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Association between MDM2 SNP309, p53 Arg72Pro, and hepatocellular carcinoma risk

A MOOSE-compliant meta-analysis

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Abstract

Epidemiological studies have determined the associations between polymorphisms on the promoter of MDM2 (SNP309) and the codon 72 on exon 4 of p53 (p53 Arg72Pro) and the risk of hepatocellular carcinoma (HCC); however, the results were not always consistent. The aim of the present meta-analysis was to evaluate the overall associations between these 2 variants and HCC risk.

The MEDLINE, Web of science, EMBASE, Cochrane Library, and CNKI databases were searched for eligibility studies and the data were synthesized under the fixed- or random-effects model. Heterogeneity among the studies was evaluated with the Cochrane test Q and I^2 statistic.

For MDM2 SNP309, the pooled odds ratio (OR) from 15 independent studies with a total of 4038 cases and 5491 controls suggested a significant association for the variant with HCC risk [allele model, G vs T: pooled OR = 1.48, 95% confidence interval (95% CI) = 1.26–1.73; pooled OR = 1.53, 95% CI = 1.26–1.81, for G/T vs T/T; pooled OR = 2.04, 95% CI = 1.54–2.71 for G/G vs T/T]. For p53 Arg72Pro, a total of 21 studies with 7285 cases and 9710 controls suggested that the variant was also associated with HCC risk under common genetic model (allele Pro vs Arg, pooled OR = 1.13, 95% CI = 1.02–1.25; Pro/Pro vs Arg/Arg, pooled OR = 1.32, 95% CI =1.06–1.64). No publication bias was found for all the meta-analysis as suggested by the Begg funnel plot and Egger tests.

These results suggested that variants MDM2 SNP309 and p53 Arg72Pro are susceptibility factors for HCC; however, more studies are warranted to validate the results.

Abbreviations: 95% CI = 95% confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MDM2 = murine double minute 2, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: hepatocellular carcinoma, MDM2 SNP309, meta-analysis, p53 Arg72Pro

1. Introduction

Liver cancer is the second leading cause of cancer deaths for men and the sixth for women worldwide. It was estimated that there were more than 782,500 new cases and 745,500 deaths occurring worldwide in 2012.[1] Seventy percent to 85% of the liver cancer cases were hepatocellular carcinoma (HCC).[2] It has been reported that chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, chronic alcohol consumption, aflatoxin-B1 (AFB1) contaminated food, and virtually all cirrhosis-inducing conditions are the major causes for HCC.[3] Other factors such as age, gender, long-term oral contraceptive use in women, certain metabolic disorder, diabetes, nonalcoholic fatty liver disorders, and genetic factors also contribute to the HCC development.[4] About 60% of the total liver cancer in the developing countries and 23% of the cases in the developed countries are caused by HBV infection.[5] Thirty-three percent of the liver cancer patients are HCV positive in the developing regions, while the number is 20% in the developed countries.[5] In China, about 350,000 new liver cancer patients were identified annually, which account for about half of the total cases worldwide.[1]

The oncogene mouse double minute 2 (MDM2), which plays multiple functions in promoting carcinogenesis, was identified 2 decades ago.[6] The gene has been found to be overexpressed in many human tumors and the elevated MDM2 levels are associated with carcinogenesis, aggressive tumor growth, and poor prognosis.[7] Tp53 is a nuclear phosphoprotein and functions as a sequence specific transcription factor.[8] It could transcript different subsets of target genes involved in apoptosis, growth arrest, DNA repair, and cellular differentiation procedures.[9] As a well-known tumor suppressor protein, it could be negatively regulated by MDM2.[10] MDM2 inhibits the transcription activity of p53 and promotes its nuclear export and degradation.[10] Nearly 50% of many human tumor types carry a p53 mutation, which can partially or completely abrogate the transcription ability of p53.[11,12] However, some mutations of p53 may gain the oncogenic properties, which are involved in the maintenance, the spreading, and the chemoresistance of the malignant tumors.[13] MDM2 is also a transcription target for

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p53 and thus an autoregulatory feedback loop exists between the 2 molecules.[14,15] Disruption of this autoregulatory loop, either through p53 mutations or overexpression of MDM2, has profound effects on tumorigenesis and cell survival, and was identified in many tumor cells.

The biological functions of a single-nucleotide polymorphism (rs2279744, T > G) in the promoter region of MDM2 were first reported by Bond et al.[16] For this locus, a T to G change extends the length of a putative Sp1 binding site, which leads to an increased affinity for Sp1 to this region.[16] It leads to an elevated level of MDM2 and subsequently the attenuation of p53 in the cell. And the variant has been found to be associated with an accelerated tumor formation both in hereditary and sporadic cancers.[16] Many studies have reported a significantly increased risk for MDM2 SNP309 in various types of cancer, including breast cancer,[17] lung cancer,[18] colorectal cancer,[19,20] gastric cancer,[21,22] cervical cancer, etc.[23,24] However, others studies found no such association.[25–28] For HCC, the SNP309 G allele was found to be significantly associated with an increased risk of HCC in the Turkish[29] and Moroccan[30] population, while no significant association was found in the Taiwanese population.[31] For p53, a common polymorphism rs1042522 at the codon 72 of exon 4 can lead to an amino acid change (Arg to Pro) of the protein.[32] An in vitro study has demonstrated that the minor allele Pro has a decreased ability in triggering apoptosis than Arg allele, which may influence cancer risk of the populations.[33] The polymorphism was reported to be significantly associated with an increased risk of lung cancer, melanoma, cervical cancer, gastric cancer, etc.[34] For HCC, there were no consistent results for the association between the HCC risk and the Arg72Pro variant. For instance, Yu et al[35] first evaluated the association of p53 Arg72Pro polymorphism and no overall increased HCC risk for Pro allele was found. However, Yoon et al[36] reported a significantly correlation between the Arg72Pro variant and HCC risk in patients with chronic HBV infection.

Thus, the aim of the present study was to perform a comprehensive assessment of the variants MDM2 SNP309 and p53 Arg72Pro and the HCC risk based on the published observational studies with the meta-analysis methods.

2. Materials and methods

2.1. Selection of studies

We performed a systematic search of the literatures before May, 2017, for MEDLINE, Web of science, EMBASE, Cochrane Library, and CNKI databases with the terms "liver cancer," "hepatocellular carcinoma" together with "MDM2," "mouse double minute 2," "p53," and"tp53" to identify potentially related studies that evaluated the association of SNP309 or p53 Arg72Pro with HCC risk. The references of the reports were also checked to identify any missing reports.

2.2. Selection criteria

Studies included should meet the following criteria: provided the frequency of the MDM2 SNP309 or p53 Arg72Pro allele in the participants; (2) had sufficient data for estimating an odds ratio (OR) with its 95% confidence interval (95% CI) for the 2 variants with HCC risk; should be case–control, cohort, or cross-sectional studies. Reviews, comments, conference abstracts, guides, etc. were excluded.

2.3. Data extraction

Information was carefully extracted from the eligible studies independently by 2 authors. The following basic data were extracted from those studies for further analysis: first author, published year, country of origin, study type, sample size, and the genotype distribution in cases and controls. In the subgroup study, the HBV and HCV status, the source of controls, and ethnicity were also extracted from the original reports.

2.4. Statistical analysis

Crude ORs and their 95% 95% CIs were used to assess the association between MDM2 SNP309 or p53 Arg72Pro and HCC risk. The inverse variance weighting method was used to get the pooled ORs with the fixed-effects model and the DerSimonian–Laird estimate was used in the random-effects model.[37] The pooled ORs were calculated under the allele contrast model, the additive model, the dominant model, and the recessive model. The heterogeneity between the studies was evaluated with the Q-test together with the I^2 statistic, which indicates the percentage of variability across the studies that is attributed to heterogeneity rather than chance. A P value less than .1 or I^2 statistic greater than 30% was considered significant heterogeneity between the studies. If there was no significant heterogeneity among the studies, the results for the fixed-effects model were reported; otherwise, the random-effects model was used. Publication bias was evaluated using the Begg funnel plot and further assessed with the Egger liner regression test.[38,39] For the sensitivity analysis, a single study was excluded from the meta-analysis each time to detect the influence of the individual study for the pooled ORs. The Hardy–Weinberg equilibrium of the control groups in each eligible study was tested using a fisher exact test. In this study, all of the statistical tests were conducted by the Stata software (version 12.0; Stata Corp., College Station, TX) and meta-analysis package.

3. Results

3.1. Characteristics of the selected studies

A total of 27 eligible studies were included in the meta-analysis (Fig. 1), with 15 papers reporting the association of MDM2 SNP309 with HCC risk,[29,31,36,40–51] 21 papers evaluating the association of p53 Arg72Pro with HCC risk,[35,36,40,41,43,45,49,50,52–64] and 7 papers evaluated both variants.[36,40,41,43,45,49,50] For MDM2 SNP309, a total of 4038 cases and 5491 controls were included in the 15 related studies (Table 1). Of them, 12 were hospital-based case–control studies and 3 were population-based case–control studies (Table 1). For p53 Arg72Pro, 21 studies were identified with a total of 7285 cases and 9710 controls, and 7 were population-based case–control studies and 14 hospital-based case–control studies (Table 2). Most of studies were conducted in the Asian populations, and no individual study was departure from the Hardy–Weinberg equilibrium for the selected variants in the control group.

3.2. Associations between variants MDM2 SNP309 and the HCC risk

The meta-analysis of the studies revealed that MDM2 SNP309 polymorphism was significantly associated with HCC. For G/T heterozygote, an increased risk of HCC was observed compared with the homozygote T/T (pooled OR = 1.53, 95%

Table 1

Main characteristics of the 15 studies in the meta-analysis for MDM2 SNP309 and HCC.

Study	Study type	Location	Ethnicity	Sample size (case/control)	Genotype distribution (case/control)		
					TT	GT	GG
Qiu et al [40]	HBCC	Guangxi, China	Asian	985/992	212/239	492/493	280/260
Su et al[41]	PBCC	Xiamen, China	Asian	160/160	23/49	80/71	57/40
Wang et al[43]	HBCC	Shenyang, China	Asian	286/375	57/124	132/168	97/83
Yang et al[45]	HBCC	Shanghai, China	Asian	350/326	89/78	176/166	85/82
Wang et al[42]	HBCC	Nanjing, China	Asian	166/157	35/49	94/87	37/21
Li et al[44]	HBCC	Ninbo, China	Asian	192/192	59/119	59/38	80/35
Wang et al[46]	HBCC	Harbin, China	Asian	310/794	29/113	116/345	165/336
Tomoda et al[47]	HBCC	Okayama and Kagawa, Japan	Asian	258/199	41/47	129/96	88/56
Di Vuolo et al[49]	HBCC	Naples, Italy	Caucasian	61/122	13/55	32/48	16/19
Akkiz et al[29]	PBCC	Adana, Turkey	Caucasian	110/110	25/47	56/48	29/15
Ezzikouri et al[48]	PBCC	Rabat and Casablanca, Morocco	African	96/222	39/120	46/89	11/13
Leu et al[31]	HBCC	Taiwan, China	Asian	58/138	11/35	37/80	10/23
Jiang [50]	HBCC	Jiangsu, China	Asian	526/1112	109/212	264/575	153/325
Yoon et al[36]	HBCC	Seoul, Korea	Asian	287/296	45/83	125/132	117/81
Dharel et al [51]	HBCC	Tokyo, Japan	Asian	187/296	31/75	95/151	61/70

HBCC = hospital-based case–control, PBCC = population-based case–control.

CI = 1.26–1.81, $P < .001$; Table 3). The G/G homozygosity carriers showed a 2.04-fold (pooled OR = 2.04, 95% CI = 1.54–2.71, $P < .001$; Fig. 2) increased risk of HCC compared with the homozygosity T/T carriers. Under the dominant model, the allele G carriers showed an increased risk of HCC (pooled OR = 1.73, 95% CI = 1.37–2.18, $P < .001$; Table 3). Under the recessive model, the pooled OR for G/G carriers compared with the G/T and T/T genotype carriers was 1.61 (OR = 1.61, 95% CI = 1.33–1.96, $P < .001$; Table 3). Significant heterogeneity between the studies was found for the meta-analysis studies (Table 3). In the stratification studies, statistically significant elevated risk was found in the hospital-based studies, the population-based studies, and the Asian populations for MDM2 SNP309 (Table 4). No publication bias was found according to the Begg funnel plot assessment, Egger linear regression test, and trim and fill method for the meta-analysis. The sensitivity studies found no significant effect of individual studies on the pooled estimates for the association between MDM2 SNP309 and HCC risk.

3.3. Associations between variants p53 Arg72Pro and the HCC risk

For p53 Arg72Pro, the meta-analysis showed a significant association between p53 Arg72Pro polymorphism and HCC risk in some comparative models. For Pro/Arg heterozygote, no risk of HCC was observed compared with the homozygote Arg/Arg (pooled OR = 1.08, 95% CI = 0.98–1.19, $P = .132$; Table 3). However, the Pro/Pro homozygosity carriers showed a 1.30-fold

Table 2

The main characteristics of the 21 studies that evaluated the p53 Arg72Pro and HCC risk.

Study	Study type	Location	Ethnicity	Sample size (case/control)	Genotype distribution (case/control)		
					Arg/Arg	Arg/Pro	Pro/Pro
Cai et al [52]	HBCC	Sichuan, China	Asian	342/347	63/65	167/173	112/109
Qiu et al [40]	HBCC	Guangxi, China	Asian	985/992	221/244	501/498	263/250
Su et al [41]	PBCC	Xiamen, China	Asian	160/160	13/29	86/78	61/53
Son et al [54]	PBCC	Korean	Asian	157/201	52/61	88/110	17/30
Wang et al [43]	HBCC	Shenyang, China	Asian	286/375	61/115	148/187	77/73
Yang et al [45]	HBC	Shanghai, China	Asian	350/326	103/117	174/160	73/49
Mohana Devi et al [55]	HBCC	South India	Caucasian	93/93	67/75	21/14	5/4
Mou and Zhang [53]	HBCC	Jinan, China	Asian	280/596	78/215	110/297	92/78
Zhang et al [56]	HBCC	Guangxi, China	Asian	985/992	221/244	501/498	263/250
Sumbul et al [57]	PBCC	Adana, Turkey	Caucasian	119/119	46/49	52/63	21/7
Di Vuolo et al [49]	HBCC	Naples, Italy	Caucasian	61/122	38/71	20/42	3/9
Xu et al [58]	PBCC	Jiangsu, China	Asian	501/548	152/162	245/262	104/124
Yoon et al [36]	HBCC	Seoul, Korea	Asian	287/296	110/124	111/135	66/37
Jiang [50]	HBCC	China	Asian	1375/2352	434/699	706/1134	235/519
Ezzikouri et al [59]	PBCC	Morocco	African	96/222	52/129	31/79	13/14
Zhu et al [60]	HBCC	Shanghai, China	Asian	246/549	65/184	133/280	48/85
Zhu et al [61]	HBCC	Shanghai, China	Asian	507/541	145/188	273/270	89/83
Leveri et al [63]	HBC	Lombardy, Italy	Caucasian	86/254	46/122	33/113	7/19
Peng et al [62]	PBCC	GuangxiChina	Asian	192/192	81/54	69/91	42/47
Anzola et al [64]	PBCC	Spain	Caucasian	97/111	46/65	47/42	4/4
Yu et al [65]	HBNCC	Taiwan, China	Asian	80/328	28/112	35/141	17/75

HBC = hospital-based cohort, HBCC = hospital-based case–control, HBNCC = hospital-based nest case–control, PBCC = population-based case–control.

Table 3

The main results for the meta-analysis of the variants and HCC risk in total studies.

Category	Studies	Genetic model	OR (95% CI)	*P*	Q/df	P_Q	I^2	*P* of Begg test	*P* of Egger test
		G vs T	1.48 (1.26–1.73)*	<.001	89.26/14	<.001	84.3%	.138	.009†
		TT	1						
MDM2 SNP309	15	GT	1.53 (1.26–1.81)*	<.001	39.32/14	<.001	64.4%	.048	.002†
		GG	2.04 (1.54–2.71)*	<.001	65.97/14	<.001	78.8%	.373	.011†
		Dominant	1.73 (1.37–2.18)*	<.001	64.33/14	<.001	78.2%	.113	.007†
		Recessive	1.61 (1.33–1.96)*	<.001	30.37/13	.004	57.2%	.322	.028†
		Pro vs Arg	1.13 (1.02–1.25)*	.016	78.94/20	<.001	74.7%	.952	.149
p53 Arg72Pro	21	ArgArg	1						
		ArgPro	1.08 (0.98–1.19)*	.132	30.48/20	.062	34.4%	.763	.747
		ProPro	1.32 (1.06–1.64)*	.013	87.45/20	<.001	77.1%	.717	.133
		Dominant	1.13 (1.01–1.27)*	.029	43.91/20	.002	54.4%	.717	.270
		Recessive	1.24 (1.03–1.50)*	.024	89.79/20	<.001	77.7%	.506	.122

CI = confidence interval, OR = odds ratio.

* Random-effects model.

† Trim and fill method validation.

(pooled OR = 1.30, 95% CI = 1.06–1.64, *P* = .013; Table 3, Fig. 3) increased risk of HCC compared with the homozygosity Arg/Arg carriers. Under the dominant model, the Pro carriers showed an increased risk of HCC (pooled OR = 1.13, 95% CI = 1.01–1.27, *P* = .029; Table 3). Under the recessive model, the pooled OR for Pro/Pro compared with the Pro/Arg and Arg/Arg carriers was 1.24 (OR = 1.24, 95% CI = 1.03–1.50, *P* = .024; Table 3). The sensitivity studies suggested that no individual study significantly affected the pooled estimates of the meta-analysis studies (data not shown). In the stratified studies, a significant association for p53 Arg72Pro and HCC risk was found in the hospital-based case–control studies but not in the population-based case–control studies (Pro/Pro vs Arg/Arg OR = 1.35, 95% CI = 1.05–1.74, *P* = .018; the recessive model OR = 1.27, 95% CI = 1.01–1.59, *P* = .043, Table 4). No publication bias was found in all the meta-analysis as suggested by the Begg funnel plot, Egger test, and trim and fill method.

3.4. The influence of hepatitis virus status on the association between the variants and HCC risk

As the hepatitis virus HBV and HCV infection are high penetrance risk factors for HCC, we explored the impacts of the HBV and HCV status on the associations between the variants and HCC risk. Four studies with 2150 HBV-positive HCC patients and 2037 HBV-negative healthy controls have determined the association between the MDM2 SNP309 and HCC risk and no significant association was found (allele G vs T,

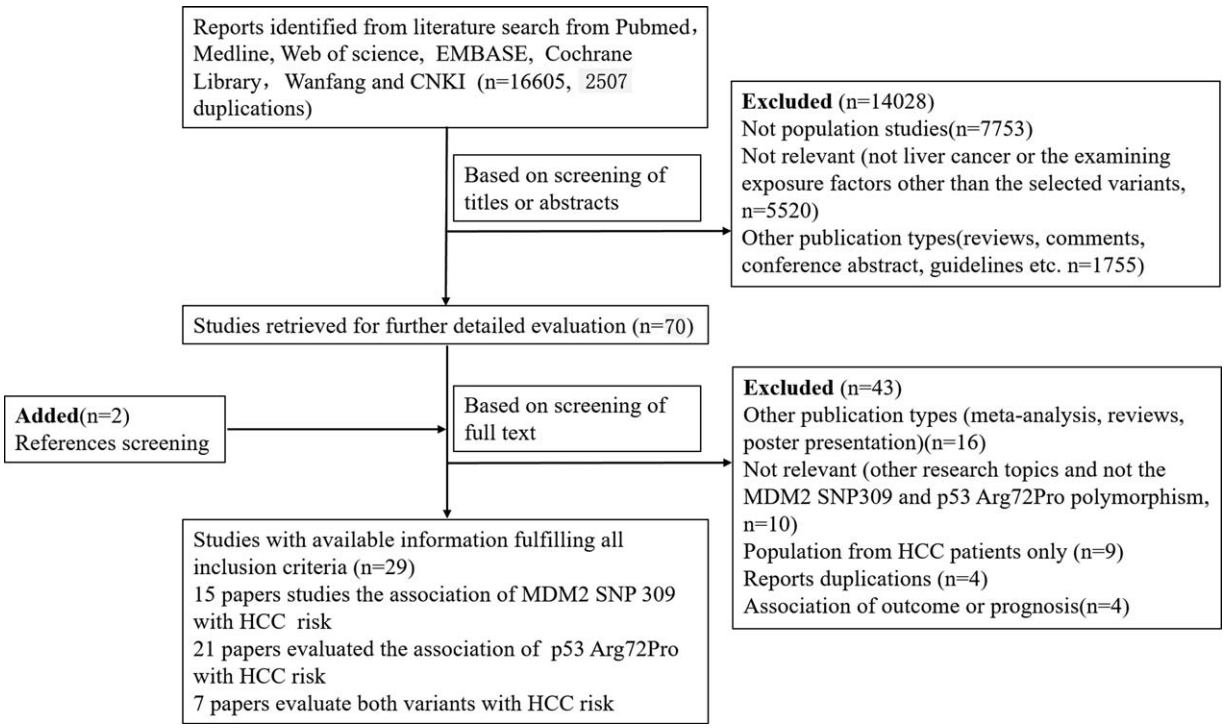

Figure 1. The working flow chart for the identification of the studies included in the meta-analysis.

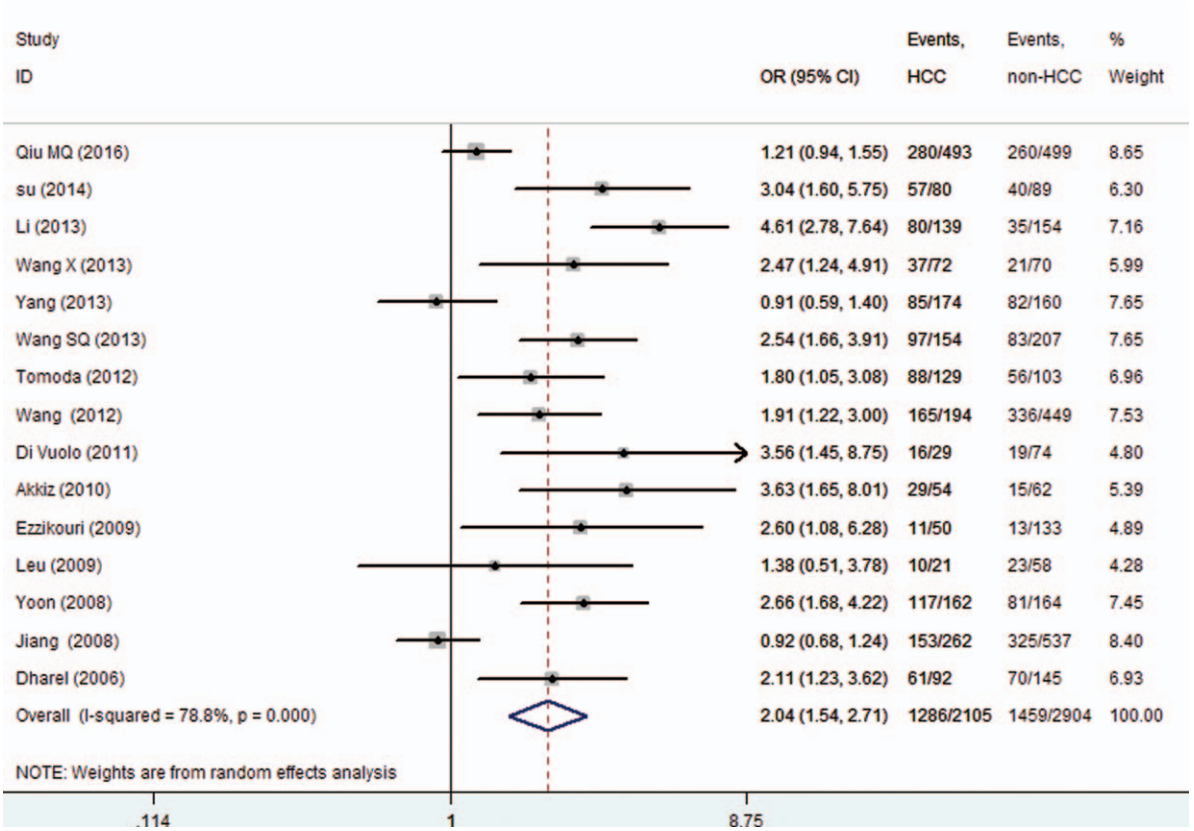

Figure 2. The forest plot of meta-analysis results of variances MDM2 SNP309 and HCC risk (GG vs TT, random-effects model).

pooled OR = 1.13, 95% CI = 0.94–1.37; Q = 11.21, df = 3, $P = .011$; $I^2 = 73.2\%$; Table 5). Five studies with 2440 HBV-positive HCC patients and 1572 HBV-positive controls have evaluated the association between MDM2 SNP309 and HCC risk. The pooled OR was 1.13 (95% CI = 0.94–1.37) for allele G versus T and 1.27 (95% CI = 0.59–2.72) for GG+GT versus TT (dominant model, Table 5). For those participants with positive HCV status (500 cases and 508 controls), a significant increased risk was found in those participants with allele G carriers (pooled OR = 1.44, 95% CI = 1.21–1.73; allele G vs T; Table 5). The pooled OR was 1.77 (95% CI = 1.33–2.36) under the dominant model with no significant heterogeneity among the studies being noticed (Table 5).

Eleven studies with a total of 7642 HBV-positive HCC patients and 7797 HBV-negative health controls have determined the association between the p53 Arg72Pro and HCC risk with no significant association being noticed under any genetic model. Nine studies have compared the allele distribution for p53 Arg72Pro in the 7567 HBV-positive HCC patients and 5401 HBV-positive healthy controls with no significant association being noticed (Table 5). In addition, no significant association was noticed between the p53 Arg72Pro and the risk for HCC in HCV-positive participants (Table 5).

4. Discussion

As an E3 ubiquitin ligase, MDM2 could bind to p53 with high affinity and promote the monoubiquitination of p53, which results in the degradation of p53 by the 26S proteasome.[10,65,66] And MDM2 could bind the N-terminal transactivation domain to inhibit the transcriptional activity of p53.[67] However, p53 could positively regulate the MDM2 at the mRNA level in the cells.[14,15] The autoregulatory loop between MDM2 and p53 was stringently regulated in the normal cells. Under conditions of oncogene activation, MDM2 overexpression or p53 mutation, which leads to a disruption of the autoregulatory loop, may cause tumorigenesis of the cell. MDM2 could also induce the tumorigenesis in the p53-independent pathways.[68] MDM2 has also been suggested to hold p53-independent functions and it could modulate other important proteins including p21, E2F1, and pRB to promote the tumorigenesis.[60,69,70]

The present meta-analysis indicated that the 2 gene polymorphism loci MDM2 SNP309 and p53 Arg72Pro were significantly associated with the HCC risk. A T to G change of MDM2 SNP309 could increase the affinity of the transcriptional activator Sp1 with the promoter of MDM2, which could lead to an increased expression of MDM2 and a downregulation of the p53.[71] It has been reported that the MDM2 SNP309 was not only associated with an increased risk with breast cancer, gastric carcinoma, and lung cancer, but it may also modify the prognostic of many cancer types.[72–75] For the 15 independent studies regarding the association of MDM2 SNP309 and liver cancer risk, there was significant association of the variant with HCC risk in the Moroccan, Japanese, Korean, Turkish, and partial Chinese populations.[29,31,36,40–51] No significant association was found in the Chinese population reported by Leu et al,[31] Jiang,[50] Yang et al,[45] which may be due to the relatively small sample size in the study. The present meta-analysis indicates that MDM2-SNP309 significantly correlates with liver cancer under the co-dominant, dominant, and the

Table 4

Subgroup meta-analysis stratified by the ethnicity and the source of control for the variants.

Category	Studies	Genetic model	OR (95% CI)	*P*	Q/df	P_Q	I^2	*P* of Begg test	*P* of Egger test
MDM2 SNP309									
		G vs T	1.41 (1.19–1.68)*	<.001	79.79/11	<.001	86.2%	.244	.064
		TT	1						
		GT	1.45 (1.18–1.79)*	.001	32.49/11	.001	66.1%	.115	.029‡
Asian	12	GG	1.88 (1.38–2.55)*	<.001	58.06/11	<.001	81.1%	.373	.046‡
		Dominant	1.63 (1.26–2.10)*	<.001	56.30/11	<.001	80.5%	.304	.039‡
		Recessive	1.45 (1.21–1.75)*	<.001	35.42/11	<.001	68.9%	.373	.093
		G vs T	1.74 (1.42–2.12)†	<.001	0.68/2	.712	0.0%	1.000	.807
		TT	1						
Population-based study	3	GT	1.98 (1.43–2.74)†	<.001	1.23/2	.540	0.0%	1.000	.270
		GG	3.10 (2.01–4.78)†	<.001	0.31/2	.856	0.0%	1.000	.867
		Dominant	2.19 (1.61–2.99)†	<.001	1.61/2	.446	0.0%	1.000	.215
		Recessive	1.88 (1.32–2.69)†	.001	0.59/2	.743	0.0%	1.000	.356
		G vs T	1.42 (1.19–1.70)*	<.001	80.50/11	<.001	86.3%	.244	.037‡
		TT	1						
		GT	1.45 (1.17–1.79)*	.001	32.41/11	.001	66.1%	.150	.013‡
Hospital-based study	12	GG	1.88 (1.38–2.56)*	<.001	57.23/11	<.001	80.8%	.304	.048‡
		Dominant	1.63 (1.26–2.11)*	<.001	55.97/11	<.001	80.3%	.304	.037‡
		Recessive	1.46 (1.21–1.76)*	<.001	35.56/11	<.001	69.1%	.451	.095
P53 Arg72Pro									
Asian	15	Pro vs Arg	1.12 (1.00–1.25)*	.05	72.01/14	<.001	80.6%	.458	.177
		ArgArg	1						
		ArgPro	1.09 (0.97–1.21)*	.144	24.79/14	.037	43.5%	.805	.694
		ProPro	1.29 (1.01–1.62)*	.043	79.27/14	<.001	82.3%	.656	.134
		Dominant	1.14 (1.00–1.30)*	.053	38.76/14	.001	63.9%	.656	.263
		Recessive	1.19 (0.98–1.46)*	.085	79.58/14	<.001	82.4%	.729	.142
		Pro vs Arg	1.14 (0.94–1.39)†	.181	5.30/4	.258	24.6%	1.000	.905
		ArgArg	1						
		ArgPro	1.05 (0.81–1.37)†	.710	5.52/4	.238	27.6%	.221	.375
Caucasian	5	ProPro	1.45 (0.89–2.35)†	.136	4.85/4	.303	17.6%	1.000	.520
		Dominant	1.10 (0.86–1.42)†	.438	5.07/4	.280	21.1%	.462	.472
		Recessive	1.52 (0.95–2.43)†	.081	5.42/4	.247	26.2%	.806	.318
		Pro vs Arg	1.07 (0.88–1.30)*	.496	17.00/6	.009	64.7%	.548	.211
		ArgArg	1						
Population-based study	7	ArgPro	1.02 (0.75–1.38)*	.915	16.99/6	.009	64.7%	.368	.474
		ProPro	1.28 (0.78–2.08)*	.332	21.18/6	.002	71.7%	.368	.188
		Dominant	1.07 (0.79–1.45)*	.669	18.47/6	.005	67.5%	.035	.264
		Recessive	1.17 (0.83–1.65)*	.374	14.48/6	.025	58.6%	.230	.193
		Pro vs Arg	1.16 (1.03–1.30)*	.016	60.60/13	<.001	78.5%	.870	.152
		ArgArg	1						
		ArgPro	1.10 (1.01–1.19)†	.023	12.02/13	.526	0.0%	1.000	.613
Hospital-based study	14	ProPro	1.35 (1.05–1.74)*	.018	65.19/13	<.001	80.1%	.870	.189
		Dominant	1.17 (1.04–1.31)*	.007	23.69/13	.034	45.1%	.870	.209
		Recessive	1.27 (1.01–1.59)*	.043	74.91/13	<.001	82.6%	.477	.190

CI = confidence interval, OR = odds ratio.

* Random-effects model.

† Fixed-effects model.

‡ Trim and fill method validation.

recessive genetic model. It was consistent with a previous study by Jin et al,[76] which reported a significant association between the MDM2 SNP309 and the HCC risk with the pooled OR equal to 1.57 (95% CI = 1.36–1.80) for allele G compared with the allele T.

P53 Arg72Pro, which leads to an amino acid change at the codon 72 of the exon 4 for p53 protein, has been found to be associated with different properties of p53 functions. The Arg allele has more efficiency in apoptosis induction under genotoxic stress than the Pro allele.[33] Furthermore, as an evolutionarily conserved inhibitor of p53, inhibitor of apoptosis-stimulating protein of p53 could bind to and regulate the activity of p53 Pro72 more efficiently than that of Arg allele.[77] These may lead to the decreased activity of apoptosis for the Pro allele. On the basis of the in vitro studies, it could be expected that the Pro allele would be associated with an increased susceptibility of many cancer types. A previous meta-analysis indicates that the Pro/Pro genotype was associated with an increased risk of thyroid, gastric, head, and neck cancer.[34] For hepatocarcinoma, the meta-analysis showed that the Pro/Pro genotype conferred a 32% increased risk of HCC (OR = 1.32, 95% CI = 1.06–1.64) compared with the Arg/Arg carriers with a total, in the stratified studies; however, a significant association for p53 Arg72Pro and HCC risk was found in the hospital-based case–control studies but not in the population-based case–control studies (Pro/Pro vs Arg/Arg OR = 1.35, 95% CI = 1.05–1.74; the recessive model OR = 1.27, 95% CI = 1.01–1.59, Table 4).

Table 5

The main meta-analysis results of HBV or HCV-related HCC with different controls.

Category	Studies	Genetic model	Pooled OR (95% CI)	*P*	Q/df	P_Q	I^2	*P* of Begg test	*P* of Egger test
HBV-positive MDM2 SNP309									
		G vs T	1.13 (0.94–1.37)*	.205	11.21/3	.011	73.2%	1.000	.738
		TT	1						
Health controls	4	GT	1.05 (0.88–1.24)†	.603	3.25/3	.335	7.7%	.734	.584
		GG	1.23 (0.88–1.72)*	.219	7.95/3	.047	62.3%	1.000	.691
		Dominant	1.27 (0.59–2.72)*	.548	55.69/3	.049	94.6%	.308	.421
		Recessive	1.05 (0.54–2.04)*	.880	60.06/3	<.001	95.0%	.089	.098
		G vs T	1.20 (0.98–1.47)*	.084	16.89/4	.002	76.3%	.462	.295
		TT	1						
HBV-positive controls	5	GT	1.18 (0.98–1.42)†	.077	5.31/4	.257	24.6%	.221	.206
	5	GG	1.41 (0.95–2.07)*	.085	14.48/4	.006	72.4%	.462	.333
	5	Dominant	1.30 (0.97–1.74)*	.078	10.72/4	.030	62.7%	.221	.239
	5	Recessive	1.21 (0.96–1.54)*	.107	10.02/4	.040	60.1%	.221	.554
p53 Arg72Pro									
	8	Pro vs Arg	1.14 (0.93–1.40)*	.211	43.85/7	<.001	84.0%	.266	.256
		ArgArg	1						
Health controls	8	ArgPro	1.02 (0.90–1.14)†	.791	9.82/7	.199	28.7%	.174	.449
	8	ProPro	1.42 (0.91–2.21)*	.126	48.23/7	<.001	85.5%	.174	.114
	11	Dominant	1.09 (0.94–1.26)*	.270	19.33/10	.036	48.3%	.392	.556
	8	Recessive	1.43 (0.95–2.15)*	.086	53.15/7	<.001	86.8%	.108	.089
		Pro vs Arg	1.14 (0.93–1.39)*	.213	41.88/8	<.001	80.9%	1.000	.209
		ArgArg	1						
HBV-positive controls	9	ArgPro	0.98 (0.87–1.11)†	.761	3.30/8	.914	0.0%	.754	.714
	9	ProPro	1.38 (0.88–2.17)*	.164	50.55/8	<.001	84.2%	1.000	.152
	11	Dominant	1.00 (0.90–1.12)†	.969	11.06/10	.353	9.6%	.484	.648
	9	Recessive	1.40 (0.90–2.19)*	.137	63.56/8	<.001	87.4%	.917	.128
HCV-positive MDM2 SNP309									
HCV-positive controls	3	G vs T	1.44 (1.21–1.73)†	<.001	1.35/2	.508	0.0%	.951	.451
		TT	1						
	3	GT	1.68 (1.22–2.32)†	.002	0.72/2	.698	0.0%	.296	.081
	3	GG	2.10 (1.44–3.05)†	<.001	0.93/2	.629	0.0%	.296	.394
	4	Dominant	1.77 (1.33–2.36)†	<.001	0.98/3	.805	0.0%	1.000	.724
	3	Recessive	1.49 (1.12–1.98)†	.007	0.89/2	.640	0.0%	.296	.481
p53 Arg72Pro									
		Pro vs Arg	0.96 (0.72–1.27)†	.763	0.32/2	.851	0.0%	.296	.036‡
		ArgArg	1						
HCV-positive controls	3	ArgPro	0.80 (0.55–1.18)†	.262	0.04/2	.980	0.0%	.296	.052
		ProPro	1.17 (0.61–2.26)†	.640	0.43/2	.805	0.0%	.296	.047‡
		Dominant	0.86 (0.60–1.23)†	.403	0.14/2	.932	0.0%	.296	.104
		Recessive	1.30 (0.69–2.46)†	.416	0.43/2	.807	0.0%	.296	.103

HBV = hepatitis B virus, HCV = hepatitis C virus.
* Random-effects model.
† Fixed-effects model.
‡ Trim and fill method validation.

In previous meta-analysis studies, the effects of the sources of the controls have drawn less attention. As the HBV and HCV are major risk factors for HCC, we explored the associations between the variants and HCC risk in participants with different HBV or HCV infection status. In the present study, the controls were divided into 2 groups, those with positive hepatitis virus status and those with health controls without the hepatitis infection. The subgroup analysis found that the MDM2 SNP309 was significantly associated with the HCC risk in subjects with HCV hepatitis (Table 5). No significant association was found when compared with the hepatitis virus negative subjects, suggested that there may be an interaction between the MDM2 genotype and HCV hepatitis status for HCC risk (data not shown). However, the null association between the MDM2 SNP309 and HCC risk in the hepatitis virus negative subjects may also be due to the relatively small sample size. For p53 Arg72Pro, no statistical association of p53 Arg72Pro with the HBV or HCV hepatitis virus positive subjects was noticed and a null was associated when compared with those participants without HBV or HCV infection. As HBV and/or HCV hepatitis virus confer a high risk of HCC, the effects of the Pro allele of p53 Arg72Pro may have been concealed by the hepatitis infection.[60] Second, the functions of p53 may have been lost in the HBV or HCV infection cells, thus the different risk of HCC for the polymorphism is eliminated due to the hepatitis infection.[60,78,79] Third, the population of the studies may be relatively small and do not have sufficient statistical power to detect the association of p53 Arg72Pro with HCC risk in the hepatitis-positive subjects. More studies are warranted to determine the association between the p53 Arg72Pro and the HCC risk in those participants with different hepatitis status.

There are several potential limitations for the current meta-analysis. First, the small size of the participants of the studies that

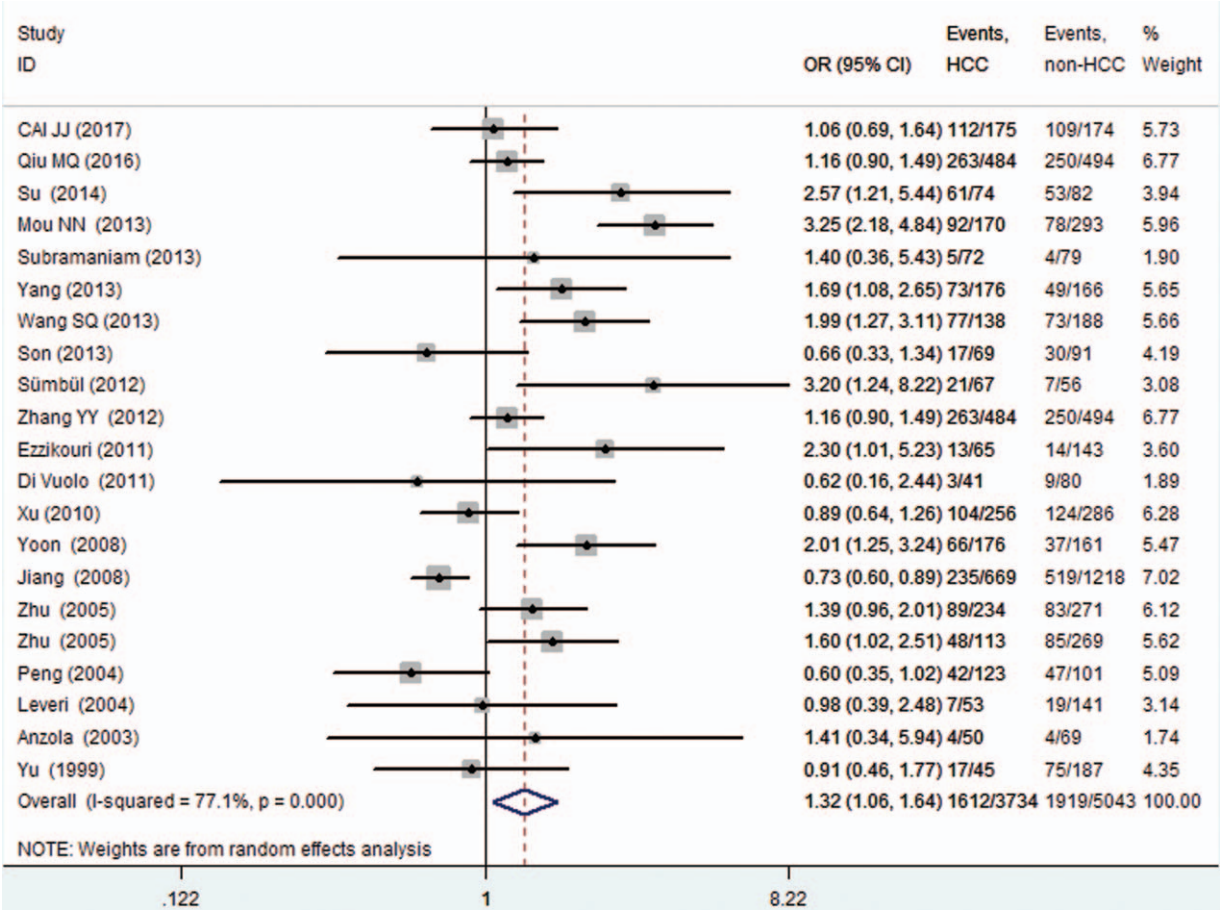

Figure 3. The forest plot of meta-analysis results of variancesp53 Arg72Pro and HCC risk (Pro/Pro vs Arg/Arg, random-effects model).

included in the present meta-analysis study may lead to the null association of the selected variants with HCC risk in the stratification study. Second, most of the data were derived from the hospital or population-based case–control studies. Subjects were recruited on the basis of their outcome (with HCC or without HCC) rather than their exposure. The potential HCC risks for the controls are immeasurable, especially for the HBV and/or HCV-positive controls. Third, as MDM2 and p53 are functional correlated, the gene–gene interactions may contribute to the susceptibility of the HCC; however, only 4 studies have determined the gene–gene interactions and all of them have found a significant interaction effect between the 2 variants (data not shown). More studies are warranted to fully address the questions.

In summary, the present meta-analysis provided a comprehensive understanding of relation between MDM2 SNP309 and p53 Arg72Pro with HCC risk. These results suggested that variants, MDM2 SNP309 and p53 Arg72Pro, are susceptibility factors for HCC. The MDM2 SNP309 and the p53 Arg72Pro may serve as markers for identification of subjects with a high risk of HCC. However, further studies with a larger sample size are warranted to confirm these findings.

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