

RESEARCH COMMUNICATION

Association Between MDM2 Promoter SNP309 T/G Polymorphism and Liver Cancer Risk - a Meta-analysis

Hong-Bo Ma*, Tao Huang, Feng Han, Wei-Yu Chen

Abstract

Background: Many studies have investigated the association between the MDM2 promoter - SNP309 T/G polymorphism and liver cancer risk, but inconsistencies make drawing definitive conclusions difficult. **Methods:** We therefore searched main databases for articles relating MDM2 SNP309 T/G polymorphism to risk of liver cancer in humans and estimated summary odds ratio (OR) with 95% confidence intervals (95% CI) to assess the possible association in a meta-analysis. **Results:** The main analysis revealed no significant heterogeneity, and the pooled ORs of fixed-effects were all significant (for G versus T, OR = 1.59, 95% CI 1.42-1.78; for GG versus TT, OR = 2.45, 95% CI 1.93-3.12; for GT versus TT, OR = 1.70, 95% CI 1.38-2.09; for GG versus GT, OR = 1.49, 95% CI 1.24-1.79; for GG and GT versus TT, OR = 1.95, 95% CI 1.61-2.38; for GG versus TT and GT, OR = 1.73, 95% CI 1.46-2.07). Subgroup analyses by ethnicity and sensitivity analyses both showed associations to remain significant. **Conclusion:** The present meta-analysis of available data showed a significant association between the MDM2 SNP309 T/G polymorphism and liver cancer risk, the MDM2 SNP309 G allele contributing to increased risk in both Asians and Caucasians in a graded, dose-dependent fashion.

Keywords: Liver cancer - MDM2 - polymorphism - risk factor - meta-analysis

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Introduction

Liver cancer is the sixth most common cancer worldwide and the third most common cause of cancer mortality in 2008 (Chen, 2009; Jemal et al., 2011; Forner et al., 2012). Most liver cancer cases occur in Eastern Asia (Kimman et al., 2012; Wiangnon et al., 2012). Though regional efforts to control liver cancer, such as greater political and public awareness and improved management of lifestyle risk factor, have been adopted, the incidence of liver cancer is still the fastest growing of cancer in Eastern Asia (Bridges et al., 2011). Thus, liver cancer is a serious fatal disease worldwide and has caused serious damage to human health (Forner et al., 2012). As a complex and multi-factorial process, the liver carcinogenesis is still not fully understood (El-Serag, 2011; Forner et al., 2012). Major risk factors for the development of liver cancer are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), liver cirrhosis and exposure to aflatoxin B1 (El-Serag, 2011; Forner et al., 2012). However, many individuals with these known environmental risk factors never develop liver cancer while many liver cancer cases develop among individuals without those known risk factors, suggesting that genetic factors also play an important role in liver carcinogenesis (El-Serag, 2011; Forner et al., 2012).

Murine double minute 2 (MDM2) directly binds to p53 and acts as a crucial negative modulator for maintaining

function of p53 through regulating its location, stability, and activity (Deisenroth and Zhang, 2010; Lauria et al., 2010; Cheok et al., 2011). A subset of tumors over expresses MDM2, which is associated with accelerated cancer progression and poor prognosis (Deisenroth and Zhang, 2010; Lauria et al., 2010; Cheok et al., 2011). This increase in MDM2 results in the direct inhibition of p53 transcriptional activity, enabling damaged cells to escape the cell-cycle checkpoint and become carcinogenic (Deisenroth and Zhang, 2010; Lauria et al., 2010; Cheok et al., 2011).

A single nucleotide polymorphism (SNP) in the promoter region of MDM2, SNP309 T/G (a change from T to G, rs2279744) can create a higher affinity binding of transcription factor SP1 to this promoter region and increase in MDM2 gene transcription and subsequent attenuation of p53 pathway (Wilkening et al., 2007; Whibley et al., 2009). The polymorphism is suggested to be associated with the risk and early onset age of various human cancers including breast cancer, lung cancer and colorectal cancer (Hu et al., 2007; Wilkening et al., 2007; Economopoulos and Sergentanis, 2010; Fang et al., 2011).

In recent years, several studies focused on the association between MDM2 SNP309 T/G polymorphism and liver cancer risk (Dharel et al., 2006; Ezzikouri et al., 2009; Akkiz et al., 2010; Wang et al., 2012), but obvious inconsistency existed among those studies. Each of these studies typically involved a few cases and

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controls and failed to confirm a strong and consistent association. Meta-analysis is a statistical procedure for combining results from published studies to acquire a precise estimation of the major effect (Stroup et al., 2000). Thus, to assess the evidence regarding the association between MDM2 SNP309 T/G polymorphism and liver cancer risk, we conducted a comprehensive meta-analysis of epidemiological studies to shed some light on these contradictory results and to decrease the uncertainty of the effect size of the estimated risk.

Materials and Methods

Search strategy

We searched PubMed, Embase and CBM databases using the following search strategy: ('liver tumor' or 'liver cancer' or 'hepatocellular carcinoma') and ('MDM2' or 'SNP309' or '309T') and ('polymorphism' or 'polymorphisms' or 'mutation' or 'mutations' or 'SNP') for papers published from January 1980 to January 2012. There was no language limitation. The retrieved studies were manually screened in their entirety to assess their appropriateness for eligibility criteria. All references cited in the studies were also reviewed to identify additional published articles not indexed in common databases.

Study eligibility and exclusion criteria

Eligibility criteria included the following: (1) Case-control design with the genotyping of individuals with and without liver cancer; (2) provided information on genotype frequency of MDM2 SNP309 polymorphism; (3) in studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in the meta-analysis. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from this review. In addition, family-based association studies were excluded because they use different study designs.

Data extraction

Two investigators independently extracted data, and disagreements were resolved through consensus. The following information was extracted from included studies: the year of publication, ethnicity of the study population, definition of liver cancer, inclusion criteria for liver cancer patients and normal controls, demographics, matching, clinical status of controls, genotyping method, and the genotype distribution of cases and controls for the MDM2 SNP309 polymorphism. All data were extracted from published articles, and we did not contact individual authors for further information. To test the population stratification in the controls, a chi-square test using a web-based program (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>) was applied to determine if MDM2 SNP309 genotype distribution in the control population reported conformed to HWE ($P < 0.05$ was considered significant).

Statistical analysis

We performed a meta-analysis to investigate the association between MDM2 SNP309 polymorphism and

liver cancer risk under the allele contrast (G versus T), the recessive (GG versus TG and TT), dominant (GG and GT versus TT), homozygote (GG versus TT), heterozygote (GT versus TT), and additive (GG versus GT) models. We calculated the pooled odds ratio (OR) with the corresponding 95% confidence interval (95%CI) to assess the strength of the association between MDM2 SNP309 polymorphism and liver cancer risk. The significance of the pooled OR was determined by the Z test and a P value of less than 0.05 was considered significant. Two models of meta-analysis for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model (Mantel and Haenszel, 1959; DerSimonian and Laird, 1986), both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated (Cochran, 1954; Higgins et al., 2003) to assess the between-study heterogeneity. I^2 values of 25%, 50%, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). If moderate or high heterogeneity existed, the random-effects model was used to pool the results; otherwise, the fixed-effects model was used to pool the results when I^2 value was less than 50%. We also performed a cumulative meta-analysis to provide a framework for updating a genetic effect from all studies and to measure how much the genetic effect changes as evidence accumulates and find the trend in estimated risk effect (Muellerleile and Mullen, 2006; Zintzaras and Lau, 2008). Since HWE is a surrogate to assess study quality, and the effect of HWE is associated with problems in the design and conduct of genetic association studies, studies with departures from HWE were excluded in the sensitivity analyses. For additional analyses, the cases and controls were sub-grouped on the basis of their ethnicity. Ethnic descent was categorized into Caucasians, Asians, and others. Publication bias was investigated by funnel plot, and the funnel-plot's asymmetry was assessed by the method of Egger's linear regression test (Egger et al.,

Table 1. Summary of Odds Ratios (OR) with Confidence Interval (CI) in the Meta-analysis

Contrasts	No. of included studies	Odds Ratio OR[95%CI]	Heterogeneity P value	I^2 (%)	P value
Analyses of total studies					
G versus T	7	1.59(1.42-1.78)	<0.001	0%	0.532
GG versus TT	7	2.45(1.93-3.12)	<0.001	0%	0.745
GT versus TT	7	1.70(1.38-2.09)	<0.001	0%	0.716
GG versus GT	7	1.49(1.24-1.79)	<0.001	0%	0.945
GG and GT versus TT	7	1.95(1.61-2.38)	<0.001	0%	0.718
GG versus TT and GT	7	1.73(1.46-2.07)	<0.001	0%	0.863
Analyses in Asians					
G versus T	4	1.53 (1.34-1.74)	<0.001	0%	0.49
GG versus TT	4	2.25(1.71-2.97)	<0.001	0%	0.681
GT versus TT	4	1.55(1.20-2.01)	0.001	0%	0.857
GG versus GT	4	1.49(1.21-1.82)	<0.001	0%	0.702
GG and GT versus TT	4	1.83(1.43-2.33)	<0.001	0%	0.822
GG versus TT and GT	4	1.67(1.38-2.02)	<0.001	0%	0.666
Analyses in Caucasians					
G versus T	3	1.82(1.45-2.28)	<0.001	0%	0.604
GG versus TT	3	3.27(2.01-5.35)	<0.001	0%	0.835
GT versus TT	3	2.00(1.41-2.82)	<0.001	0%	0.433
GG versus GT	3	1.51(0.95-2.39)	0.079	0%	0.867
GG and GT versus TT	3	2.21(1.59-3.08)	<0.001	0%	0.367
GG versus TT and GT	3	2.10(1.36-3.25)	0.001	0%	0.952

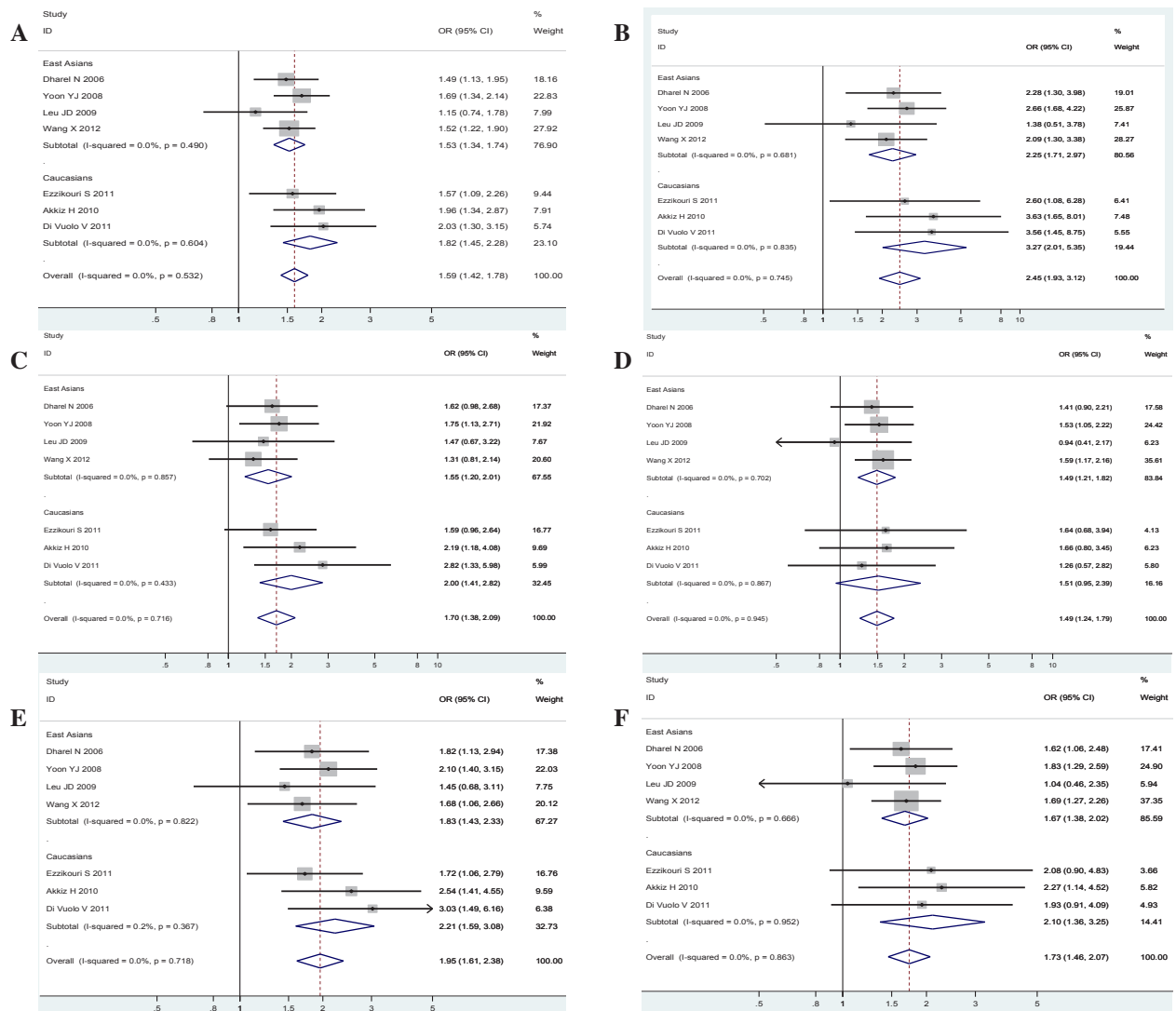


Figure 1. Forest Plots Showed Associations Between MDM2 SNP309 T/G Polymorphism and Risk of Liver Cancer (Results of individual and summary OR estimates, 95% CI and weights of each study were shown. Horizontal lines represented 95% CI and dotted vertical lines represent the value of the summary OR)

1997). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). A P value < 0.05 was considered statistically significant, except where otherwise specified.

Results

Characteristics of included studies

With our search criterion, 78 individual records were found, but only 8 full-text publications were preliminarily identified for further detailed evaluation (Dharel et al., 2006; Yoon et al., 2008; Ezzikouri et al., 2009; Leu et al., 2009; Akkiz et al., 2010; Di Vuolo et al., 2011; Ezzikouri et al., 2011; Wang et al., 2012). According to the exclusion criteria, 1 publication was excluded for containing overlapping data (Ezzikouri et al., 2011). Finally, data were available from 7 individual case-control studies with a total of 2725 subjects (Dharel et al., 2006; Yoon et al., 2008; Ezzikouri et al., 2009; Leu et al., 2009; Akkiz et al., 2010; Di Vuolo et al., 2011; Wang et al., 2012). These seven individual case-control studies were published from 2006 to 2012. The sample size arranged from 183 to 780, with a mean of 389. Ethnic groups among these studies

were as following: 4 (57.1%) were East Asians and 3 (42.9%) were Caucasians. The MDM2 SNP309 genotype distribution in the control population conformed to HWE ($P > 0.05$) in all studies except for one study (Leu et al., 2009). All 7 studies were published in English.

Meta-analysis results

Table 1 showed the results for the association between the MDM2 SNP309 T/G polymorphism and liver cancer risk (Table 1). The main analysis for investigating the association between the MDM2 SNP309 T/G polymorphism and liver cancer risk revealed no significant heterogeneity, and the fixed effects pooled ORs were all significant (For G versus T, fixed effects OR = 1.59, 95% CI 1.42-1.78; For GG versus TT, fixed effects OR = 2.45, 95% CI 1.93-3.12; For GT versus TT, fixed effects OR = 1.70, 95% CI 1.38-2.09; For GG and GT versus TT, fixed effects OR = 1.49, 95% CI 1.24-1.79; For GG and GT versus TT and GT, fixed effects OR = 1.95, 95% CI 1.61-2.38; For GG versus TT and GT, fixed effects OR = 1.73, 95% CI 1.46-2.07) (Figure 1). Sensitivity analyses by omitting that study with controls not in HWE did not materially alter the overall combined ORs (Data not shown). The cumulative meta-

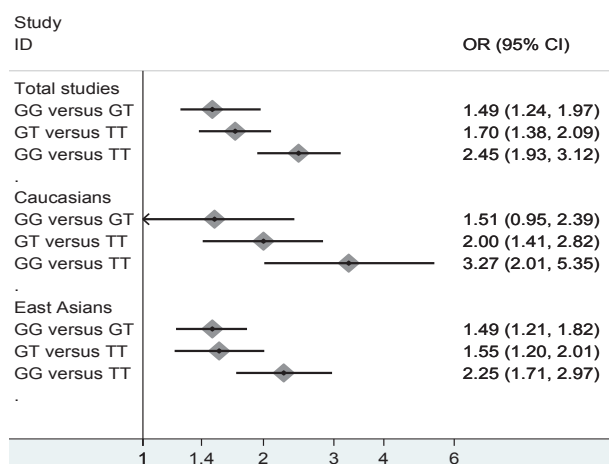


Figure 2. Pooled Risk Estimates for Liver Cancer Associated with the GT and GG Genotypes of MDM2 SNP309 Polymorphism Compared with the TT Genotype in the Total Studies, Caucasians and East Asian groups

analyses for the contrast models all showed a trend of association as information accumulated (Data not shown). Thus, MDM2 SNP309 T/G polymorphism contributed to liver cancer susceptibility under all contrast models. Besides, another finding of this analysis is that the MDM2 SNP309 T/G polymorphism is associated with increased risk of liver cancer in a graded, dose-dependent fashion (Table 1, Figure 2). In subgroup analysis by ethnicity, MDM2 SNP309 T/G polymorphism contributed to liver cancer susceptibility under all contrast models in Caucasians and Asians (Table 1).

Publication bias

Funnel plot and Egger’s test were both performed to assess the publication bias of this meta-analysis. The shape of the funnel plots for most genetic contrast models seemed symmetrical, and the outcomes from Egger’s test providing statistical evidence of funnel plot symmetry (Data not shown). Thus, publication bias was not evident in present meta-analyses.

Discussion

The strength of the present analysis investigating the relationship between the MDM2 SNP309 T/G polymorphism and susceptibility to liver cancer is based on the large amount of published data giving greater information to detect significant differences. In the present study, the consistency of genetic effects across populations from different ethnicities was investigated. And the cumulative meta-analyses were also performed. The stability in the relative changes in ORs indicates that there is enough evidence to draw safe conclusions about the risk effect of the MDM2 SNP309 T/G polymorphism in liver cancer. The main analysis revealed the pooled ORs of fixed-effects were all significant (For G versus T, OR = 1.59, 95% CI 1.42-1.78; For GG versus TT, OR = 2.45, 95% CI 1.93-3.12; For GT versus TT, OR = 1.70, 95% CI 1.38-2.09; For GG versus GT, OR = 1.49, 95% CI 1.24-1.79; For GG and GT versus TT, OR = 1.95, 95% CI 1.61-2.38; For GG versus TT and GT, OR = 1.73, 95%

CI 1.46-2.07). Besides, another finding of this analysis is that the MDM2 SNP309 T/G polymorphism polymorphic variant G is associated with increased risk of liver cancer in a graded, dose-dependent fashion (Table 1, Figure 2). Thus, these findings support a significant association between MDM2 SNP309 T/G polymorphism and liver cancer risk, and MDM2 SNP309 G allele contributes to increased risk of liver cancer in both Asians and Caucasians with a graded, dose-dependent fashion.

MDM2 protein is a direct negative regulator for the p53 tumor suppressor protein, which accounts for 50% of human cancers after loss of MDM2 function (Stommel and Wahl, 2005; Gajjar et al., 2012). This increase in MDM2 results in the direct inhibition of p53 transcriptional activity, enabling damaged cell to escape the cell-cycle checkpoint and become carcinogenic (Dongiovanni et al., 2010; Embade et al., 2012). Overexpression of MDM2 by up to four-fold in transgenic mice harboring wild-type p53 can lead to carcinogenesis (Stommel and Wahl, 2005; Gajjar et al., 2012). These findings suggest that MDM2 may play an important role in cancer development and progression (Jung et al., 2010; Embade et al., 2012). MDM2 SNP309 T/G is located 309 base pair downstream from intron 1 in the promoter of MDM2. SNP309 G allele has been shown to increase the affinity of Sp1, resulting in higher levels of MDM2 RNA and protein and subsequent attenuation of p53 pathway (Dharel et al., 2006). The G allele increases the binding affinity of Sp1 to the promoter of MDM2, resulting in increased MDM2 expression and attenuated the p53 tumor suppressor pathway, and thus increase the susceptibility of liver cancer (Dharel et al., 2006). Thus, there is obvious biochemical evidence supporting the association between MDM2 SNP309 T/G polymorphism and liver cancer risk. Besides, MDM2 overexpression is also associated with poor survival and is a useful predictive factor for poor prognosis in patients with liver cancer (Zhang et al., 2009), which further identified the role of MDM2 in liver carcinogenesis and progression.

As with all meta-analyses, our analysis had several limitations that must be considered when interpreting the finding. First, our main analysis was based on unadjusted estimates owing to lack of adjusted estimates. However, a more precise analysis could be performed if adjusted estimates were available in all studies. Second, as no prospective studies have addressed our question, all included studies followed a retrospective case-control design. Thus, the possible increased reporting bias associated with case-control studies could not be eliminated in this meta-analysis, and this aspect should be one of the limitations of our meta-analysis. Future prospective studies can investigate whether routine screening for the presence of MDM2 SNP309 T/G polymorphism can predicate the development of liver cancer. Finally, gene-gene and gene-environmental factors interactions were not fully addressed in this meta-analysis for the lack of sufficient data. HBV, HCV and several gene polymorphisms, such as P53 codon72, GSTM1 and GSTT1, are associated with liver cancer, and there may be gene-gene or gene-environmental factors interactions (Wang et al., 2010, Ding et al., 2012). However, we

could not perform gene-gene and gene-environmental analyses owing to the limited reported information on such associations in the included studies. Future studies may further assess the possible gene-gene and gene-environmental interactions. However, some possible limitations in our meta-analysis should be acknowledged.

Despite of those limitations, this meta-analysis suggests a significant association between MDM2 SNP309 T/G polymorphism and liver cancer risk, and MDM2 SNP309 G allele contributes to increased risk of liver cancer in both Asians and Caucasians with a graded, dose-dependent fashion.

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

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