MTHFR Gene Polymorphisms are Not Involved in Pancreatic Cancer Risk: A Meta-analysis

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Abstract

Purpose: Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms have been reported to be associated with pancreatic cancer, but the published studies have yielded inconsistent results. This study assessed the relationship between MTHFR gene polymorphisms and the risk for pancreatic cancer using a meta-analysis approach. Methods: A search of Google scholar, PubMed, Cochrane Library and CNKI databases before April 2012 was performed, and then associations of the MTHFR polymorphisms with pancreatic cancer risk were summarized. The association was assessed by odds ratios (ORs) with 95% confidence intervals (CIs). Publication bias was also calculated. Results: Four relative studies on MTHFR gene polymorphisms (C677T and A1298C) were included in this meta-analysis. Overall, C677T (TT vs. CC: OR=1.61, 95% CI=0.78-3.34; TT vs. CT: OR=1.41, 95% CI=0.88-2.25; Dominant model: OR=0.68, 95% CI=0.40-1.17; Recessive model: OR=0.82, 95% CI=0.52-1.30) and A1298C (CC vs. AA: OR=1.01, 95% CI=0.47-2.17; CC vs. AC: OR=0.99, 95% CI=0.46-2.14; Dominant model: OR=1.01, 95% CI=0.47-2.20; Recessive model: OR=1.01, 95% CI=0.80-1.26) did not increase pancreatic cancer risk. Conclusions: This meta-analysis indicated that MTHFR polymorphisms (C677T and A1298C) are not associated with pancreatic cancer risk.

Keywords: Pancreatic cancer - MTHFR - gene polymorphism - meta-analysis
Inclusion and exclusion criteria

Two investigators (Yuliang Tu and Shibin Wang) reviewed all identified studies independently to determine whether an individual study was eligible for inclusion. The following criteria were used to include published studies: (1) case-control studies were included to evaluate the association between MTHFR polymorphism and pancreatic cancer risk; (2) sufficient genotype data were presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs); (3) Genotype distribution of the pancreatic cancer patients and the controls must be in Hardy-Weinberg equilibrium (HWE). The exclusion criteria were as follows: (1) not case-control studies that evaluated the association between MTHFR polymorphism and pancreatic cancer risk; (2) case reports, letters, reviews, meta-analysis and editorial articles; (3) studies that were based on incomplete raw data and those with no usable data reported; (4) duplicate data were included in the studies; (5) healthy controls were not in HWE.

Data extraction

Two investigators (Yuliang Tu and Shibin Wang) extracted the data independently, and the result was reviewed by a third investigator (Xianglong Tan). The following characteristics were collected from each study: first author, years of publication, ethnicity (country) of study population, the number of patients and controls for a study, and evidence of HWE.

Statistical analysis

The strength of the association between MTHFR polymorphisms and pancreatic cancer risk was estimated by ORs with 95% CI under a homozygote comparison (AA vs aa), a heterozygote comparison (AA vs Aa), a dominant model and a recessive model between groups. In this study, the dominant model was defined as Aa+aa vs AA, where “A” and “a” are major and minor alleles, respectively, and the recessive model as aa vs AA+Aa. The distribution of genotypes in the included studies was tested for HWE using the $\chi^2$ test. We also quantified the effect of heterogeneity by the Q-test and I² test. I² ranges between 0 and 100%, and I² values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-test (P<0.10) or I² > 50% indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was calculated. Begg’s test was used to provide evidence of publication bias, which was shown as a funnel plot (P<0.05 was considered a significant publication bias). Analyses were conducted using Stata 12.0 (Stata Corporation, College Station, TX, USA). All P values are two-tailed.

Results

Eligible studies

Based on the search criteria, 18 articles were found. Of these, 10 papers were excluded after reading the title or abstract because of obvious irrelevance to our study aim. In addition, 1 duplicated publications and 2 reviews were excluded. And 1 paper did not have the control group were further excluded. Therefore, Only 4 studies for the association between MTHFR polymorphisms and pancreatic cancer were included in the final meta-analysis (Li, 2005; Wang, 2005; Matsubayashi, 2005; Suzuki, 2008). A flow chart summarizing the process of study inclusion/exclusion is depicted (Figure 1). The characteristics of the included studies are listed in Table 1. All the 4 eligible studies were hospital-based case-control studies. Of the 4 included studies, 2 used restriction fragment length polymorphism (PCR-RFLP) method (Li, 2005; Wang, 2005), 1 used real-time polymerase chain reaction method (Matsubayashi, 2005) and 1 used TaqMan Assays (Suzuki, 2008). All studies were consistent with HWE law in controls (P>0.05).

Meta-analysis

For MTHFR C677T polymorphism, a total of 970 cases and 1,775 controls were identified. The C677T polymorphism was not associated with the risk of
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Table 2. Summary ORs and 95% CI of the Included Studies for Meta-analysis

| Genetic model | Sample size | Type of model | Test of heterogeneity | Test of association | Begg’s test |
|---------------|-------------|---------------|-----------------------|---------------------|-------------|
| C677T         |             |               |                       |                     |             |
| TT vs. CC     | 970         | Random        | 85.9% 0.00 1.61 0.78-3.34 0.00 0.91 |
| TT vs. CT     | 1775        | Random        | 68.7% 0.02 1.41 0.88-2.25 0.00 1.00 |
| Dominant model |            | Random        | 79.3% 0.00 0.68 0.40-1.17 0.00 1.00 |
| Recessive model |           | Random        | 85.4% 0.00 0.82 0.52-1.30 0.00 1.00 |
| A1298C        |             |               |                       |                     |             |
| CC vs. AA     | 813         | Random        | 67.0% 0.05 1.01 0.47-2.17 0.00 1.00 |
| CC vs. AC     | 990         | Random        | 67.5% 0.05 0.99 0.46-2.14 0.00 1.00 |
| Dominant model |            | Random        | 70.2% 0.04 1.01 0.47-2.20 0.00 1.00 |
| Recessive model |           | Fixed         | 0.0% 0.46 1.01 0.80-1.26 1.04 0.30 |

Publication bias

Begg’s test showed no evidence of publication bias in the present meta-analysis of the MTHFR polymorphisms. (Table 2), which implied that the publication bias was low in the present meta-analysis.

Discussion

Although several research studies have evaluated the association between MTHFR polymorphisms and pancreatic cancer, the specific association is still controversial. Our meta-analysis quantitatively assessed the association between MTHFR polymorphisms and pancreatic cancer risk. In the current meta-analysis, we examined the association between MTHFR polymorphisms and the risk of pancreatic cancer by critically including all published studies. Finally, 4 case-control studies were included and assessed, from which we selected 4 studies on MTHFR C677T polymorphism and 3 studies on MTHFR A1298C polymorphism.

To our knowledge, this is the first meta-analysis considering MTHFR polymorphisms and the risk of pancreatic cancer. Previous meta-analyses have shown the MTHFR 677TT genotype increase gastric cancer risk (Boccia, 2008), the possible mechanism is 677T allele contributes to DNA hypomethylation, which in turn may lead to altered gene expression and the polymorphism decrease the risk of colorectal cancer (Botto, 2000; Kono, 2005; Sanjoaquin, 2005; Taioli, 2009). It may be due to C677T polymorphism exert a protective effect by increasing the levels of the MTHFR substrate (essential for DNA synthesis). So it is not straightforward to interpret the MTHFR-cancer association. And our current pooled data suggested no evidence for a major role of MTHFR C677T polymorphism in the risk of pancreatic cancer.
These conflicting findings might reflect different folate status of ethnic differences in genetic backgrounds and the environment in which they lived. In addition, genomic DNA hypomethylation does not always facilitate cancer development because in Apc min mice DNMT1 hypomorphs have a reduced risk of gastrointestinal neoplasia (Eads, 2002). As for the A1298C genotype, studies showed no important effects on pancreatic cancer. The number of studies in the literature on the association of MTHFR gene polymorphisms and pancreatic cancer was comparatively few, so we can not use subgroup analysis to investigate the confounding factors, pending further research.

There were still some limitations in our meta-analysis. First, the random effect model was partly used to calculate ORs, it may affect the precision of the result. Secondly, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. Finally, the genotype information stratified for the main confounding variables was not available in the original papers, such as age, sex, ethnicity and exposures, and the confounding factors might cause serious confounding bias.

In summary, this meta-analysis evaluated the effect of MTHFR polymorphisms on the risk of pancreatic cancer. And there is no evidence that MTHFR polymorphisms (C677T, and A1298C) are associated with pancreatic cancer risk.

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The author(s) declare that they have no competing interests.

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