

Role of an snp in gastric cancer risk



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ThePre-miR-196a2 rs11614913 (T> C) Polymorphism and GastricCancerRisk

Yunzhao Zhao, M. D

Abstract

Background and Purpose s. Several studies have explored the association between pre-miR-196a2 rs11614913 (T> C) polymorphism and gastric cancer susceptibility. However, the results remained inconsistent. Therefore, we performed a meta-analysis of these studies to assess the effect of polymorphism on gastric cancer risk.

Methods. The PubMed, Web of science, and Embase databases were searched for articles on the rs11614913 polymorphism and gastric cancer risk published up to March 20, 2014. Combined odds ratio (OR) and corresponding 95 % confidence intervals (CIs) were used to assess the strength of the association.

Results. Seven studies with a total of 3441 cases and 4133 controls were eligible for analysis. Overall, we found null association between rs11614913 and gastric cancer risk (CC vs. TT: OR= 1. 45, 95 % CI 0. 82-2. 58; CT vs. TT: OR= 1. 11, 95 % CI, 0. 92-1. 33; CC/CT vs. TT : OR = 1. 26, 95 % CI 0. 92-1. 73; C vs. T: OR= 1. 23, 95 % CI 0. 89-1. 71). Subgroup analysis by ethnicity revealed that the rs11614913 (T> C) were associated with a elevated risk of gastric cancer in Caucasian (CT vs. TT: OR= 1. 89, 95 % CI 1. 29-2. 77; P = 0. 001) , but not in East Asians.

Conclusions. This meta-analysis suggested that the rs11614913 polymorphism might not be associated with risk of gastric cancer, while further studies are needed to corroborate this finding.

Key Words: Pre-miR-196a2; Polymorphism; Gastric Cancer;

Susceptibility Introduction

Gastric cancer is the fourth most common cancer and the second most common cause of cancer-related death all over the world, especially in East Asia.¹ Carcinogenesis of gastric is caused by various risk factors, including genetic predisposition, environment, and microbial infections. It is well-known that *Helicobacter pylori* infection is a critical event in the development gastric cancer. Many single-nucleotide polymorphisms (SNPs) have been implicated in gastric carcinogenesis^{2, 3}.

MicroRNAs (miRNAs) are naturally occurring, small, noncoding, single-stranded RNA molecules, which prevent translation of their target mRNAs are critical regulators of the transcriptome.⁴ MiRNAs regulate many biological processes, including cell differentiation, proliferation, apoptosis, and development; deregulation of which plays important roles in carcinogenesis.^{5, 6} Some miRNAs act as either oncogenes or cancer suppressor genes.⁷ Single-nucleotide polymorphisms (SNPs) are the most common genetic variation in human genome. SNPs in miRNA genes may affect the property of the respective miRNAs in three ways: transcription of the primary transcript, pri-miRNA and pre-miRNA processing, and influencing miRNA-mRNA interactions.⁸ Thus, polymorphisms in miRNAs can modulate individual's

cancer susceptibility.⁹⁻¹¹ A common variant rs11614913 (T> C) in pre-miR-196a2 was identified and implicated in the development of multiple-type cancers, including gastrointestinal cancer.¹²⁻¹⁵ Several studies have evaluated the effect of this polymorphism on gastric cancer risk in different ethnicities.¹⁶⁻²¹ However, the role of rs11614913 in gastric tumorigenesis is inconclusive. Therefore, we did a meta-analysis of these studies to assess the association of this polymorphism and gastric cancer risk.

Materials and Methods

Identification and Eligibility of Relevant Studies

The English literature was searched for relevant studies using the PubMed, and Web of Science, and Embase databases. Combinations of the following terms were used in the search: pre-miR-196a2, microRNA, gastric cancer, cancer, polymorphism, and rs11614913. Last search was update on March 20, 2014. All eligible studies were retrieved, and only published studies with sufficient data for calculated crude odds ratios (ORs) were included in our meta-analysis. Of the studies with the same or overlapping data published by the same investigators, only the most recent or complete study was selected.

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were (1) evaluation of the association of the rs11614913 (T> C) polymorphism with gastric cancer risk, (2) case-control studies, and (3) sufficient data for calculating odds ratios (ORs) with 95% confidence intervals (CIs). The exclusion criteria were: (1)

duplication of previous studies; (2) publication as an abstract, review, or editorial; and (3) publication in a language other than English.

Data Extraction

Information was carefully extracted from all eligible articles independently by two of the authors according to the inclusion criteria. Disagreements about extraction of data were resolved via discussion between the two of the investigators. If they could not reach a consensus, a third investigator was consulted to resolve the dispute, and a final decision was made by vote. Study characteristics abstracted from the publications included the last name of the first author, year of publication, country of origin, ethnicities, and genotype distribution.

Statistical Analysis

Crude ORs with 95% CIs were used to estimate the strength of association between the rs11614913 polymorphism and gastric cancer risk. Combined ORs were calculated for four contrast models: homozygote model (CC vs. TT), heterozygote model (CT vs. TT), dominant model (CC/CT vs. TT), and allele contrast model (C vs. T). Combined ORs were calculated using the DerSimonian and Laird random effects model.²² In this study, we applied the random effects model for the absence of significant heterogeneity does not imply homogeneity. Thus, the analyses should use the more conservative random effects model. Formal tests of heterogeneity (such as Cochran's Q statistics or I² index) were not carried out. Subgroup analysis by ethnicity was conducted. Publication bias was assessed using both Begg's test²³ and

Egger's test²⁴. A two-tailed P value of < 0.05 was considered to be statistically significant. All of these statistical tests were performed using Stata (version 12.0; StataCorp, College Station, TX) software programs.

Results

Study Characteristics

In one studies, genotype frequencies were presented separately according to test set and validation set, and thus each of these studies was considered separately for meta-analysis. There are six articles for seven studies including 3441 cases and 4133 controls that met our inclusion criteria.¹⁶⁻²¹ Table 1 lists the main characteristics of these studies, including first author, year of publication, country of origin, ethnicities and genotype distributions. All gastric cancer cases in these studies were pathologically or histologically confirmed.

Quantitative analysis

Overall, we found that the rs11614913 polymorphism was not associated with risk of gastric cancer (CC vs. TT: OR= 1.45, 95% CI 0.82-2.58; CT vs. TT: OR= 1.11, 95% CI, 0.92-1.33; CC/CT vs. TT : OR = 1.26, 95% CI 0.92-1.73; C vs. T: OR= 1.23, 95% CI 0.89-1.71). (Table. 2). In the subgroup analysis by ethnicity, we found significant associations between the rs11614913 polymorphism and gastric cancer susceptibility in heterozygote model (CT vs. TT: OR= 1.89, 95% CI 1.29-2.77; $P = 0.001$)(Table. 2)in Caucasian. However, we did not find any associations between the

rs11614913 polymorphism and gastric cancer risk in East Asians. The results of our meta-analysis are summarized and listed in Table 2.

Evaluation of Publication Bias

We did not detect any evidence of potential publication bias using Begg's test or Egger's test.

Discussion

In this study, we did a meta-analysis of seven recent studies to explore the association of rs11614913 polymorphism in pre-miR-196a2 and gastric cancer risk. We observed that the pre-miR-196a2 rs11614913 polymorphism was not associated with significant gastric cancer risk. However, stratified analysis by ethnicity revealed that the pre-miR-196a2 rs11614913 CT genotype was associated with an elevated risk of gastric cancer in Caucasian but not East Asians. In this meta-analysis, we did not detect any evidence of potential publication bias.

Many studies have revealed that miR-196 plays important roles in normal development and in the pathogenesis of human disease processes such as cancer.²⁵ miR196 family comprises miR-196a-1, miR196-a2, and miR-196b. The miR-196a-2 and miR-196a-2 genes generate the same functional mature miRNA sequence miR-196a, whereas miR-196b gene produces a small RNA, which differs from the sequence of miR-196a by one nucleotide.²⁶ miR-196a could play important roles in tumorigenesis by targeting its putative targets, such as HOX gene, HMGA2 and annexin A1.²⁶ Dysregulation of miR-196 expression has been reported in multiple cancer cell lines. Mature miR-196a

is over-expressed in gastric cancer tissues, suggesting it also play roles in the development of gastric cancer.²⁷ Sequence alterations in miRNA genes, including pri-miRNAs, pre-miRNAs and mature miRNAs, could potentially affect miRNA biogenesis and activity.²⁸ Studies have implicated that the rs11614913 SNP in miR-196a2 might affect mature miR-196a expression in hepatocellular carcinoma and non-small lung cancer tissues, thus influencing the cancer susceptibility.^{29, 30} In our study, we failed to find any association between rs11614913 and gastric risk in the overall analysis. However, subgroup analysis demonstrated that the pre-miR-196a2 rs11614913 CT genotype was associated with an increased risk of gastric cancer in Caucasian. This might be illustrated by the following reasons: first, there were differences in genetic background and gene-environment interactions in the etiology of gastric carcinogenesis; second, this happened to chance due to limited sample size. Several previous meta-analyses systematically assessed the potential association of the rs11614913 with cancer susceptibility.^{31, 32} A recent meta-analysis have evaluated the association of miR-196a2 rs11614913 polymorphism with gastrointestinal cancer risk, and the results demonstrates that this polymorphism is significantly associated with risk of gastrointestinal cancers including gastric cancer.¹⁵ However, the major concern is clinical heterogeneity brought by inherent difference between different cancer types. This may limit the reliability of the conclusions of the previous meta-analyses. It is need for further investigation of this SNP in different tumors.

Our meta-analysis has several limitations, which may mask a potential true association of this polymorphism with gastric cancer risk. First, lack of the <https://assignbuster.com/role-of-an-snp-in-gastric-cancer-risk/>

original data of the included studies limited our further evaluation of potential gene–gene, gene–environment interactions. Second, we restricted our meta-analysis to studies in the English literature, which might bias the results. Third, for all four studies, our meta-analysis results were based on unadjusted estimates of odds ratio, whereas a more comprehensive analysis could have been performed if individual data such as *Helicobacter pylori* infection status, diet, tobacco smoking and alcohol consumption were available. Fourth, our analysis was limited to in Caucasian and East Asians; therefore, it is uncertain whether these results can be generalized to other ethnicities. In spite of these, our meta-analysis has some advantages. First, we enlarged the sample size, which significantly increased statistical power of the analysis. Second, we used more conservative random-effect model for our analysis.

In conclusion, the results of our meta-analysis suggest that the pre-miR-196a2 rs11614913 polymorphism might not correlate with gastric cancer risk. In the Future, larger-scale and more well-designed studies based on homogeneous gastric cancer patients are needed to clarify the association.

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Tables and Figures Legend:

Table 1 Main Characteristics of the Four Studies Assessed in the Meta-analysis

Table 2 Pre-miR-27a Genotype Distribution in the Four Studies in the Meta-analysis