European Review for Medical and Pharmacological Sciences 2014; 18: 2097-2101

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

Y.-M. YANG, T.-T. ZHANG, L. YUAN, Y. REN

Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, China

Abstract. – OBJECTIVES: Methylenetetrahydrofolate 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 cancer[1]. In recent years, the incidence of thyroid cancer is increasing year by year[2]. Up to now, the etiology of thyroid cancer is still unclear, and exposure to radiation is the only well known risk factor for thyroid cancer[3]. 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 cancer[3,4]. 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 cancer[5-9], such as the C677T polymorphism in the *MTHFR* gene[9].

Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of folate[10]. This enzyme irreversibly catalyzes the reaction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is the primary circulating form of folate[11]. The most common polymorphism is *MTHFR* C677T, which results in an alanine to valine exchanges and is associated with reduced enzyme activity[12]. 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 al[9] 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.

Corresponding Author: Yan Ren, MD; e-mail: renyan922@163.com

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*, Methylenetetrahydrofolate reductase; and thyroid cancer, thyroid carcinoma; and polymorphism, or mutation.

Inclusion criteria

Publications must meet to 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 I^2 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 Revman5.2.0 and Stata11.0 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]. The publication year ranged from 2008 to 2011. The 4 studies were conducted among Iran, India, Turkey and Saudi Arabia. Two studies were consistent with HWE for the genotype distribution of the controls[15,16], while two not[9,8]. The characteristics of each studies are presented in Table I.

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.

Author	Country	Case			Control			Case		Control		HWE
		CC	CT	TT	CC	CT	TT	C	T	C	T	
Fard-Esfahani P[9]	Iran	69	71	14	82	108	8	209	99	272	124	No
Ozdemir S[15]	Turkey	28	25	7	33	14	3	81	39	80	20	Yes
Prasad VV[16]	India	86	10	1	228	12	1	182	12	468	14	Yes
Siraj AK[8]	Saudi Arabia	30	18	1	372	26	13	78	20	770	52	No

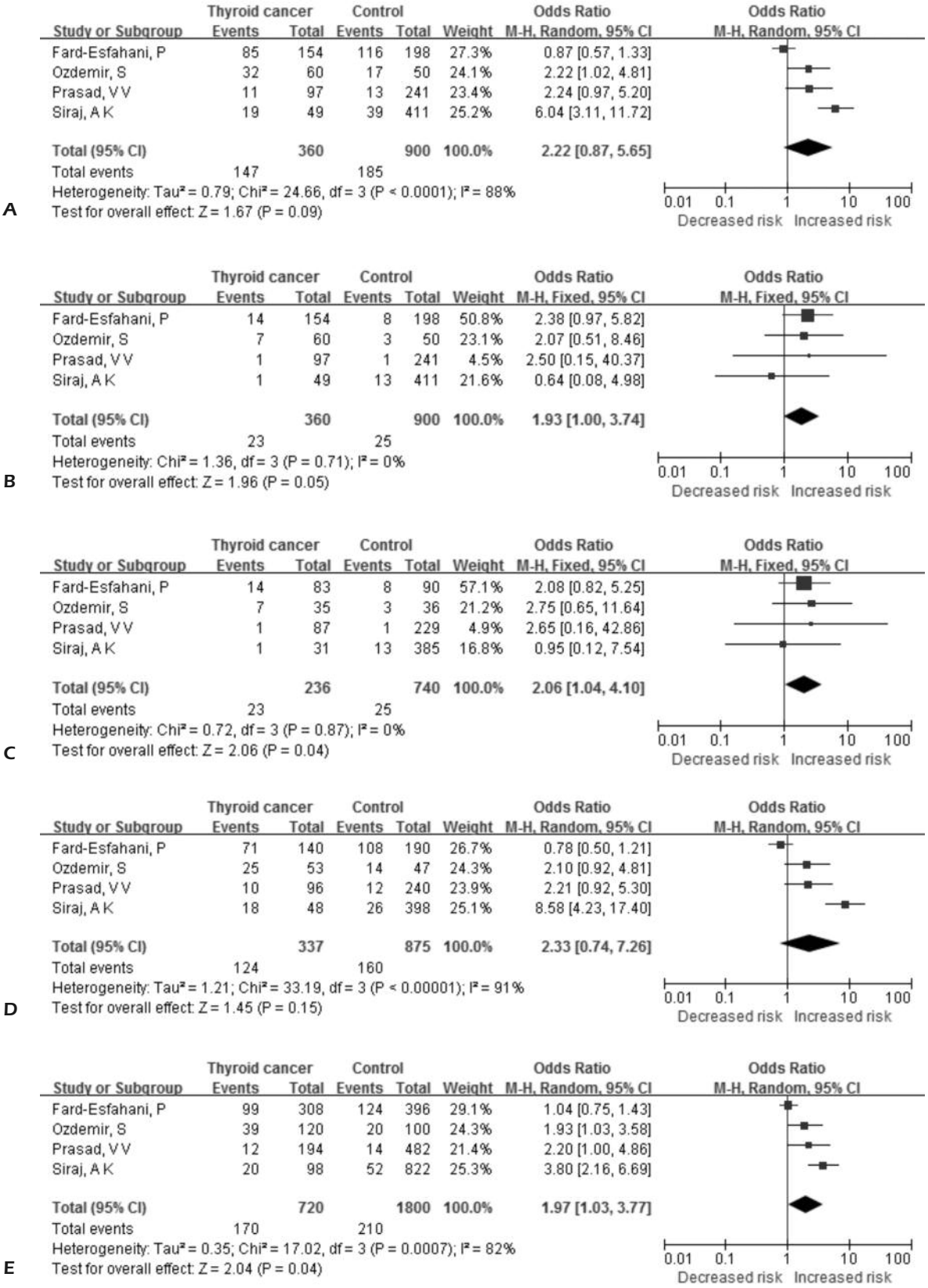

Figure 1. *MTHFR* C677T polymorphism and thyroid cancer risk: **A**, TT+TC vs. CC; **B**, TT vs. CC+TC; **C**, TT vs. CC; **D**, TC vs. CC; **E**, T vs. C.

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% 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 study 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 support by the Applied Basic Research Projects of Sichuan Province (2012JY0056).

References

1) Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W, European Thyroid Cancer T. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787-803.
2) Wu B, Guo D, Guo Y. Association between p53 Arg72Pro polymorphism and thyroid cancer risk: a meta-analysis. Tumour Biol 2014; 35: 561-565.
3) Wang YL, Feng SH, Guo SC, Wei WJ, Li DS, Wang Y, Wang X, Wang ZY, Ma YY, Jin L, Ji QH, Wang JC. Confirmation of papillary thyroid cancer susceptibility loci identified by genome-wide association studies of chromosomes 14q13, 9q22, 2q35 and 8p12 in a Chinese population. J Med Genet 2013; 50: 689-695.
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.
5) Eun YG, Kim SK, Chung JH, Kwon KH. Association study of integrins beta 1 and beta 2 gene polymorphism and papillary thyroid cancer. Am J Surg 2013; 205: 631-635.
6) Zhang F, Xu L, Wei Q, Song X, Sturgis EM, Li G. Significance of MDM2 and P14 ARF polymorphisms in susceptibility to differentiated thyroid carcinoma. Surgery 2013; 153: 711-717.
7) Rahimi M, Fayaz S, Fard-Esfahani A, Modarressi MH, Akrami SM, Fard-Esfahani P. The role of Ile3434Thr XRCC7 gene polymorphism in differentiated thyroid cancer risk in an Iranian population. Iran Biomed J 2012; 16: 218-222.
8) Siraj AK, Ibrahim M, Al-Rasheed M, Abubaker J, Bu R, Siddiqui SU, Al-Dayel F, Al-Sanea O, Al-Nuaim A, Uddin S, Al-Kuraya K. Polymorphisms of selected xenobiotic genes contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. BMC Med Genet 2008; 9: 61.
9) Fard-Esfahani P, Fard-Esfahani A, Saidi P, Fayaz S, Mohabati R, Majdi M. An increased risk of differentiated thyroid carcinoma in Iran with the 677C-->T homozygous polymorphism in the MTHFR Gene. Cancer Epidemiol 2011; 35: 56-58.
10) Liu XM, Liu FH, Tang Y, Li Q. MTHFR C677T polymorphism and pancreatic cancer risk: a meta-analysis. Asian Pac J Cancer Prev 2012; 13: 3763-3766.
11) Jakovljevic K, Malisic E, Cavic M, Radulovic S, Jankovic R. Association between methylenetetrahydrofolate reductase polymorphism C677T and risk of chronic myeloid leukemia in Serbian population. Leuk Lymphoma 2012; 53: 1327-1330.
12) Nie Y, Gu H, Gong J, Wang J, Gong D, Cong X, Chen X, Hu S. Methylenetetrahydrofolate reductase C677T polymorphism and congenital heart disease: a meta-analysis. Clin Chem Lab Med 2011; 49: 2101-2108.
13) Wang YX, Hu D, Yan X. Diagnostic accuracy of Cyfra 21-1 for head and neck squamous cell carcinoma: a meta-analysis. Eur Rev Med Pharmacol Sci 2013; 17: 2383-2389.
14) Cao C, Liu S, Lou SF, Liu T. The +252A/G polymorphism in the Lymphotoxin-alpha gene and the risk of non-Hodgkin lymphoma: a meta-analysis. Eur Rev Med Pharmacol Sci 2014; 18: 544-552.
15) Ozdemir S, Silan F, Hasbek Z, Uludag A, Atik S, Erselcan T, Ozdemir O. Increased T-allele frequency of 677 C>T polymorphism in the methylenetetrahydrofolate reductase gene in differentiated thyroid carcinoma. Genet Test Mol Biomarkers 2012; 16: 780-784.
16) Prasad VV, Wilkhoo H. Association of the functional polymorphism C677T in the methylenetetrahydrofolate reductase gene with colorectal, thyroid, breast, ovarian, and cervical cancers. Onkologie 2011; 34: 422-426.