Int J Clin Exp Med 2015;8(4):5822-5830
www.ijcem.com /ISSN:1940-5901/IJCEM0006632

*Original Article*

# MDM2 SNP309 variation confers the susceptibility to hepatocellular cancer: a meta-analysis based on 4271 subjects

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Received February 2, 2015; Accepted April 3, 2015; Epub April 15, 2015; Published April 30, 2015

**Abstract:** Previous reports have indicated that MDM2 T309G polymorphism might be a risk factor for various cancers. Increasing studies have been conducted on the association of MDM2 T309G polymorphism with hepatocellular carcinoma (HCC) risk. However, the results remain inconclusive. Thus, the present study aimed to address this controversy by meta-analysis. Relevant literature up to Oct 2014 was searched and screened. Necessary information was rigorously extracted for data pooling and analyzing. Separate analyses on ethnicity, source of controls, sample size and P53 polymorphism status were also performed. As a result, eleven case-control studies were selected and the overall data indicated a significant association of MDM2 T309G polymorphism with HCC risk (GG vs. TT: OR=2.31; 95% CI=1.66-3.20; dominant model: OR=1.83; 95% CI=1.36-2.47; recessive model: OR=1.73; 95% CI=1.49-2.00). Similar results could be shown in the subgroups regarding ethnicity, source of controls and sample size. Interestingly, in the subgroup analysis regarding P53 codon 72 polymorphism, increased HCC risk could be observed in the Pro/Pro+Pro/Arg subgroup under a recessive model (OR=1.78; 95% CI=1.29-2.44). In conclusion, the results of the present study suggest that MDM2 T309G polymorphism might be a low-penetrant risk factor for HCC. Homozygous GG alleles might interact with Pro of P53 and thus confer the susceptibility to HCC.

**Keywords:** MDM2 T309G, hepatocellular, carcinoma, susceptibility, meta-analysis, polymorphism

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the underlying mechanism for its genesis has been not fully understood. Evidence suggests that hepatitis B and C virus infection, exposure to aflatoxin B, cigarette smoking and alcohol consumption as well as liver fluke infection might be possible risk factors for HCC [1, 2]. Moreover, exposure to environmental polluted air and water is also thought to be one of the important risk factors [3]. However, though people are exposed to the environmental risk factors and life styles, HCC develops only in a small proportion of the exposed people, indicating that internal factors such as genetic variations might play a critical role in its carcinogenic mechanisms.

Previously, several genetic polymorphisms have been identified as risk factors for HCC by meta-analyses. Polymorphisms of TNFa, TP53 and XRCC1 have been reported to increase HCC risk [4-6]. Conversely, genetic variants of KIF1B and MTHFR might play a protective role in the genesis of hepatocellular carcinoma [7, 8]. Thus, the roles of genetic variation on cancer genesis vary from gene to gene.

P53 is a well-known tumor suppressor and murine double minute-2 (MDM2) is one of its key negative regulator that has been reported to be mutated in a variety of malignancies [9]. MDM2 can directly bind to the P53 protein and inhibit its activity, thus resulting in its degradation via the ubiquitination pathway [10]. A MDM2 single nucleotide polymorphism at the 309$^{th}$ nucleotide in the first intron (rs2279744), with a T to G change, could increase the affinity for stimulatory protein (Sp) 1 binding and thus result in increased MDM2 expression and subsequent attenuation of the P53 pathway [11]. The increased MDM2 protein expression can

cause suppression of P53 activity, enhancing the ability of damaged cells to escape the cell-cycle checkpoint. As a consequence, hepatocellular tumorigenesis might be initiated and developed.

A number of investigations have been conducted on the association of MDM2 T309G polymorphism with HCC risk. Nevertheless, the results were inconclusive. Two published meta-analyses on this issue in 2011 [12] and 2013 [13] including less than eight studies revealed a possible relationship between MDM2 T309G polymorphism and HCC risk. However, both the number of the included studies and the sample size were very small. Moreover, the results of the two meta-analyses were conflicting. Up to date, a growing number of relevant studies have been published. In the present study, we performed an updated meta-analysis that involved a total of eleven case-control studies considering more confounding factors with the published data up to Oct 2014 that might derive a more precise estimation of the relationship.

## Materials and methods

### *Literature search strategy*

We conducted an internet search in the databases such as Medline, EMBASE, OVID, Sciencedirect, and Chinese National Knowledge Infrastructure (CNKI) without a language limitation. Papers published up to Oct 2014 were covered. A combination of the following keywords was used for literature search: *Murine double minute-2, MDM2, hepatocellular, liver, neoplasm, tumor, cancer, variation* and *polymorphism*. All searched studies were retrieved and the bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand searched to find additional eligible studies.

### *Inclusion criteria*

The following criteria were used for the literature selection: first, studies should concern association of MDM2 T309G polymorphism with HCC risk; second, studies must be observational studies (case-control or cohort); and third, papers must offer the size of the sample, odds ratios (ORs) and their 95% confidence intervals (CIs), the genetic distribution or the information that can help infer the results. Conversely, papers with the following characteristics should be excluded: first, the design of the research was obviously different from those of the selected papers; second, the essential information for data collection and analysis was not offered; third, reviews or duplicated publications. After rigorous searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

### *Data extraction*

Relevant information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. For conflicting evaluations, an agreement was reached following a discussion. If a consensus could not be reached, another author was consulted to resolve the dispute and then a final decision was made by the majority of the votes. Extracted information was entered into a database.

### *Statistical analysis*

The odds ratio (OR) of MDM2 T309G polymorphism and HCC risk was estimated for each study. The pooled ORs were performed for a homozygote comparison model (GG versus TT), a dominant model (GG+GT versus TT) and a recessive model (GG versus GT+TT). For detection of any possible sample size bias, the OR and its 95% confidence interval (CI) for each study was plotted against the number of participants. A chi-square based Q statistic test was performed to assess heterogeneity. If $P>0.1$ for a given Q-test indicated a lack of heterogeneity among the studies, then ORs were pooled according to the fixed-effect model (Mantel-Haenszel) [14]. Otherwise, the random-effect model (DerSimonian and laird) was used [15]. The significance of the pooled ORs was determined using the Z-test. The Hardy-Weinberg equilibrium (HWE) was assessed via Fisher's exact test. Publication bias was assessed by visual inspection of funnel plots [16], in which the standard error of log (OR) of each study was plotted against its log (OR). In the plot was asymmetrical, a possible publication bias might exist. Symmetry of the funnel plot was further evaluated by Egger's linear regression test [17]. Statistical analysis was undertaken using the program STATA 11.0 software (Stata Corporation, Texas).

**Table 1.** Characteristics of studies included in the meta-analysis

| First author | Publication year | Number of cases (male/female) | Number of controls (male/female) | Type of controls | Mean age, year (cases/controls) | Racial decent | Country |
|---|---|---|---|---|---|---|---|
| Dharel | 2006 | 187 (119/68) | 48 (41/7) | Healthy controls (PB) | 65.0/59.0 | Asian | Japan |
| Yoon | 2008 | 287 (228/59) | 296 (236/60) | Non-cancerous controls (HB) | 52.3/36.7 | Asian | Korea |
| Ezzikouri | 2009 | 96 (58/38) | 222 (127/95) | Healthy controls (age-, sex-, ethnicity-matched; PB) | 59.3/56.4 | Mixed | Morocco |
| Leu | 2009 | 58 (45/13) | 138 (42/96) | Non-cancerous controls (HB) | 65.9/40.2 | Asian | China |
| Akkiz | 2010 | 110 (89/21) | 110 (89/21) | Healthy controls (gender-, age-, alcohol consumption-matched; PB) | 57.4/57.5 | Mixed | Turkey |
| Di Vuolo | 2011 | 61 (48/13) | 122 (122/0) | Non-cancerous controls (HB) | 68.7/59.4 | Caucasian | Italy |
| Tomoda | 2012 | 265 (182/82) | 203 (100/103) | Non-cancerous controls (HB) | 68.4/57.7 | Asian | Japan |
| Wang | 2012 | 310 (209/101) | 480 (338/142) | Healthy controls (PB) | 53.6/45.5 | Asian | China |
| Li | 2013 | 192 (170/22) | 192 (170/22) | Healthy controls (PB) | 47.7/47.6 | Asian | China |
| Wang | 2013 | 166 (133/33) | 157 (88/69) | Healthy controls (PB) | 55.0/52.0 | Asian | China |
| Yang | 2013 | 350 (311/39) | 96 (46/50) | Healthy controls (PB) | NA/NA | Asian | China |

NA: not available; PB: population-based; HB: hospital-based.

**Table 3.** Main results of the pooled data in the meta-analysis

| | No. (cases/ controls) | GG vs TT | | | (GG+GT) vs TT | | | GG vs (GT+TT) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *P* | *P* (Q-test) | OR (95% CI) | *P* | *P* (Q-test) | OR (95% CI) | *P* | *P* (Q-test) |
| Total | 2211/2060 | 2.31 (1.66-3.20) | 0.000 | 0.003 | 1.83 (1.36-2.47) | 0.000 | 0.000 | 1.73 (1.49-2.00) | 0.000 | 0.166 |
| Ethnicity | | | | | | | | | | |
| Asian | 1944/1606 | 2.08 (1.39-3.12) | 0.000 | 0.001 | 1.68 (1.14-2.48) | 0.009 | 0.000 | 1.69 (1.44-1.97) | 0.000 | 0.068 |
| Caucasian | 61/122 | 3.56 (1.45-8.75) | 0.006 | - | 3.03 (1.49-6.16) | 0.002 | - | 1.93 (0.91-4.09) | 0.087 | - |
| Mixed | 206/332 | 3.13 (1.74-5.64) | 0.000 | 0.580 | 2.02 (1.39-2.93) | 0.000 | 0.316 | 2.20 (1.29-3.74) | 0.004 | 0.877 |
| Source of controls | | | | | | | | | | |
| PB | 1547/1305 | 2.35 (1.42-3.89) | 0.001 | 0.001 | 1.76 (1.11-2.77) | 0.015 | 0.000 | 1.83 (1.52-2.21) | 0.000 | 0.107 |
| HB | 664/755 | 2.27 (1.66-3.12) | 0.000 | 0.380 | 1.95 (1.50-2.54) | 0.000 | 0.436 | 1.56 (1.23-1.98) | 0.000 | 0.442 |
| Sample size | | | | | | | | | | |
| <300 | 416/418 | 2.82 (1.82-4.42) | 0.000 | 0.460 | 2.21 (1.57-3.12) | 0.000 | 0.504 | 1.82 (1.25-2.64) | 0.000 | 0.506 |
| ≥300 | 1795/1642 | 2.15 (1.40-3.30) | 0.000 | 0.001 | 1.69 (1.13-2.54) | 0.011 | 0.000 | 1.71 (1.46-2.01) | 0.000 | 0.068 |
| P53 codon 72 polymorphism | | | | | | | | | | |
| Pro/Pro+Pro/Arg | 468/317 | 1.80 (0.70-4.63) | 0.223 | 0.023 | 1.24 (0.34-4.45) | 0.746 | 0.000 | 1.78 (1.29-2.44) | 0.000 | 0.977 |
| Arg/Arg | 299/210 | 1.46 (0.54-3.94) | 0.457 | 0.047 | 1.36 (0.80-2.34) | 0.259 | 0.196 | 1.23 (0.54-2.83) | 0.620 | 0.042 |

PB: population-based; HB: hospital-based.

**Table 2.** Distribution of MDM2 T309G genotype among hepatocellular cancer cases and controls included in the meta-analysis

| First author | Year | Genotyping method | Cases | | | Controls | | | HWE (control) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | GG | GT | TT | GG | GT | TT | Chi-squre | P |
| Dharel | 2006 | Taqman | 61 | 95 | 31 | 9 | 26 | 13 | 0.397 | >0.05 |
| Yoon | 2008 | PCR-RLFP | 117 | 125 | 45 | 81 | 132 | 83 | 3.457 | >0.05 |
| Ezzikouri | 2009 | PCR-RLFP | 11 | 46 | 39 | 13 | 89 | 120 | 0.438 | >0.05 |
| Leu | 2009 | PCR-RLFP | 10 | 37 | 11 | 23 | 80 | 35 | 3.907 | <0.05 |
| Akkiz | 2010 | PCR-RLFP | 29 | 56 | 25 | 15 | 48 | 47 | 0.239 | >0.05 |
| Di Vuolo | 2011 | PCR-RLFP | 16 | 32 | 13 | 19 | 48 | 55 | 2.325 | >0.05 |
| Tomoda | 2012 | MassArray | 88 | 129 | 41 | 56 | 96 | 47 | 0.219 | >0.05 |
| Wang | 2012 | PCR-RLFP | 165 | 116 | 29 | 193 | 216 | 71 | 0.687 | >0.05 |
| Li | 2013 | Taqman | 80 | 59 | 59 | 35 | 38 | 119 | 50.031 | <0.05 |
| Wang | 2013 | PCR | 37 | 94 | 35 | 21 | 87 | 49 | 3.287 | >0.05 |
| Yang | 2013 | Taqman | 140 | 192 | 148 | 27 | 50 | 19 | 0.230 | >0.05 |

## Results

*Study characteristics*

Possible relevant publications were retrieved and screened. As a result, a total of one hundred and sixty seven publications were identified, of which one hundred and forty seven irrelevant papers were excluded. Then, two review articles [12, 18] and four studies that were not related to polymorphism [19-22] were abandoned. Afterwards, one article that concerned a 40-bp insertion/deletion polymorphism of MDM2 rather than T309G polymorphism [23], and one study that was not being case-control designed [24] as well as a duplicate publication [25] were further discarded. Consequently, eleven studies regarding MDM2 T309G polymorphism with respect to HCC were selected [26-36].

Of the selected publications, all were written in English except for two articles that were written in Chinese [34, 35]. We established a database according to the extracted information from each study. The relevant information was listed in **Table 1.** According to this table, the first author and the number and characteristics of cases and controls for each study as well as other necessary information were presented.

In the included studies, there were one group of Caucasians [31], eight of Asians [26, 27, 29, 32-36] and two of mixed population [28, 30]. Information regarding P53 codon 72 polymorphism could be extracted from only two studies [27, 36].

The distributions of MDM2 T309G genotype as well as the genotyping methods of the included studies are presented in **Table 2.** The genetic distributions of the control groups in all studies were consistent with HWE except for two studies [29, 34].

*Test of heterogeneity*

As shown in **Table 3**, we analyzed the heterogeneity for the three genetic models. Evident heterogeneity was observed for overall data in the homozygote comparison model ($P$=0.003 for Q-test) and dominant model ($P$=0.000 for Q-test), except for the recessive model ($P$= 0.166 for Q-test). Thus, a fixed-effect model was used in the recessive model while a random-effect model was used in the remaining models, respectively.

However, when subgroup analyses regarding ethnicity, sample size and source of controls were further conducted, we found a reduced or loss of heterogeneity in some of the subgroups.

*Meta-analysis results*

**Table 3** lists the main results of the meta-analysis. The overall data in the homozygote comparison (OR=2.31; 95% CI=1.66-3.20; $P$=0.003 for heterogeneity), dominant (OR=1.83; 95% CI=1.36-2.47; $P$=0.000 for heterogeneity) and recessive (OR=1.73; 95% CI=1.49-2.00; $P$= 0.166 for heterogeneity) showed a marked association of MDM2 T309G polymorphism with HCC risk, indicating that individuals who

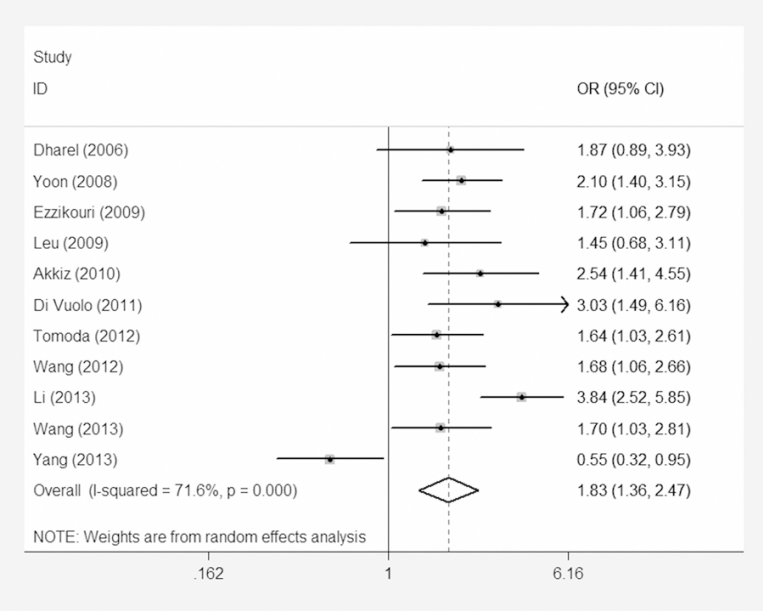


**Figure 1.** Meta-analysis for the association of HCC risk with MDM2 T309G polymorphism (GG+GT versus TT; overall data).

bear G allele might have an increased HCC risk compared with those who carry wild-type T allele (**Figure 1**).

In subgroup analyses (**Table 3**), when data were divided according to ethnicity, increased cancer risk was observed among Asians, Caucasians and mixed ethnicities, respectively. Likewise, when data were stratified by sample size and source of controls, significant increased cancer risk were also observed in the subgroups. Interestingly, we further assessed the possible effect of interaction between MDM2 T309G polymorphism and P53 codon 72 polymorphism on HCC risk. The data extracted from two studies showed that increased cancer risk could only be observed in the Pro/Pro+Pro/Arg subgroup under a recessive model (OR=1.78; 95% CI=1.29-2.44; *P*=0.977 for heterogeneity), indicating that individuals who bear both homozygous GG alleles and variants of TP53 (Pro) might have an increased HCC susceptibility compared with those who carry other genotypes.

*Sensitivity analysis*

When the effect-models were changed, the significance of the overall data for the three models was not statistically altered (data not shown). Next, we deleted the studies whose genetic distributions in controls deviated from HWE [29, 34]. The results were also not significantly changed. In addition, one-way sensitivity analysis [37] was also performed to evaluate the stability of the meta-analysis. The statistical significance of the results was not altered when any single investigation was deleted (data not shown), suggesting the stability and credibility of the results.

*Bias diagnostics*

Funnel plots were created for assessment of possible publication bias. Then, Egger's linear regression tests were used for assessment of the symmetries of the plots. The funnel plots appeared to be symmetrical for the overall data of the three models, respectively (**Figure 2A**). Additionally, results of the Egger's tests also support the notion that the funnel plots were symmetrical (GG vs. TT: t=-0.15, *P*>0.05; dominant model: t=-0.51, *P*>0.05; recessive model: t=0.25, *P*>0.05) (**Figure 2B**).

## Discussion

For the overall data, the results showed that MDM2 T309G might have a correlation with increased HCC risk. Moreover, the subgroup analyses revealed a possible interaction between MDM2 T309G and P53 codon 72 genetic variations.

Previous meta-analyses conducted on the association of MDM2 T309G polymorphisms with cancer risk showed that MDM2 T309G variation could increase risk of leukemia, gastric and colorectal cancer [38-40]. Conversely, variant G allele may play a preventive role for head and neck cancer and prostate cancer [41, 42]. Therefore, MDM2 T309G polymorphism might play different roles in the genesis of different cancers. As for HCC, a previous published meta-analysis in 2011 included only five studies comprising 738 cases and 1014 controls [12]. A recent published meta-analysis in 2013 containing eight case-control studies

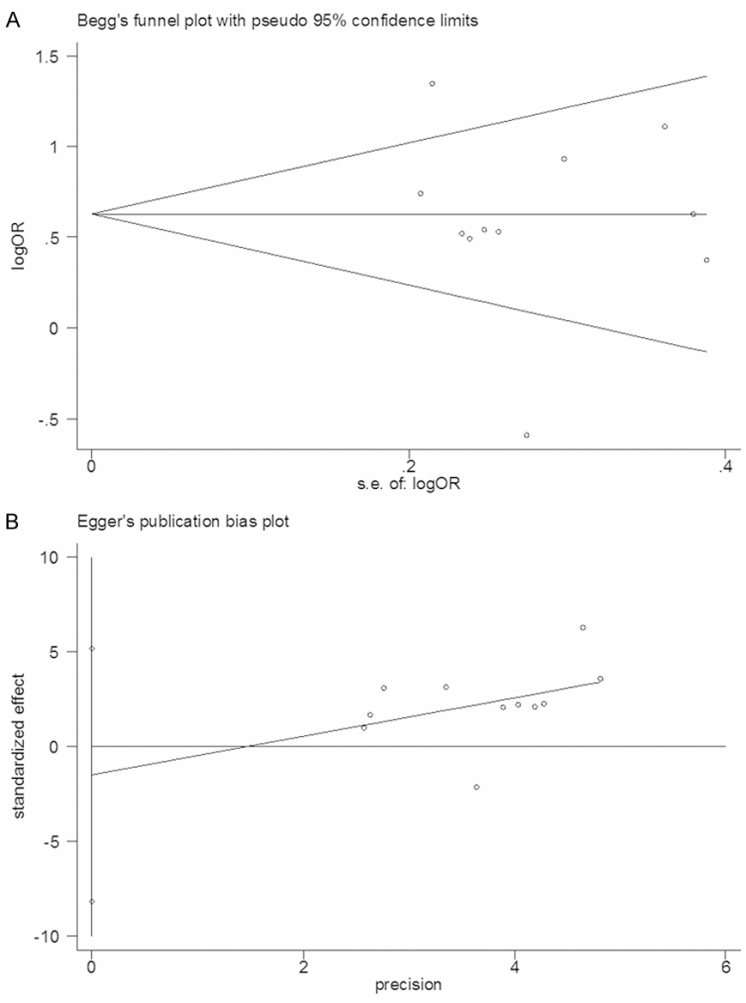


**Figure 2.** Publication bias test for the overall data (GG+GT versus TT; A: Funnel plot; B: Egger's linear regression test).

[13] showed the similar results and indicated that the increased HCC risk could be shown in Caucasians. Nevertheless, the results were inconclusive because of the limited sample sizes. In the present one, a total of eleven studies concerning 2211 cases and 2060 controls were involved. Obviously, the data may be more convincible due to the much larger number of the included studies and participants. Moreover, in addition to ethnicity and source of controls, subgroup analyses regarding sample size and P53 codon 72 polymorphism were also carried out. This might help to get a more confidential estimation.

When the data were stratified by ethnicity, marked increased cancer risk was observed among Asians, Caucasians and mixed population, consistent with the overall data. The results indicated that interactions between MDM2 polymorphism and ethnic variations might have little influence on HCC risk. However, MDM2 variations may differ among various ethnicities and exert different effects on cancer risk among different races [40]. Since this study only involved one Caucasian group with limited sample size, the results may be due to chance because the limited number of included studies and small sample size may give rise to insufficient statistical power to assess a minor effect. Therefore, the data should be interpreted with caution. Future investigations with large sample sizes on Caucasians are required to address this issue.

Since MDM2 is a negative regulator of tumor suppressor gene P53, several studies investigated the interaction between MDM2 T309G and a widely studied polymorphism of P53 (codon 72). The G to C SNP at TP53 codon 72 results in an arginine (Arg; CGC) or proline (Pro; CCC) polymorphism (rs1042522). This polymorphism is of particular interest owing to its functionality, although its biological function is controversial [43]. In the present analysis, information could be extracted from two included studies comprising 767 cases and 527 controls. Interestingly, the results suggested that the presence of both GG alleles and Pro might confer HCC risk, indicating a possible interaction of P53 with MDM2 polymorphism in the susceptibility to hepatocellular carcinoma. However, the sample size was small due to the limited number of the relevant studies. Further large sample studies are needed to evaluate the possible effects of gene-gene interactions on cancer risk.

In general, men are two to four times more often associated with HCC than women, indicating that sex hormones including progester-

one may play any roles in HCC [44]. Also, our recent meta-analysis revealed that MDM2 T309G genetic variation might confer lung cancer risk in a gender-specific manner [45]. MDM2 may act as a strong contributor through the P53-independent pathway during the process of estrogen-induced cell proliferation [46] that has been thought to play a role in the genesis of HCC [47]. However, the subgroup analysis according to gender and sex has not been conducted due to the lack of sufficient data in the primary studies. Moreover, the subgroup analysis regarding HBV or HCV infection has not been carried out on account of the same reason. Thus, relevant analyses need to be conducted in future primary research.

The present study has several limitations. First, in this meta-analysis, the subgroup analysis concerned only Caucasians, Asians and mixed population. Data about Caucasian could only be extracted from one study with small sample size. Therefore, a number of investigations on varied ethnicities are needed to clarify the potential effect of MDM2 ethnic variation on HCC susceptibility. Second, hospital-based controls were used in several included studies. Since they could not be always representative of the whole population, non-differential misclassification bias might exist. Third, though we endeavored to extract information regarding the confounding factors as we could for subgroup analysis, the data about age, gender, smoking, drinking and other factors were insufficient for use. Therefore, studies on the confounding factors and gene-gene and gene-environment interactions should also be performed in future studies.

In summary, in the present updated meta-analysis, the data indicated that MDM2 T309G genetic variation might increase HCC risk. Homozygous GG alleles might interact with variant Pro of P53 and contribute to elevated HCC susceptibility. Further investigations are required to test the association and get more confidential results.

## Acknowledgements

This work was partly supported by the special foundation for the 1130 Project of Xinqiao Hospital of Third Military Medical University (2012).

## Disclosure of conflict of interest

None.

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