

RESEARCH COMMUNICATION

MTHFR Polymorphisms and Pancreatic Cancer Risk: Lack of Evidence from a Meta-analysis

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Abstract

Objective: Methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms have been reported to be associated with pancreatic cancer, but the published studies had yielded inconsistent results. We therefore performed the present meta-analysis. **Methods:** A search of Google scholar, PubMed, Cochrane Library and CNKI databases before April 2012 was conducted to summarize associations of MTHFR polymorphisms with pancreatic cancer risk. Assessment was with odds ratios (ORs) and 95% confidence intervals (CIs). Publication bias were also calculated. **Results:** Four relative studies on MTHFR gene polymorphisms (C667T and A1298C) were involved in this meta-analysis. Overall, C667T (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. **Conclusion:** This meta-analysis indicated that MTHFR polymorphisms (C667T and A1298C) were not associated with pancreatic cancer risk.

Keywords: Pancreatic cancer - MTHFR - gene polymorphism - meta-analysis

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Introduction

Pancreatic cancer is the tenth most common cause of cancer in the United States and is apparently the fourth leading cause of cancer mortality, it is estimated that 44030 new cases and 37660 associated deaths of the pancreatic cancer in 2011 (<http://seer.cancer.gov/statfacts/html/pancreas.html>). Both genetic and environmental factors play a role in the in the development of the disorder. There are some factors may potentially result in pancreatic cancer: cigarette smoking, age, race, gender, religious background, chronic pancreatitis, diabetes, peptic ulcer surgery, diet (Jang et al., 2012; Genkinger et al., 2012). In addition, up to 5% to 10% of pancreatic cancer cases are believed to be caused by genetic factors (Lam et al., 2012; Klein, 2012).

There is growing evidence that folate deficiency (a low normal level) is associated with risk of pancreatic cancer (Nikfam et al., 2012; Sanchez et al., 2012). The methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism that converts 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (Papandreou et al., 2012). Two significant functional polymorphisms of the MTHFR gene (C677T and A1298C) have been related to a reduced enzyme activity and increased the risk of pancreatic cancer, however the published results have been inconsistent (Frosst et al., 1995; Weisberg et al., 1998). In the present study,

we investigated whether or not the MTHFR gene polymorphisms is associated with pancreatic cancer by performing a meta-analysis.

Materials and Methods

Literature search

We searched the Google scholar, PubMed, Cochrane Library and CNKI (China National Knowledge Infrastructure) databases for all studies on the association between MTHFR polymorphisms and pancreatic cancer risk before April 2012. The following key words were used: "methylene tetrahydrofolate reductase", "MTHFR", "pancreatic adenocarcinoma", "pancreatic cancer", "polymorphism", "mutation" and "variant". We recruited data from published papers and abstracts without restriction of language. The reference lists of reviews and retrieved articles were hand searched at the same time. In the case of more than one article was published by the same author using the same case series, the latest published results were used.

Eligible Studies

Two investigators 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

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Table 1. Characteristics of the Included Studies for Meta-analysis

SNPs	Author	Year	Area	cases	controls	Genotypes for cases			Genotypes for controls			P for HWE
						CC	CT	TT	CC	CT	TT	
C667T	Li et al	2005	American	347	348	150	117	36	149	138	20	0.1
	Wang et al	2005	China	163	337	31	79	53	135	149	53	0.27
	Matsubayashi et al	2005	American	303	305	145	115	43	134	135	36	0.82
	Suzuki et al	2008	Japan	157	785	57	80	20	291	366	128	0.47
A1298C	Li et al	2005	American	347	348	129	145	29	133	137	40	0.61
	Wang et al	2005	China	163	337	124	37	2	243	86	8	0.9
	Matsubayashi et al	2005	American	303	305	133	134	36	144	140	21	0.09

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	
	Case	Control		I ²	P	OR	95% CI	z	P
C667T									
TT vs. CC	970	1775	Random	85.9%	0.00	1.61	0.78-3.34	0.00	0.91
TT vs. CT			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	990	Random	67.0%	0.05	1.01	0.47-2.17	0.00	1.00
CC vs. AC			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

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).

Data Extraction

Two investigators extracted the data independently, and the result was reviewed by a third investigator. 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 mode 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 χ^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

Characteristics of the 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 et al., 2005; Wang et al., 2005; Matsubayashi et al., 2005; Suzuki et al., 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 et al., 2005; Wang et al., 2005), 1 used real-time polymerase chain reaction method (Matsubayashi et

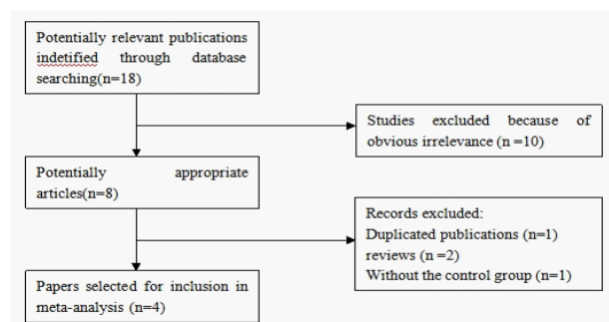


Figure 1. Flow Diagram of Study Searching and Selection Process

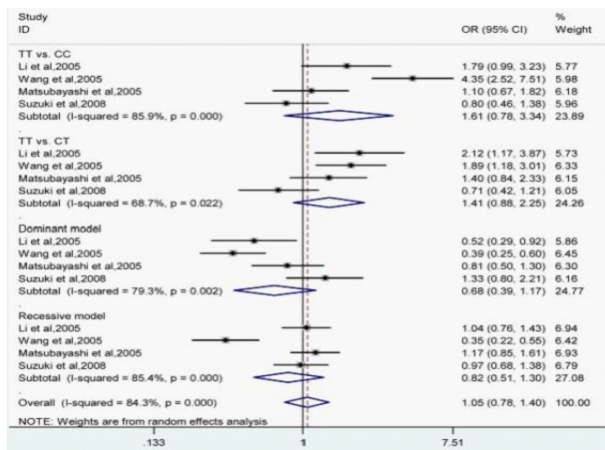


Figure 2. Forest Plots of ORs with 95% CI for MTHFR C677T Polymorphism and Risk for Pancreatic Cancer. Studies were ordered by year of publication. Square sizes are proportional to the weight of each study in the meta-analysis

al., 2005) and 1 used TaqMan Assays (Suzuki et al., 2008). All studies were consistent with HWE law in controls ($P > 0.05$).

Meta-analysis results

For MTHFR C677T polymorphism, a total of 970 cases and 1,775 controls were identified. The C677T polymorphism were not associated with the risk of pancreatic cancer (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). (Figure 2, Table 2). A total of 813 cases and 990 controls were identified for MTHFR A1298C polymorphism. The A1298C polymorphism did not have an increased risk of pancreatic cancer (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) (Figure 3, Table 2).

Publication Bias

Begg's test showed no evidence of publication bias in the present meta-analysis of the MTHFR polymorphisms (Table 2).

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.

Previous meta-analyses have shown the MTHFR 677TT genotype increase gastric cancer risk (Boccia et al., 2008), the possible mechanism is 677T allele

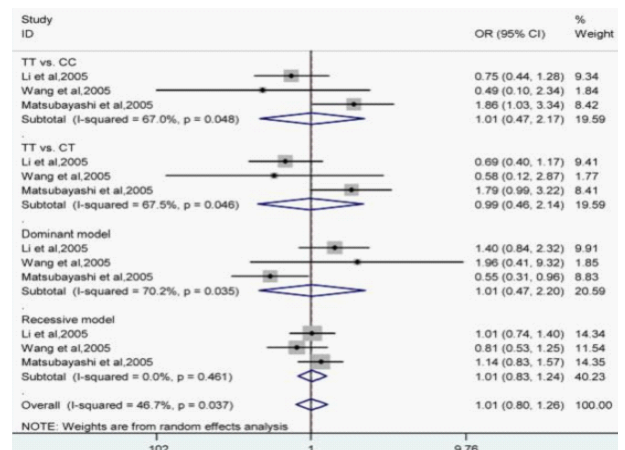


Figure 3. Forest Plots of ORs with 95% CI for MTHFR A1298C Polymorphism and Risk for Pancreatic Cancer. Studies were ordered by year of publication. Square sizes are proportional to the weight of each study in the meta-analysis

contributes to DNA hypomethylation, which in turn may lead to altered gene expression. And the polymorphism decrease the risk of colorectal cancer (Botto et al., 2000; Taioli et al., 2009; Lee et al., 2012; Ramsey et al., 2012). 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 in different study populations because of gene-folate interaction as discussed above. 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 et al., 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 provided no evidence that MTHFR polymorphisms (C677T, and A1298C) are associated with pancreatic cancer risk.

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