The association between the C677T polymorphism in MTHFR gene and the risk of thyroid cancer: a meta-analysis

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Abstract. – OBJECTIVES: Methylene tetrahydrofolate reductase (MTHFR) enzyme plays an important role in folate metabolism and MTHFR C677T polymorphism has been suggested as a risk factor to various cancers. It is a common genetic alteration and may affect the host susceptibility to thyroid cancer. The aim of this study was to investigate the association between MTHFR C677T polymorphism and thyroid cancer risk by performing a meta-analysis.

MATERIALS AND METHODS: PubMed, EMBASE, CNKI and Wanfang databases were searched for case-control studies investigating the association between MTHFR C677T polymorphism and thyroid cancer risk. OR with 95% CI was used to assess this possible association. Four individual case-control studies with a total of 360 cases and 900 controls were included into this meta-analysis.

RESULTS: Meta-analyses showed there was significant association between MTHFR C677T polymorphism and thyroid cancer risk: TT vs. CC: OR = 2.06, 95% CI = 1.04-4.10, p = 0.04; T vs. C: OR = 2.06, 95% CI = 1.97-3.77, p = 0.04.

CONCLUSIONS: This meta-analysis supports an association between MTHFR C677T polymorphism and thyroid cancer risk. Further studies with large sample size and careful design are needed to identify this association more comprehensively.

Keywords: MTHFR, Polymorphism, Thyroid cancer, Meta-analysis.

Introduction

Thyroid cancer accounts for < 1% of all human cancers, but is the most frequent endocrine cancer1. In recent years, the incidence of thyroid cancer is increasing year by year2. Up to now, the etiology of thyroid cancer is still unclear, and exposure to radiation is the only well known risk factor for thyroid cancer3. Nevertheless, only a small number of population exposures to radiation develop thyroid cancer, suggesting genetic factors also play important roles in the development of thyroid cancer4,5. Various studies have focused their attention on the investigation of polymorphism impact on thyroid cancer, and many polymorphisms have been suggested as risk factors for thyroid cancer5-9, such as the C677T polymorphism in the MTHFR gene9.

Methylene tetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of folate10. This enzyme irreversibly catalyzes the reaction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the primary circulating form of folate11. The most common polymorphism is MTHFR C677T, which results in an alanine to valine exchanges and is associated with reduced enzyme activity12. The C677T polymorphism has been studied as candidate genetic factors for thyroid cancer risk. The first report evaluating the role of MTHFR C677T polymorphism in the development of thyroid cancer was conducted by Siraj et al (2008)8. The findings suggested that MTHFR C677T polymorphism might not contribute to the risk of thyroid cancer. Later, Fard-Esfahani et al13 found the polymorphism might be associated with increased risk of thyroid cancer. Since then, several study reported the association of MTHFR gene and the risk of thyroid cancer, but the results were inconsistent. In order to elucidate the role of MTHFR C677T polymorphism in thyroid cancer, we performed this meta-analysis to derive a more precise estimation of the association of MTHFR C677T polymorphism with thyroid cancer. This is, to our knowledge, the first meta-analysis regarding the association between the MTHFR C677T polymorphism in thyroid cancer.
Materials and Methods

Search strategy
Two investigators independently made a comprehensive literature search of the PubMed, Embase, CNKI and Wanfang databases for relevant case–control studies up to February 1st, 2014. The reviews and references of all eligible studies were also hand-searched for additional publications. The search items were as follows: MTHFR, Methylentetrahydrofolate reductase; and thyroid cancer, thyroid carcinoma; and polymorphism, or mutation.

Inclusion criteria
Publications must meet the following inclusion criteria: (1) estimating the association between the MTHFR C677T polymorphism and thyroid cancer risk, (2) using case–control designs, and (3) providing enough information for the frequency of alleles and genotypes in cases and controls.

Data extraction
Two investigators independently extracted data from all eligible studies. The following data were extracted: the first author, publication year, country, ethnicity, genotyping methods, sample size of cases and controls, source of controls. Discrepancies were resolved by consensus.

Statistical analysis
The pooled odds ratio (OR) with corresponding 95% confidence interval (95% CI) was calculated to assess the strength of the association between the MTHFR C677T polymorphism and thyroid cancer risk. The models including TT+TC vs. CC, TT vs. TC+CC, TT vs. CC, TC vs. CC and T vs. C were compared. The between-study heterogeneity was estimated by chi-square-based Q statistic test and I² test 13. The fixed-effect model (the Mantel-Haenszel’s method) was used if the between-study heterogeneity was not significant; otherwise, the random-effect model (the DerSimonian and Laird’s method) was applied when the between-study heterogeneity was significant. The Begg’s funnel plot and Egger’s test were applied to assess the publication bias risk 14. The Revman 5.2.0 and Stata 11.0 was used for all statistical analyses.

Results

Literature search and meta-analysis databases
Relevant publications were retrieved and preliminarily screened. 16 results were identified after initial search. Among these publications, 12 results were excluded because they were review articles, case reports, and conference abstract. Thus, 4 articles were left for data assessment. All these studies included the C677T polymorphism and thyroid cancer risk and, thus, these studies were left for data extraction. A total of 4 case-control studies were extracted from these articles. In addition, none studies were excluded for data overlapped. Thus, a total of 4 case-control studies were used for data analysis 9,15,16,8.

MTHFR C677T polymorphism and thyroid cancer risk
A total of 360 thyroid cancer cases and 900 controls were included for data analysis. The main results of the meta-analysis are shown in Figure 1. Overall, significant associations were found between the MTHFR C677T polymorphism and thyroid cancer risk when all studies were pooled into the meta-analysis (TT+TC vs. CC: OR = 2.22, 95% CI = 0.87-5.65, p = 0.09; TT vs. TC+CC: OR = 1.93, 95% CI = 1.00-3.74, p = 0.05, TT vs. CC: OR = 2.06, 95% CI = 1.04-4.10, p = 0.04, TC vs. CC: OR = 2.33, 95% CI = 0.74-72.6, p = 0.15; T vs. C: OR = 2.06, 95% CI = 1.97-3.77, p = 0.04).

Table I. The characteristics of the included studies.

<table>
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<tr>
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**MTHFR variant and thyroid cancer risk**

**Figure 1.** MTHFR C677T polymorphism and thyroid cancer risk: A, TT+TC vs. CC; B, TT vs. CC+TC; C, TT vs. CC; D, TC vs. CC; E, T vs. C.
Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's test. The shape of the funnel plots for the TT+TC VS. CC genetic model appeared symmetrical, suggesting the absence of publication bias. Then, Egger's test was used to provide statistical evidence of funnel plot asymmetry ($t = 1.45, p = 0.285$), which indicated a lack of publication bias of the current meta-analysis. Other results also did not suggest any evidence of publication bias (TT vs. TC+CC: $t = -0.87, p = 0.475$; TT vs. CC: $t = -0.32, p = 0.777$, TC vs. CC: $t = 1.36, p = 0.308$ and T vs. C: $t = 1.77, p = 0.218$).

Discussion

Although thyroid cancer currently accounts for less than 1% of human cancers, its incidence is increasing year by year. Polymorphisms are the most common form of human genetic variations, and may contribute to individual’s susceptibility to cancer; however, the underlying molecular mechanism is unknown. Previous studies suggested that some variants, especially those in the promoter regions of genes, may affect either the expression or activity levels of protein and, therefore, may be mechanistically associated with cancer risk. Previous studies on the relationship between MTHFR C677T polymorphism and thyroid cancer risk were contradictory. These inconsistent results are possibly because of a small effect of the polymorphism on thyroid cancer risk or the relatively low statistical power of the published studies. Hence, the meta-analysis was needed to provide a quantitative approach for combining the results of various studies with the same topic, and for estimating and explaining their diversity.

Meta-analysis has great power for elucidating genetic factors in cancer. On the bases of the character of cancer, the effect of one genetic component on the development of the disease can be easily masked by other genetic and environmental factors. A meta-analysis potentially investigates a large number of individuals and can estimate the effect of a genetic factor on the risk of the diseases. The present study included data from 4 association studies that had investigated the relationship between the MTHFR C677T polymorphism and thyroid cancer.

This present meta-analysis, including 360 thyroid cancer cases and 900 controls, concerned the C677T polymorphism of MTHFR gene and thyroid cancer risk. In the meta-analysis, we found that the variant genotype of the MTHFR C677T polymorphism was significantly associated with thyroid cancer risk. Although the MTHFR C677T polymorphism may be associated with DNA repair activity, no results were performed to analyze the association between the polymorphism with different environmental factors, suggesting future studies should be performed to assess these associations.

We would like to underline/some criticisms to this meta-analysis. First, the numbers the included studies for our study were relatively small, with possible insufficient statistical power to investigate the real association; second, our results were based on unadjusted estimates, whereas a more precise analysis should be conducted if raw data from each individual study were available. This would allow for the adjustment by other co-variants including age, gender, environmental factors, and other lifestyle. Third, we only included the articles written in English, which may potential miss some articles. Fourth, meta-analysis is a retrospective study that may lead to subject selection bias and, thereby affecting the reliability of our results. Furthermore, we performed a highly sensitive literature search strategy for electronic databases. A manual search of the reference lists from the relevant articles was also conducted to find other potential articles. The selection process of eligible articles was based on strict inclusion and exclusion criteria. Importantly, rigorous statistical analysis of polymorphism data provided a basis for pooling of information from individual studies.

Conclusions

This meta-analysis indicated that MTHFR C677T polymorphism was associated with thyroid cancer susceptibility. However, interactions of gene variants and environmental risk factors, such as radiation exposure, drinking and infection should also be considered in the analysis. Such studies including more samples with different ethnicities, environmental factors, and sufficient biological evidence for the polymorphism functions may lead to a better, comprehensive understanding of the association between the MTHFR C677T polymorphism and thyroid cancer risk.
Conflict of Interest
The Authors declare that there are no conflicts of interest.

Acknowledgements
This study is supported by the Applied Basic Research Projects of Sichuan Province (2012Y0056).

References


4) Kim SK, Park HJ, Hong IK, Chung JH, Eun YG. A missense polymorphism (rs11466653, Met326Thr) of toll-like receptor 10 (TLR10) is associated with tumor size of papillary thyroid carcinoma in the Korean population. Endocrine 2013; 43: 161-169.


