Original Article
Role of MUC1 rs4072037 polymorphism in gastric cancer: a meta-analysis

Peixi Liu, Mingxi Zeng

Department of Gastroenterology, Sichuan People Hospital, Chendu, China

Received April 29, 2015; Accepted April 17, 2017; Epub March 1, 2020; Published March 15, 2020

Abstract: Background and objective: To further determine the association between mucin 1 (MUC1) rs4072037 polymorphism and gastric cancer risk on the basis of previously published studies. Methodology: PubMed and Embase were used to search all the available publications. The relative risk of the correlation was shown as odds ratio (OR) with 95% confidence interval (95% CI) under all the genetic comparisons. Subgroup analyses based on ethnicity, study design and HWE were also executed to detect effects of specific factors on the risk of gastric cancer. Results: MUC1 rs4072037 polymorphism was observed to reduce the risk of gastric cancer under the five genetic comparisons [(GG versus AA: OR (95% CI)=0.72 (0.61, 0.84); GG + GA versus AA: OR (95% CI)=0.82 (0.76, 0.88); GG versus AA + GA: OR (95% CI)=0.83 (0.71, 0.96); G versus A: OR (95% CI)=0.78 (0.72, 0.84); GA versus AA: OR (95% CI)=0.80 (0.74, 0.87)]. This decreased risk of gastric cancer was also detected in subgroup analyses based on ancestry (Asian and Caucasian), study design (population-based and hospital-based) and HWE (P_HWE>0.05). Conclusions: MUC1 rs4072037 polymorphism may have an important role in gastric cancer, and this protective effect may vary among different ethnic populations and control subjects.

Keywords: MUC1, polymorphism, gastric cancer, risk

Introduction

As a world focus, cancer is a major threat to people health in spite of progress in clinical diagnosis and treatment [1]. Gastric cancer, the fourth most common malignancy in the world, makes up 3% to 10% of all deaths caused by cancers [2]. According to global cancer statistics, there were 989,600 new cases developing gastric cancer and 738,000 deaths related to gastric cancer in the year of 2008 [3]. Although the morbidity and mortality of gastric cancer have decreased on the whole, gastric cancer still ranks first in cancer-related mortality in developing countries [3, 4]. Cancer occurs due to the interactions between environmental and genetic factors, in which the latter have been uncovered to play an important part in the pathogenesis of cancer [5, 6].

Mucin 1 (MUC1), also named polymorphic epithelial mucin (PEM), is a type of mucin with 120-225 kDa encoded by the MUC1 gene in human [7, 8]. Meanwhile, MUC1 is a glycoprotein with massive O-linked glycosylation in its extracellular region. Mucins distribute on the apical surface of epithelial cells in several organs, such as the stomach, lung, and intestine [9]. Mucins can prevent the body from being infected by pathogens binding to oligosaccharides in the extracellular region [10], and the over-expression of MUC1 has been reported to correlate with various cancers, including cancers of breast, lung, pancreatic, and colon [11].

One of the single nucleotide polymorphisms (SNPs) within MUC1 gene located on 1q22, rs4072037, is a synonymous polymorphism in the second exon of the gene [12]. MUC1 rs4072037 has been indicated to relate to reduce intracellular levels of reactive oxygen species and epithelial infection and inflammation [13]. Since a large number of SNPs in genes are associated with altered gene expression levels, thus leading to occurrence of diseases, we conducted a meta-analysis to analyze whether MUC1 rs4072037 had some specific influence on the risk of gastric cancer.
Materials and methods

Identification of available studies

Two foreign databases including PubMed and Embase were used to seek all the eligible studies concerning MUC1 rs4072037 polymorphism and gastric cancer. Literature research was carried out up to June, 2016. The main words used for searching were as follows: “gastric cancer”, “mucin”, “polymorphism”, “variant”. We put restrictions on English language and published articles. If there appeared references in retrieved studies with seemingly proper abstracts and titles, they would be selected into this meta-analysis for further evaluation.

Selection criteria

After identifying available studies, we further screened them according to the following selection criteria: case-control study; discussing the correlation of gastric cancer with MUC1 rs4072037 polymorphism; having useful genotype data; providing sufficient statistical information necessary for the calculation of odds ratio (OR) with its 95% confidence interval (95% CI). Talks, abstracts and documentations would be precluded from the meta-analysis.

Extraction of useful information

In order to ensure the accuracy of the extracted information, two of the authors independently fulfilled the data extraction with a same standard. The items of information abstracted were described in an extraction form and included name of first author and reference, publication year, nation, ancestry (Asian, Caucasian or Hispanic), study design (population-based or hospital based), methods of genotyping, sample sizes of cases and controls, and conformity of genotype frequencies in controls to Hardy-Weinberg Equilibrium (HWE). If two or more studies were incorporated in the same article, they would be treated as independent studies, and their information would be extracted separately. Any cases with divergence on data items from the included studies were fully discussed between the two authors until a consensus was obtained.

Quality assessment of included studies

The quality of the eligible studies was assessed using the scoring standard of Newcastle-Ottawa scale (NOS) Quality assessment. According to scoring standard, if the total points was less than 4 points, the study was considered as poor. The moderate study was defined with the score of 4-6, while more than 6 was defined as good quality.

Statistics

With the assistance of STATA software, V.12.0 (STATA Corp), the overall and subgroup analyses stratified by ancestry and study design were done for the exploration of MUC1 rs4072037 polymorphism and gastric cancer risk. We assessed the existence of heterogeneity among studies by using $^2$-based Q test. When the P value was less than 0.10, which meant a significant heterogeneity, we applied the random-effects model to summary the ORs. If there was no obvious heterogeneity, we used the fixed-effects model. We detected potential risk of publication bias using Begg’s funnel plot and Egger’s regression test. To check the impact of any individual study on the overall meta-analysis results, we conducted the sensitivity analysis. All the P values in the tests described above were two-sided.

Results

Study search and characters

As shown in Figure 1, based on the search methods and selection criteria, 11 papers (15
studies) [12, 14-23] with 10,092 gastric cancer cases and 15,236 controls were enrolled in the meta-analysis from 103 initially selected studies though databases. The additional 91 articles were excluded due to the following reasons: irrelevant records; animal researches; about gastritis and other diseases; not about MUC1 rs4072037 polymorphism; not case-control studies; absence of sufficient genotype frequencies. As displayed in Table 1, among the 11 studies, 7 studied Asian populations, 3 studied Caucasian populations and only one studied Hispanic populations; 8 studies applied population-based source and the other 3 applied hospital-based source. The most frequently used technique for genotyping was TaqManSNP.

Meta-analysis

Table 2 listed the results about MUC1 rs4072037 polymorphism and gastric cancer risk. An overall decreased risk of gastric cancer was associated with MUC1 rs4072037 polymorphism under all the genetic contrasts [GG versus AA: OR (95% CI)=0.72 (0.61, 0.84); GG + GA versus AA: OR (95% CI)=0.75 (0.67, 0.85); GG versus AA + GA: OR (95% CI)=0.79 (0.70, 0.88); G versus A: OR (95% CI)=0.79 (0.70, 0.88)]. The protective effects of MUC1 rs4072037 polymorphism were also observed in the subgroup analyses based on ancestry for Asians: GG versus AA: OR (95% CI)=0.70 (0.59, 0.84); GG + GA versus AA: OR (95% CI)=0.77 (0.67, 0.90); GG versus AA + GA: OR (95% CI)=0.78 (0.70, 0.88); G versus A: OR (95% CI)=0.80 (0.72, 0.88); GA versus AA: OR (95% CI)=0.80 (0.73, 0.89); GA versus AA: OR (95% CI)=0.81 (0.73, 0.89); GA versus AA: OR (95% CI)=0.81 (0.73, 0.89); GA versus AA: OR (95% CI)=0.81 (0.73, 0.89).
### Table 2. MUC1 rs4072037 polymorphism and gastric cancer risk

<table>
<thead>
<tr>
<th></th>
<th>GG versus AA</th>
<th>GG + GA versus AA</th>
<th>GG versus AA + GA</th>
<th>G versus A</th>
<th>GA versus AA</th>
<th>OR (95% CI)</th>
<th>Phetogenity</th>
<th>OR (95% CI)</th>
<th>Phetogenity</th>
<th>OR (95% CI)</th>
<th>Phetogenity</th>
<th>OR (95% CI)</th>
<th>Phetogenity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.67 (0.52, 0.86)</td>
<td>0.308</td>
<td>0.80 (0.73, 0.87)</td>
<td>0.103</td>
<td>0.72 (0.56, 0.92)</td>
<td>0.436</td>
<td></td>
<td>0.74 (0.67, 0.81)</td>
<td>0.017</td>
<td>0.80 (0.73, 0.88)</td>
<td>0.163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.74 (0.60, 0.92)</td>
<td>0.660</td>
<td>0.85 (0.74, 0.98)</td>
<td>0.910</td>
<td>0.90 (0.74, 1.10)</td>
<td>0.384</td>
<td></td>
<td>0.86 (0.77, 0.97)</td>
<td>0.545</td>
<td>0.79 (0.67, 0.94)</td>
<td>0.934</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.85 (0.41, 1.79)</td>
<td>0.000</td>
<td>0.93 (0.62, 1.39)</td>
<td>0.000</td>
<td>0.90 (0.44, 1.83)</td>
<td>0.000</td>
<td></td>
<td>0.92 (0.66, 1.29)</td>
<td>0.000</td>
<td>0.92 (0.58, 1.45)</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>0.75 (0.63, 0.90)</td>
<td>0.882</td>
<td>0.83 (0.77, 0.90)</td>
<td>0.580</td>
<td>0.86 (0.72, 1.02)</td>
<td>0.679</td>
<td></td>
<td>0.82 (0.77, 0.88)</td>
<td>0.311</td>
<td>0.82 (0.75, 0.89)</td>
<td>0.674</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>0.58 (0.39, 0.84)</td>
<td>0.109</td>
<td>0.72 (0.58, 0.88)</td>
<td>0.196</td>
<td>0.71 (0.50, 1.01)</td>
<td>0.080</td>
<td></td>
<td>0.66 (0.57, 0.75)</td>
<td>0.227</td>
<td>0.68 (0.53, 0.87)</td>
<td>0.547</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P_{HWE}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.05</td>
<td>0.68 (0.56, 0.81)</td>
<td>0.520</td>
<td>0.81 (0.75, 0.88)</td>
<td>0.292</td>
<td>0.76 (0.64, 0.91)</td>
<td>0.643</td>
<td></td>
<td>0.81 (0.73, 0.89)</td>
<td>0.093</td>
<td>0.81 (0.74, 0.88)</td>
<td>0.391</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.05</td>
<td>0.86 (0.61, 1.19)</td>
<td>0.863</td>
<td>0.85 (0.70, 1.05)</td>
<td>0.466</td>
<td>1.07 (0.79, 1.44)</td>
<td>0.694</td>
<td></td>
<td>0.90 (0.75, 1.09)</td>
<td>0.294</td>
<td>0.79 (0.62, 1.01)</td>
<td>0.602</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.72 (0.61, 0.84)</td>
<td>0.648</td>
<td>0.82 (0.76, 0.88)</td>
<td>0.430</td>
<td>0.83 (0.71, 0.96)</td>
<td>0.475</td>
<td></td>
<td>0.78 (0.72, 0.84)</td>
<td>0.018</td>
<td>0.80 (0.74, 0.87)</td>
<td>0.604</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MUC1 rs4072037 polymorphism and gastric cancer risk in the subgroup analysis by ancestry.

![Figure 2](image2.png)

Figure 2. MUC1 rs4072037 polymorphism and gastric cancer risk in the subgroup analysis by ancestry.

MUC1 rs4072037 polymorphism and gastric cancer risk in the subgroup analysis by study design.

![Figure 3](image3.png)

Figure 3. MUC1 rs4072037 polymorphism and gastric cancer risk in the subgroup analysis by study design.

**Sensitivity analysis**

We performed the sensitivity analysis to examine the reliability and stability of the whole meta-analysis results. After sequential omission of each single study, no apparent changes appeared, showing our results were comparatively convincing.

**Test of heterogeneity and publication bias**

As Table 2 showing, we did not observe any significant heterogeneity under all the genetic contrasts (GG versus AA: Ph=0.648; GG + GA versus AA: Ph=0.430; GG versus AA + GA: Ph=0.475; GA versus AA: Ph=0.604) except the G versus A model (Ph=0.018), thus we estimated the pooled ORs using the random-effects model under the G versus A contrast, and the fixed-effects model under the other four contrasts. In order to investigate the potential publication bias of the present meta-analysis, we adopted Begg’s funnel plot and Egger’s regression test. From the perspective of the shape of funnel plot, no remarkable asymmetry was observed (Figure 4). In addition, Egger’s regression test provided a further statistical verification for this symmetry (P=0.351). Therefore, there existed no evident publication bias affecting the overall results.

**Discussion**

Gastric cancer is a common malignant tumor, and has been identified as an outcome caused by combined actions of various factors, including oncogenes, tumor suppressor genes, DNA repair genes, telomerase activity and genetic instability. At the phrase of intestinal metaplasia, helicobacter pylori (H pylori) infection induces the abnormal proliferation of positive hTERT cells, leading to the onset of gastric cancer [24]. Thus, the occurrence of gastric cancer...
is a multi-gene and multi-stage process, and is caused by interactions of environmental and individual genetic factors. A mass of evidences have indicated different populations living in the same environment have great differences in risk of developing gastric cancer, suggesting that the outbreak of gastric cancer is associated with individual susceptibility in some degree. Therefore, using some molecular biological markers such as susceptibility genes to recognize the high risk populations is beneficial for the prevention and treatment of gastric cancer.

Genetic polymorphism is one of the main causes for difference in individual susceptibility, and SNP is the most common type of genetic variations in humans [12]. In recent years, extensive research has been conducted about the association between genetic susceptibility to gastric cancer and SNPs, and dozens of SNPs concerning cell proliferation [25] and DNA repair [26] have been reported to closely correlate with occurrence and progression of gastric cancer.

MUC1, a member of mucin family, mainly expresses near the surface of glandular lumens in epithelial tissues of the respiratory tract, breast, gastrointestinal tract, and genitourinary tract. Participating in the metastasis and proliferation of tumor cells [27], abnormal expression of MUC1 is related to the occurrence and metastasis of tumors [28, 29]. In tumor tissues, the malformed or inadequate glycosyl-

ation of muc1 makes the core protein expose new protein epitopes or carbohydrate antigens distributing on the surface of the whole tumor cell, which can be recognized by immune system and become the tumor-specific antigens [30-32].

In a study on MUC1 rs4072037 polymorphism, Xu et al. found that compared with carriers with AG + GG genotype, those with AA genotype were at 1.92-fold higher risk of gastric cancer (95% CI=1.06-3.50) [14]. Jia et al. conducted a comprehensive analysis of common genetic variants within MUC1, MUC5AC and MUC6 genes, and provided further evidence for the MUC1 rs4072037 associated with increased risk of gastric cancer [15]. And similar results were also demonstrated in some other studies [16, 17, 33]. However, in this meta-analysis with 10,092 gastric cancer cases and 15,236 controls, MUC1 rs4072037 polymorphism was protective against the onset of gastric cancer. Moreover, Zhang et al. found rs4072037 at 1q22 was significantly correlated with reduced risk of gastric cancer with per allele OR of 0.72 [95% CI=0.63-0.81; \(P=2.98\times10^{-7}\)] [18], which was supported by later published studies [19-21]. Some other studies even found a null association of gastric cancer with MUC1 rs4072037 [22, 23]. Therefore, differences in sample size, phrase of gastric cancer progression as well as consideration of confounding factors contributed to disparate study results to a large extent.

As a large-sized meta-analysis, our results were relatively robust. However, the omission of unpublished articles and inconsideration of interactions of relevant factors may impact the precision of the findings. More association studies are necessary to deepen the understanding of the pathophysiology of gastric cancer in relation to MUC1 rs4072037 polymorphism.

Disclosure of conflict of interest

None.
Address correspondence to: Dr. Mingxi Zeng, Department of Gastroenterology, Sichuan People Hospital, Chendu, China. E-mail: hanlifire@163.com

References


MUC1 rs4072037 polymorphism and gastric cancer

Malfertheiner P. PSCA and MUC1 gene polymorphisms are linked with gastric cancer and pre-malignant gastric conditions. Anticancer Res 2014; 34: 7167-7175.


