RESEARCH ARTICLE

# Meta-analysis of the MDM2 T309G Polymorphism and Gastric Cancer Risk

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## Abstract

**Background: *Mdm2* binds to the amino-terminus of p53 to induce its degradation and a single nucleotide polymorphism in the *MDM2* promoter region (T309G) has been reported to increase the risk of several carcinomas, such as gastric cancer. However, the results of published studies to analyze the association between *MDM2* T309G and gastric cancer havve often conflicted. Methods: To better illustrate the filiation between *MDM2* T309G and gastric cancer, we performed a meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of the relationship. The pooled ORs were performed for 4 models, additive, recessive, co-dominant model, and dominant. Results: Nine published case-control studies including 3,225 gastric cancer cases and 4,118 controls were identified. The *MDM2* T309G polymorphism was associated with a significantly increased risk of gastric cancer risk when all studies were pooled into the meta-analysis (GG versus TT, OR=1.57; 95%CI=1.57-2.12; *p*=0.003) and GG versus GT/TT, OR=1.52; 95%CI=1.217-1.90; *p*<0.001). Furthermore, Egger's test did not show any evidence of publication bias (*P* = 0.608 for GG versus TT). Conclusion: Our results suggest that the *MDM2* T309G polymorphism is indeed associated with a significantly increased risk of gastric cancer.**

**Keywords:** Gastric cancer - *Mdm2* T309G - meta-analysis

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## Introduction

Gastric cancer (GC) is one of the major cancer and the second most frequent cause of cancer in the world (Saeki et al., 2013).The five-year survival rate for Gastric cancer less than 50% (Alakus et al., 2009). As is reported, over 60% of GC cases and deaths are in developing countries, such as China (Jemal et al., 2011; Zhao et al., 2010). The reason of GC development are involved in environment, bacterial infecting, such as Helicobacter pylori which is the one of the important increased risk factors to cause GC (Zou et al., 2013). In recent years, researchers have focused on the relationship between single-nucleotide polymorphisms and GC cases (Li et al., 2011; Xu et al., 2013; Zhang et al., 2013).

The fetal tumor suppress gene p53 located chromosome 17p13 is associated with important cellular events, including cell cycle regulation, DNA repair, apoptosis and senescence (Levine & Oren, 2009).The p53 occurs mutant approximately half of all human cancers (Brosh & Rotter, 2009). *Mdm2* is an important negative regulator of p53 and has been involved in carcinogenesis. On the one hand, *Mdm2* can reduce the expression of p53 by blocking the transcription of p53, and degrade the p53 protein by ubiquitination. On the other hand, p53 can also regulate the synthesis of *Mdm2* (Yang et al., 2012). *Mdm2* T309G (rs2279744), located in the first intron of *Mdm2* where is the core promoter region, affects binding inefficient of the transcription factor Sp1 resulting in the higher affinity to the G allele than to the T allele. Therefore, the transcription of *Mdm2* is higher than normal *Mdm2*. As a consequence, the tumor suppressor function of p53 has been inhibits (Pan et al., 2013).

In the present studies, the researchers have reported the role of *Mdm2* T309G polymorphism in gastric carcinoma risk. Whereas the outcome are indeterminacy. Partially because of the data is due to the relatively small size. Consequently, we carried out a meta-analysis on case-control studies to estimate effect of the *Mdm2* T309G polymorphism on the risk of gastric risk.

## Materials and Methods

*Identification and eligibility of relevant studies*

We searched the PubMed, Embase and Chinese biomedicine databases for all correlative articles (the last search update was June 2, 2013). The following terms were used: *Mdm2*, polymorphism, gastric cancer. The results were identified by a hand search of original studies. We selected the most recent articles. These studies have

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**Table 1. Characteristics of Literatures Included in the Meta-analysis**

| Author | Year | Country | Sample size (cases/control) | HWE[a] | Cases | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TT | GT | GG | TT | GT | GG |
| Yang et al., 2007 | 2007 | China | 500/1000 | 0.88 | 107 | 250 | 143 | 298 | 498 | 204 |
| Wang et al., 2009 | 2009 | China | 260/260 | 0.06 | 74 | 120 | 66 | 82 | 141 | 37 |
| Zhang, 2011 | 2011 | China | 268/190 | 0.61 | 56 | 146 | 66 | 39 | 98 | 53 |
| Er. et al., 2012 | 2012 | China | 188/142 | 0.16 | 45 | 84 | 59 | 41 | 78 | 23 |
| Cao. et al., 2007 | 2007 | China | 212/642 | 0.3 | 21 | 91 | 100 | 117 | 299 | 226 |
| Ohmiya et al., 2006 | 2006 | Japan | 410/438 | 0.04 | 98 | 188 | 124 | 99 | 241 | 98 |
| Cho et al., 2008 | 2008 | Korea | 239/299 | 0.68 | 64 | 110 | 65 | 61 | 152 | 86 |
| Pan et al., 2013 | 2013 | China | 574/574 | 0.06 | 173 | 260 | 141 | 199 | 296 | 79 |

[a]HWE, Hardy-Weinberg equilibrium

**Table 2. Meta-analysis of the MDM2 T309G Polymorphism on Gastric Cancer**

| | OR[a] | (95% C.I) | *p* | *P*[b] |
|---|---|---|---|---|
| GG/GT vs. TT (dominant) | 1.175 | 0.954-1.446 | 0.129 | 0.009 |
| GG vs. GT/TT (recessive) | 1.522 | 1.217-1.903 | <0.001 | 0.002 |
| GT vs. TT | 1.025 | 0.845-1.245 | 0.801 | 0.043 |
| GG vs. TT | 1.572 | 1.572-2.12 | 0.003 | 0.001 |

[a]Random-effects model was used when *P* value for heterogeneity test, 0.05; otherwise, fix-effects model was used. [b]*P* value of Q-test for heterogeneity test

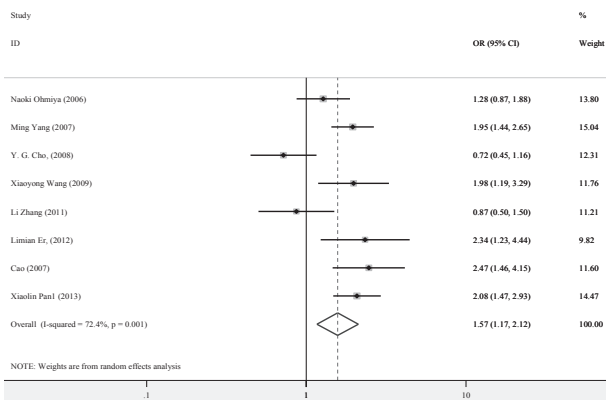


**Figure 1. Forest Plot of Gastric Cancer Risk Associated with the MDM2 T309G (GG vs. TT).** The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the summary OR and 95% CI

the following criteria: (a) evaluation of *Mdm2* T309G polymorphism and gastric cancer risk, (b) a case-control design was used, and (c) have genotype frequencies for both patients and control populations.

*Data Extraction*

Two investigators independently extracted the data and reached consensus on all project. For each study, the following data were considered: author name, year of publication, country of study, and numbers of genotyped cases and controls.

*Statistical Analysis*

For control group of each study, the observed genotype frequencies of the *Mdm2* T309G polymorphism were assessed for Hardy Weinberg –Equilibrium (HWE) using the $\chi^2$ test. The strength of association between *Mdm2*

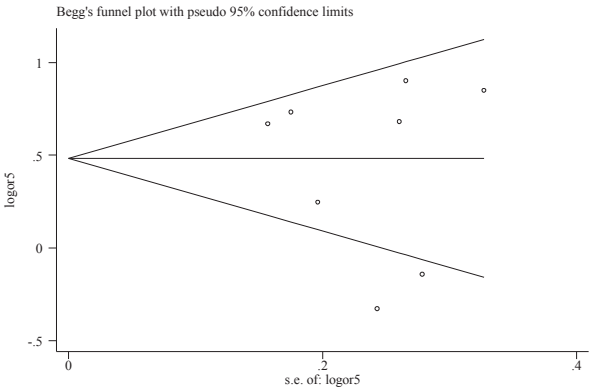


**Figure 2. Begg's Funnel Plot for Publication Bias Test (GG vs. TT)**

gene and gastric cancer was accessed by calculating crude odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs were performed for dominant model (GG/GT versus TT), recessive model (GG vs. GT/TT), codominant model (GG versus TT, GT versus TT). Heterogeneity assumption was evaluated by a chi-square based Q-test. A *P*-value of <0.05 for the Q-test indicated a lack of heterogeneity among the studies, the summary OR estimate of each study was calculated by the random effects model (DerSimonian & Laird, 1986; Mantel & Haenszel, 1959). The potential for publication bias was examined by a Begg's test (funnel plot method) and Egger's linear regression test (*P*<0.05 considered representative of statistical significance) (Egger et al., 1997). All analyses were performed using Stata software (version 8.2; Stata Corporation, College Station, TX).

## Results

*Characteristics of Studies*

There were 8 published papers were searched. A total of 2651 cases and 3545 controls were included (Table 1). These studies were all in Asia, 6 of them were from China, and the rest were from Japan and Korea. The distribution of genotypes in the controls of all the studies was in agreement with Hardy-Weinberg equilibrium (Ma et al., 2013).

*Main results*

The results of the association between the *Mdm2* T309G polymorphism and gastric cancer test were shown in Table 2. Overall, the *Mdm2* T309G genotype with

GG were a higher risk than wild-type TT (OR=1.57; 95%CI=1.57-2.12; $p$=0.003; Figure 1). Simultaneously, the GG genotype could significantly increase the risk of gastric compared with other genotypes (OR=1.52; 95%CI=1.217-1.90; $p$<0.001).

*Publication bias*

Funnel plot and Egger's test were done to estimate the publication bias of literatures. The results of Egger's test provided statistical evidence for funnel plot symmetry (Figure 2)

## Discussion

Gastric cancer is still a serious public health problem in the world. The incidence and mortality rates of gastric cancer have decreased, which is the second leading cause of cancer death around the world (Shibata et al., 2009). However, the mechanism of Gastric Cancer remains relative unclear. Single nucleotide polymorphisms (SNPs) can be used as a tool in investigating genetic variations and disease susceptibility. The previous study has conflicting results about the correlation between the *Mdm2* T309G and the risk of gastric cancer, which is limited by the relative small size of samples. The results form Ohmiya et al. (2006) and Yang et al. (2007) showed that subjects with variant G allele in *Mdm2* T309G polymorphism had increased risk of gastric cancer. In consideration of the vital function of *Mdm2* in the regulation of p53, the *Mdm2* T309G polymorphism increases the affinity of Sp1 for the promoter of *Mdm2* and results overexpression of *Mdm2*. The results could be tested by cell test, which showed the cell lines with GG and TG genotypes expressed higher levels of *Mdm2* than those with the TT genotypes (Bond et al., 2004). However, Cho et al. and Zhang et al. reported that there was no signification association between the *Mdm2* T309G polymorphism and gastric cancer risk.

According to exist the conflict, a meta-analysis of 8 studies including 2651 cases and 3545 controls was analyzed to derive a more precise estimation of the association by relative large and latest data. Our results suggest that the *Mdm2* T309G polymorphism is associated with a significantly increased risk of gastric cancer.

There are some limitations of this meta-analysis, which mainly relate to the lack of other factors, such as misclassification on disease status, diet custom. In these cases, few studies reported confirmed status by pathology or gold standard method. And there were seldom researches to investigate patients' diet custom. Secondly, our results were based on unadjusted estimates, while a precise analysis should be employed suppose that individual data were available, which would adjust by other variants, such as environment factors.

In conclusion, this meta-analysis showed that the homozygous GG geotype had increased risk of gastric cancer (OR=1.52; 95%CI=1.217-1.90; $p$<0.001), suggests the *Mdm2* T309G polymorphism may be associated with the risk of gastric cancer. Future well designed large studies might be necessary to validate this association in different populations incorporated with environmental factors in the susceptibility of gastric.

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