 indicated a statistical difference in terms of heterogeneity, and the random-effect model was more appropriate to synthesize the results; otherwise, the fixed-effect model was used. Potential publication bias was investigated by Egger's linear regression test and the method of Begg's funnel plots (Egger, 1997;

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

All studies First author	Ethnicity	Method	Distribution of C677T MTHFR genotype						HWE
			CC		CT		TT		P value
Published year			Case	Control	Case	Control	Case	Control	
Shen (2001)	Caucasian	PCR–RFLP	241	245	252	252	57	57	0.51
Jeng (2003)	Asian	PCR–RFLP	36	123	22	95	1	14	0.44
Siemianowicz (2003)	Caucasian	PCR–RFLP	38	18	60	20	48	6	0.91
Heijmans (2003)	Caucasian	PCR–RFLP	23	399	17	329	4	65	0.81
Shi (2005)	Caucasian	PCR–RFLP	483	498	468	519	100	124	0.52
Zhang (2005)	Asian	PCR–RFLP	120	160	230	231	155	109	0.14
Shen (2005)	Asian	RT-PCR	33	53	65	42	18	16	0.12
Hung (2007)	Caucasian	RT-PCR	1009	1397	929	1147	231	259	0.29
Suzuki (2007)	Asian	RT-PCR	182	379	256	474	77	177	0.17
Jin (2007)	Asian	PCR–RFLP	24	39	52	48	24	13	0.77
Gemignani et al. (2007)	Caucasian	Microarray	104	131	107	103	36	25	0.47
Liu (2008)	Caucasian	Golden GateTM Assay	157	149	245	265	98	103	0.45
Liu (2009)	Asian	PCR–RFLP	205	362	124	291	29	63	0.68
Yao (2010)	Asian	PCR–RFLP	27	36	46	51	20	19	0.90
Yang (2010)	Asian	MassARRAY	49	62	52	75	19	28	0.52
Cui (2011)	Asian	RT-PCR	58	121	240	325	140	195	0.48
Arslan (2011)	Caucasian	PCR–RFLP	30	29	27	29	7	3	0.21
Kiyohara (2011)	Asian	PCR–RFLP	153	158	201	170	108	51	0.62
Cui (2011)	Asian	PCR–RFLP	1361	540	1909	862	668	298	0.15
Cheng (2011)	Asian	PCR–RFLP	49	47	58	88	71	45	0.77

PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; RT-PCR: reverse transcription PCR; HWE: Hardy–Weinberg equilibrium.