

RESEARCH ARTICLE

Association Between MDM2 SNP309 T>G and Risk of Gastric Cancer: A Meta-analysis

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Abstract

Background: As a negative regulator of P53, MDM2 plays an important role in carcinogenesis; a polymorphism in its promoter region, SNP309 T>G, is known to increase the expression of MDM2, thus being considered related to higher susceptibility to neoplasia. However, no agreement has been achieved regarding its effects on gastric cancer. **Methods:** The present systematic meta-analysis was performed based on comprehensive literature search from Pubmed, Web of science and CBM databases. **Results:** It was suggested from 6 independent studies that the GG genotype is associated with a significantly increased risk of gastric cancer (Recessive: OR = 1.43, 95% CI = 1.08-1.91, $P = 0.013$), and subgroup analysis also confirmed the relationship (English publications-recessive model: OR = 1.45, 95% CI = 1.10-1.91, $P = 0.009$; Studies in China-recessive model: OR = 1.58, 95% CI = 1.08-2.30, $P = 0.017$). No publication bias was detected. **Conclusion:** The meta-analysis indicated a significant inverse association between GG genotype carriage and elevated risk of gastric cancer. However, more studies and detailed information are needed to fully address the topic.

Keywords: MDM2 - polymorphism - gastric cancer - meta-analysis

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Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death in the world. It is estimated 21,600 newly diagnosed cases of gastric cancer and 10,990 deaths would occur in the USA in 2013, although gastric cancer (3.1%) enjoyed the second largest annual declines in death rates over the past 10 years of data (2000-2009) (Siegel et al., 2013; Society, 2013). It is reported nearly two-thirds of gastric cancer cases and deaths occur in developing countries, such as China, Korea, Central and South America and Middle East (Crew et al., 2006; Zhao et al., 2010; Jemal et al., 2011). Take China as an example, the crude gastric cancer mortality rate was 22.97 per 100,000 in urban areas and 25.58 per 100,000 in rural areas in 2004-2005 (Yang et al., 2006; Jemal et al., 2010).

The famous tumor suppressor gene TP53 is mutated in minimally half of all cancers. As a negative regulator of p53, mouse double minute 2 (MDM2) could bind to it with high affinity, leading to the reduction of p53 expression and functional inhibition; on the other hand, p53 enhances MDM2 transcription, which forms an important feedback-loop (Eischen et al., 2009). A polymorphism in MDM2

promoter region (SNP309T>G) has been found to associate with increased Sp1 binding and elevated MDM2 transcription, resulting in the subsequent attenuation of the p53 and disturbance of the MDM2-P53 feedback loop (Bond et al., 2004; Bond et al., 2005).

It is reported that the MDM2 SNP309T>G could accelerate tumor formation in both hereditary and sporadic cancers (Bond et al., 2004). Ma showed a significant relationship between the MDM2 SNP309T>G and liver cancer risk, and the G allele contributed to increased risk in a graded, dose-dependent manner (Ma et al., 2012), and Cai indicated the functional genetic variant may play an important role in sarcoma carcinogenesis (Cai et al., 2012); however, Chen reported the polymorphism is a protective factor against prostate cancer risk in Europeans (Chen et al., 2012) and Liu suggested the G allele probably acted as a protective factor in head and neck squamous cell carcinomas in Caucasians (Liu et al., 2011). Similarly, several publications focused on the association between gastric cancer and the polymorphism, nevertheless, no agreement was achieved. Ohmiya (Ohmiya et al., 2006) reported the overall risk of gastric cancer was significantly increased with the polymorphism under recessive model but Cho, et al (2008) stated that MDM2 SNP309T>G

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Table 1. Main Characteristics of Studies Identified for the Meta-analysis

Study First Author, Year	Location	Study design	Sample Size (case/control)	Genotype Distribution (case/control)			OR 95%CI; P (Recessive)	OR 95%CI; P (Dominant)	Adjustment	Publication language
				TT	TG	GG				
Naoki Ohmiya, 2006	Nagoya, Japan	Hospital-based	410/438	98/99	188/241	124/98	1.45 (1.02-2.05); 0.039	1.03 (0.72-1.49); 0.86	Sex, age, and H pylori seropositivity	English
Ming Yang, 2007	Beijing, China	Population-based	500/1000	107/298	250/498	143/204	1.94 (1.42-2.64); NA	1.37 (1.05-1.80); <0.001	Sex, age, and smoking status	English
Y. G. Cho, 2008	Seoul, Korea	Population-based	239/299	64/61	110/152	65/86	0.81 (0.45-1.47); NA	0.84 (0.49-1.43); NA	Age and sex	English
Xiaoyong Wang, 2009	Jiangsu, China	Population-based	260/260	74/82	120/141	66/37	2.05 (1.31-3.20); 0.002	1.16 (0.79-1.69); 0.45	Age, sex, and Helicobacter pylori infection	English
Yuqin Li, 2010	Jiangsu, China	Population-based	574/574	173/179	260/316	141/79	2.03 (1.40-2.75); 0.001	1.05 (0.81-1.35); 0.72	Age, sex, and Helicobacter pylori infection	Chinese
Li Zhang, 2011	Chongqing, China	Hospital-based	268/190	56/39	146/98	66/53	1.22 (0.79-1.86); NA	1.05 (0.66-1.68); NA	Age, sex, and Helicobacter pylori infection	Chinese
Limian Er, 2012	Hebei, China	Hospital-based	188/142	45/41	84/78	59/23	NA	NA	NA	Chinese

was not associated with an increased gastric cancer risk in Korean population. Therefore, a meta-analysis with comprehensive investigation is required on the topic.

Materials and Methods

Literature search

Systematic literature search was performed on Pubmed, Web of science and CBM databases to identify relevant studies published prior to Feb 1st, 2013 by 2 independent researchers. Terms “MDM2” and “gastric cancer” were used with no further restriction to achieve a thorough inclusion. Due to the high incidence rate of gastric cancer in China, we conclude publications in Chinese and conducted relevant subgroup analysis. The references of eligible articles were also checked to find other potential studies.

Inclusion and Exclusion Criteria

Publications met the following criteria were included in our analysis: (1) case-control studies; (2) studies examining the association between MDM2 SNP309T>G and gastric cancer risk; (3) studies providing Odds Ratios (ORs) and corresponding 95% confidence intervals (95% CIs) as well as detailed genotype distributions or (4) studies providing data that could be used for calculation of the genotype information; (5) publications in English or Chinese.

Data Extraction

We extracted the following information from each eligible study by two independent investigators: first author's name and published year; the location of the study; study design; genotype distribution; estimate effects (ORs and 95% CIs and *P* values under both recessive and dominant models); adjustments; and publication language.

Statistical Analysis

R software Version R-2.15.2 (<http://www.r-project.org/>) and its package “meta” were used to calculate the available data from each study. We conducted calculations with inverse variance weighting method. Crude ORs and 95% CIs were applied to estimate the association between MDM2 309T>G polymorphism and gastric cancer risk. Co-dominant models (GT vs. TT and GG vs. TT), recessive model and dominant model were all used in overall and subgroup analysis. Between-study heterogeneities were estimated with Cochran's Q-statistic and *I*² test; and *P* < 0.05 or *I*² > 50% was considered to be the indication of statistical significance. Fixed-effects model was used when there was no heterogeneity while random-effects model was applied when significance

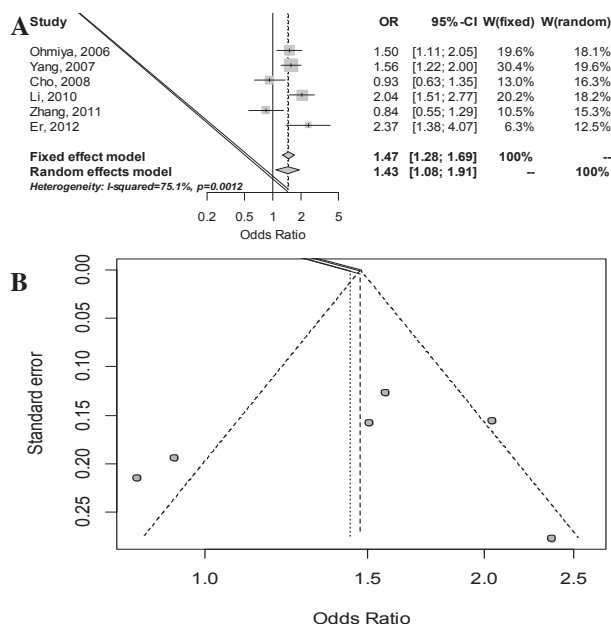


Figure 1. Forest Plot of the Association Between MDM2 309T>G Polymorphism and Risk of Gastric Cancer under Recessive Model from Overall Studies (A) and Funnel Plot of the Publication Bias (B)

heterogeneity existed. Sensitivity test was conducted by omitting one study each time to assess the stability of final results. We also tested publication bias with Begger's funnel plots and Egger's linear regression tests, and a *P* value less than 0.05 was the representative of significant publication bias. All calculations were two-sided.

Results

The characteristics of included studies

We identified 8 eligible studies through literature search (Ohmiya et al., 2006; Yang et al., 2007; Cho et al., 2008; Er et al., 2009; Wang et al., 2009; Li et al., 2010; Zhang et al., 2011; Er et al., 2012), 4 of which were written in English while the rests were in Chinese. Two publications used overlapped population (Wang et al., 2009; Li et al., 2010) and we used the one in Chinese in overall analysis because it contained more cases and controls, and the English one was used in subgroup analysis of studies published in English. Similarly, two Chinese publications (Er et al., 2009; Er et al., 2012) overlapped in population and we chose the latest one in analysis. Therefore, 2,179 cases and 2,643 controls from 6 studies were included in overall calculations. All the studies were conducted in Asia; 5 of them were in China while one in Korea and one in Japan respectively. 4 of the studies were population-based and the rests were hospital-based. 4 of them reported significant association

Table 2. Overall and Subgroup Analysis of the Association Between Gastric Cancer and the Polymorphism

Category	Genetic model	Fixed effects model		Random effects model			Heterogeneity Publication bias		
		OR	95%CI	P	OR	95%CI	P	I ²	P
Overall	TG vs. TT	0.97 [0.84; 1.11]	0.651	0.94 [0.75; 1.19]	0.619	58.4%	0.034	0.558	
	GG vs. TT	1.48 [1.25; 1.75]	<0.001	1.39 [0.98; 1.96]	0.064	74.6%	0.001	0.383	
	Dominant	1.11 [0.97; 1.26]	0.135	1.07 [0.84; 1.35]	0.597	64.3%	0.016	0.413	
	Recessive	1.47 [1.28; 1.69]	<0.001	1.43 [1.08; 1.91]*	0.013	75.1%	0.001	0.689	
Study design	Population-based	TG vs. TT	1.01 [0.85; 1.20]	0.904	0.96 [0.64; 1.44]	0.829	80.6%	0.006	0.605
		GG vs. TT	1.59 [1.29; 1.95]	<0.001	1.41 [0.82; 2.44]	0.214	84.7%	0.002	0.137
		Dominant	1.16 [0.98; 1.36]	0.079	1.07 [0.71; 1.62]	0.742	83.2%	0.003	0.445
		Recessive	1.53 [1.29; 1.81]	<0.001	1.46 [0.98; 2.18]	0.065	80.4%	0.006	0.599
	Hospital-based	TG vs. TT	0.89 [0.69; 1.13]	0.339	0.89 [0.69; 1.13]	0.339	0	0.601	0.207
		GG vs. TT	1.30 [0.98; 1.72]	0.073	1.33 [0.82; 2.17]	0.245	62.5%	0.069	0.776
		Dominant	1.01 [0.80; 1.28]	0.920	1.01 [0.80; 1.28]	0.920	0	0.543	0.423
		Recessive	1.38 [1.10; 1.73]	0.005	1.42 [0.84; 2.38]	0.189	78.5%	0.010	0.877
Language	English	TG vs. TT	1.01 [0.85; 1.19]	0.952	0.94 [0.67; 1.31]	0.717	72.4%	0.012	0.140
		GG vs. TT	1.47 [1.21; 1.79]	<0.001	1.39 [0.90; 2.15]	0.143	78.1%	0.003	0.502
		Dominant	1.14 [0.97; 1.34]	0.112	1.06 [0.75; 1.50]	0.738	77.1%	0.004	0.159
		Recessive	1.46 [1.24; 1.71]	<0.001	1.45 [1.10; 1.91]*	0.009	63.0%	0.044	0.909
Location	China	TG vs. TT	1.07 [0.91; 1.27]	0.420	1.06 [0.81; 1.39]	0.668	55.8%	0.079	0.868
		GG vs. TT	1.75 [1.43; 2.14]	<0.001	1.67 [1.18; 2.37]*	0.004	61.1%	0.052	0.620
		Dominant	1.24 [1.06; 1.45]*	0.008	1.22 [0.96; 1.55]	0.099	49.0%	0.118	0.744
		Recessive	1.60 [1.35; 1.89]	<0.001	1.58 [1.08; 2.30]*	0.017	77.5%	0.004	0.920

* indicates significance; Value in BOLD was chosen

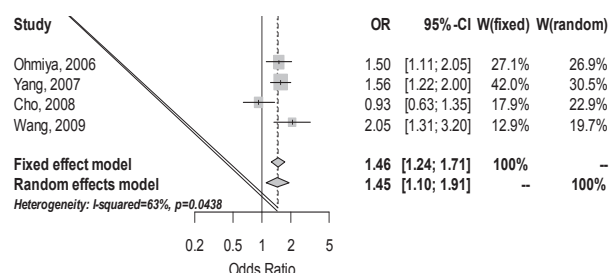


Figure 2. Forest Plot of the Association Between MDM2 309T>G Polymorphism and Risk of Gastric Cancer under Recessive Model from Studies Published in English

between the polymorphism and higher gastric cancer risk, two found no significance and the left one did not provide estimate effects directly. The basic characteristics of studies included were shown in Table 1.

Overall analysis

2,179 cases and 2,643 controls from 6 eligible case-control studies (Ohmiya et al., 2006; Yang et al., 2007; Cho et al., 2008; Li et al., 2010; Zhang et al., 2011; Er et al., 2012) revealed significant association between the gene variant and higher risk of gastric cancer under recessive model. A 43% increased risk was detected in GG genotype population (Recessive: OR = 1.43, 95% CI = 1.08-1.91, P = 0.013). Heterogeneity between studies was found under each genetic model (GT vs. TT: I² = 58.4%, P = 0.034; GG vs. TT: I² = 74.6%, P = 0.001; Dominant: I² = 64.3%, P = 0.016; Recessive: I² = 75.1%, P = 0.001), therefore, we chose results under random-effects model in analysis. There was no publication bias of overall studies (GT vs. TT: P = 0.558; GG vs. TT: P = 0.383; Dominant: P = 0.413; Recessive: P = 0.689), Figure 1.

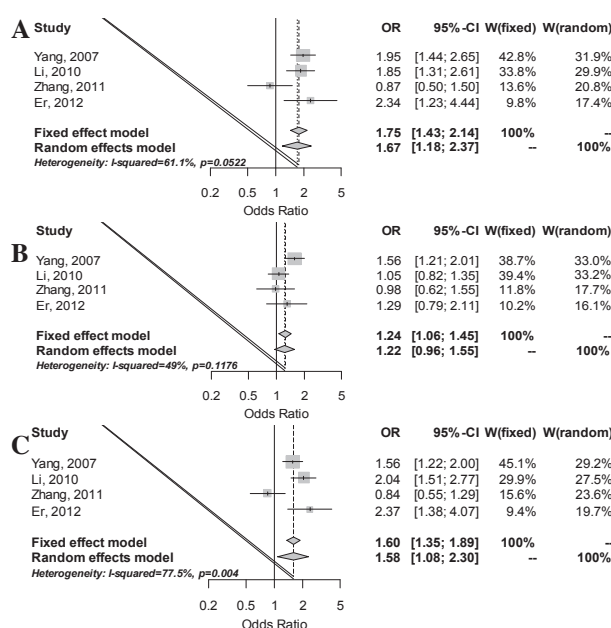


Figure 3. Forest Plots of the Association Between MDM2 309T>G Polymorphism and Risk of Gastric Cancer under (A) GG vs. TT Model, (B) Dominant Model, and (C) Recessive Model from Studies Conducted in China

Subgroup analysis

We performed 4 subgroup analysis stratified by study design, language and study location. No significance was detected in population-based and hospital-based studies no matter what kind of genetic model was used, Table 2. Heterogeneity between studies was found in every calculation except TG vs. TT and dominant models in hospital-based analysis (TG vs. TT: I² = 0%, P = 0.601; Dominant: I² = 0%, P = 0.543). No publication bias was

found in both population-based and hospital-based studies, Table 2.

In studies written in English, subgroup analysis suggested a 45% increase in gastric cancer risk under recessive model while no other calculation revealed such significance (Recessive: OR = 1.45, 95% CI = 1.10-1.91, $P = 0.009$). Moreover, when the study of Cho (Cho et al., 2008) was excluded, GG genotype carriers showed significance in increased gastric cancer risk under GG vs. TT and recessive model (GG vs. TT: OR = 1.70, 95% CI = 1.28-2.26, $P = 0.0003$; Recessive: OR = 1.61, 95% CI = 1.35-1.92, $P < 0.001$). All genetic models showed heterogeneity between studies while no publication bias was found, Table 2 & Figure 2.

Finally, we detected significant association between MDM2 309 polymorphism and higher susceptibility of gastric cancer under three models from studies conducted in China (GG vs. TT: OR = 1.67, 95% CI = 1.18-2.37, $P = 0.004$; Dominant: OR = 1.24, 95% CI = 1.06-1.45, $P = 0.008$; Recessive: OR = 1.58, 95% CI = 1.08-2.30, $P = 0.017$), and sensitivity assessment also indicated significance under GT vs. TT model after omitting Li's study (Li et al., 2010) (OR = 1.24, 95% CI = 1.00-1.54, $P = 0.05$). Heterogeneity existed but no publication bias was found under any model in this subgroup analysis, Figure 3 & Table 2.

Discussion

We revealed from the systematic meta-analysis of 2,179 cases and 2,643 controls that there is a significant increase (> 40%) in gastric cancer risk in GG genotype carriers; and subgroup analysis indicated statistically obvious association between MDM2 variant and gastric cancer risk from three genetic models in Chinese population and from recessive model of English publications. Actually, only two studies we identified reported no association between the two (Cho et al., 2008; Zhang et al., 2011).

Our meta-analysis has several limitations, one of which is that the final estimate effects calculated were crude ORs without adjustments. And we included studies published in Chinese in the analysis to pool with English publications because the existing studies were mainly performed in China. To avoid bias in final analysis, we conducted subgroup calculation based on English studies only and also found significant association between the polymorphism and higher gastric cancer risk under recessive model, which indicated the GG genotype was in significant inverse association with gastric cancer risk. Besides, we pooled studies concerning gastric cancer without differentiation in detailed cancer types because we intended to make a more complete coverage of the publication. Therefore, we could not conduct subgroup analysis stratified by distinct gastric cancer types. Finally, gastric cancer always correlated with *Helicobacter pylori* infection in Chinese population (Stolte et al., 1998; Crew et al., 2006; Yang et al., 2006), which we did not have sufficient information for subgroup analysis or adjustment.

During our calculation of the association, we found heterogeneity between studies almost in every group of analysis, revealing disparities among the studies we

included. Under this circumstance, we applied random-effects model in almost every calculation. On the other hand, we detected no publication bias in any analysis, which contributed to the strength and reliability of final results.

MDM2 regulates P53 by binding to its N terminus and promoting either p53 monoubiquitination and nuclear export or p53 polyubiquitination and degradation by the 26S proteasomal pathway; besides, MDM2 could regulate p53 via its interaction with L26 or directly by binding to the p53 mRNA (Gajjar et al., 2012). The polymorphism 309 T>G, found in the MDM2 promoter, was reported to increase the affinity of transcriptional activator Sp1, thus resulting in the higher expression of MDM2 and subsequent disturbance of MDM2-P53 feedback loop balance (Stommel et al., 2005). It is well-accepted that MDM2 amplification is associated with tumor formation. Therefore, the variant 309 T>G of MDM2 was believed to be associated with higher susceptibility to different types of malignancies (Bond et al., 2004). What needs to mention is that there is another polymorphism in the promoter of MDM2, SNP 285 G>C, which could reduce Sp1 transcription factor binding and diminish the expression of MDM2 (Knappskog et al., 2011; Knappskog et al., 2011). However, this gene variant rarely existed in Asian population and the studies we identified for analysis were all conducted in Asian, so we did not take the polymorphism into consideration.

Interestingly, although being responsible for elevated level of MDM2, the polymorphism 309 T>G did not always correlate with increased cancer risk. Liu reported that the variant G allele may act as a protective factor against head and neck squamous cell carcinomas in Caucasians and Chen also suggested the polymorphism seemed to be a favorable factor to prostate cancer risk in Europeans (Liu et al., 2011; Chen et al., 2012). The inconsistency reminded us of the different etiology and pathology of different types of cancers, in which the polymorphism probably played distinctive roles. Here, we should notice that the protective effects of MDM2 309 T>G against cancer risk were detected only in Caucasians, in which the other variant 285 G>C existed and would probably act as a confounding factor. And moreover, other gene backgrounds and living habits differences between Caucasian and other population may also be important aspects we should take into account.

In conclusion, we found a significant inverse association between gastric cancer risk and MDM2 309 T>G polymorphism under recessive models from 6 independent population, and English studies as well as those conducted in China also proved such relationship. More studies and detailed information are warranted to confirm our analysis with more comprehensive consideration of *Helicobacter pylori* infection status, gastric cancer types, complete gene backgrounds and living habits as well.

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

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