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ORIGINAL ARTICLE

Thymidylate synthase genetic polymorphisms and colorectal cancer risk: A meta-analysis

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Summary
Aim: The effects of thymidylate synthase (TS) polymorphisms on susceptibility to colorectal cancer (CRC) have been investigated in many studies, but the results remain conflicting rather than conclusive. To resolve these conflicts, we performed a quantitative synthesis of the evidence on the association between these two polymorphisms and CRC risk.
Methods: All eligible case-control studies published up to September 2013 were identified by searching PubMed, Web of Science and CNKI. Effect sizes of odds ratio (OR) and 95% confidence interval (95% CI) were calculated by using a fixed- or random-effect model.
Results: A total of 11 case-control studies were included, including 10 studies (3324 cases and 4622 controls) for TSER polymorphism and 9 studies (3223 cases and 3886 controls) for TS1494del6 polymorphism. Overall, no significant association between the TS polymorphisms and CRC risk was found. In the subgroup analysis by ethnicity, a significantly association were found among Caucasian populations for TSER polymorphism; but for TS1494del6 polymorphism, no significantly association was observed in both Asian and Caucasian populations. When stratifying by source of controls, we found there was a statistically significant association between TSER polymorphism and risk of CRC in the population-based population; however, we detected no association in both population-based and hospital-based populations for TS1494del6 polymorphism.
Conclusions: This meta-analysis suggests that the TSER polymorphism in *TS* gene but not TS1494del6 polymorphism might be a protective factor for CRC among Caucasian populations.

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Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal tumors worldwide [1]. Epidemiological studies have demonstrated that some risk factors and interactions between genetic and environmental factors may play important roles in the pathogenesis of that cancer [2,3].

Thymidylate synthase (TS) is an important enzyme involved in folate metabolism and catalyzes methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), which is essential for DNA replication [4]. There are several polymorphism sites in the *TS* gene and two functionally polymorphisms are the most extensively studied: thymidylate synthase enhancer region (TSER), a tandem repeat polymorphism, which contains triple (3R) or double (2R) repeats of a 28-bp sequence in TS 5′-untranslated enhanced region, may be involved in modulation of TS mRNA expression [5], and a 6-bp ins/del polymorphism on the 3′ UTR (position TS1494, del6 or ins6), which may influence mRNA stability [6]. Recently, several studies have been performed to elucidate the effect of the polymorphisms on CRC susceptibility [7—17]. However, the results of these studies remain controversial.

In this study, we performed a meta-analysis to clarify the associations of the two polymorphisms in the *TS* gene with CRC susceptibility in diverse populations.

Materials and methods

Search strategy

A literature research was conducted using PubMed, Web of Science and CNKI up to September 2013 without language restrictions. Relevant studies were identified using the terms: ['thymidylate synthase or TS'] AND ['genetic polymorphism or polymorphisms or SNP'] AND ['colorectal cancer/neoplasms or colon cancer/neoplasms or rectal cancer/neoplasms']. The search was restricted to humans. Additional studies were identified by a hand search of references of original or review articles on this topic. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria and exclusion criteria

Studies were included if they met the following criteria:

- studies that evaluated the association between the TS polymorphism and colorectal cancer;
- in a case-control study design;
- had detailed genotype frequency of cases and controls or could be calculated from the article text.

While major exclusion criteria were:

- case-only study, case reports, and review articles;
- studies without the raw data of the genotype of TS;
- repetitive studies;
- studies that compared the TS variants in precancerous lesions (such as colorectal adenoma).

Data extraction and quality assessment

The two investigators independently extracted data and reached consensus on all of the items. If the two investigators generated different results, they would check the data again and have a discussion to come to an agreement. If they could not reach an agreement, an expert was invited to the discussion. Data extracted from the selected articles included the first author's name, year of publication, country of origin, ethnicity of study population, genotyping methods, source of control, gender, diagnosis criteria, tumor location, stage, number of cases and controls, minor allele frequency (MAF) for the control and HWE in controls (*P* value).

Statistical analysis

The risk of CRC associated with the two TS polymorphisms was estimated for each study by odds ratio (OR) and 95% confidence interval (95% CI). Four different ORs were calculated: the dominant model (homozygous + heterozygous vs. wild-type), the recessive model (homozygous vs. heterozygous + wild-type), heterozygote comparison (heterozygous vs. wild-type), and homozygote comparison (variant homozygous vs. wild-type). A χ^2-test-based Q statistic test was performed to assess the between-study heterogeneity [18]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P > 0.05$) or $I^2 < 50\%$ indicated heterogeneity across studies, the fixed-effects model was used [19], or else the random-effects model was used [20]. Before the effect estimation of TS polymorphism in CRC, we tested whether genotype frequencies of controls were in HWE using χ^2-test. We performed stratification analyses on ethnicity. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg' funnel plot and Egger's regression test [21,22]. $P < 0.05$ was regarded as statistically significant. Statistical analysis was performed using the Cochrane Collaboration RevMan 5.1 (Copenhagen, 2008) and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

The search strategy retrieved 117 potentially relevant studies. According to the inclusion criteria, 11 studies [7—17] with full-text were included in this meta-analysis and 106 studies were excluded. The flow chart of study selection in summarized on Fig. 1. As shown in Table 1, there were 10 case-control studies [7—10,12—17] with 3324 CRC cases and 4622 controls concerning TSER polymorphism and 9 case-control studies [7—12,14,16,17] with 3223 cases and 3886 controls concerning TS1494del6 polymorphism. Three ethnicities were addressed: four studies [10,12,15,17] focused on Asian descents, five studies [7—9,14,16] on Caucasian populations and one study [13] on mixed populations for TSER polymorphism; three studies [10,12,17] focused on Asian descents, five studies [7—9,14,16] on Caucasian