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The Study of MDM2 rs937283 Variant and Cancer Susceptibility in a Central Chinese Population

Bifeng Chen, PhD[1], Jingdong Wang, MSc[1], Jieling Wang, MSc[1], Jingli Zhang, PhD[1], Xiuli Gu, MM[2,3], and Xianhong Feng, MM[4]

Abstract

The rs937283 variant, locating in murine double minute 2 promoter region, has been previously reported to potentially alter the promoter activity and to influence cancer susceptibility. In this study, we investigated the association of murine double minute 2 rs937283 variant and cancer susceptibility in a central Chinese population, followed by a meta-analysis. A total of 1058 healthy controls, 480 patients with breast cancer, 384 patients with cervical cancer, 480 patients with liver cancer, 426 patients with colon cancer, and 361 patients with rectal cancer were recruited in this case–control study. The murine double minute 2 rs937283 was genotyped by polymerase chain reaction restriction fragment length polymorphism and confirmed by sequencing. Our case–control analysis revealed that rs937283 was associated with the susceptibility to breast and liver cancer, but not cervical, colon, or rectal cancer. Specifically, the G allele of rs937283 conferred a significantly increased risk of breast and liver cancer. Moreover, results of meta-analysis demonstrated that rs937283 was significantly associated with cancer susceptibility, and this significant association remained in Asian (Chinese) population, but not in Caucasian population. Collectively, the murine double minute 2 rs937283 variant may serve as a potential biomarker for cancer predisposition in Chinese population.

Keywords

MDM2, rs937283, genetic variation, cancer susceptibility, meta-analysis

Abbreviations

CI, confidence interval; DTC, differentiated thyroid carcinoma; ESCC, esophageal squamous cell carcinoma; HWE, Hardy-Weinberg equilibrium; LaC, laryngeal carcinoma; LuC, lung cancer; MDM2, murine double minute 2; mRNA, messenger RNA; OR, odds ratio; OSCC, oral squamous cell carcinoma; PCR, polymerase chain reaction; RB, retinoblastoma; SCCHN, squamous cell carcinoma of the head and neck; SGC, salivary gland carcinoma.

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Introduction

The murine double minute 2 (*MDM2*) gene, encoding an apoptosis inhibiting protein, has been shown to play a pivotal role in a variety of physiological and pathological processes.[1] Moreover, elevated expression of MDM2 occurs in diverse human cancers and is linked to carcinogenesis or malignant transformation.[2] The underlying mechanism may be attributed to the fact that the MDM2 protein forms a complex with the TP53 protein, attenuates the activity of TP53, and promotes the subsequent degradation of TP53 by acting as an ubiquitin E3 ligase for TP53.[3] Thus, MDM2 is regarded as a modifier gene in cancer development.

Human cancers have been the serious diseases affecting human health and life. Because of various carcinogenic factors and accumulated exposure to carcinogenic conditions, the

[1] Department of Biological Science and Technology, School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan, China
[2] Center of Reproductive Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3] Department of Reproductive Genetics, Wuhan Tongji Reproductive Medicine Hospital, Wuhan, China
[4] Clinical Laboratory, Wuhan Xinzhou District People's Hospital, Wuhan, China

Corresponding Authors:
Bifeng Chen, PhD, Department of Biological Science and Technology, School of Chemistry, Chemical Engineering and Life Sciences, Wuhan University of Technology, Wuhan, China.
Email: cbifeng@whut.edu.cn

Xianhong Feng, MM, Clinical Laboratory, Wuhan Xinzhou District People's Hospital, Wuhan, China.
Email: xianhong_feng@hotmail.com

incidences of human cancers have increased year by year during the past decade in China.[4] The current knowledge suggests that occurrence of human tumor is the result of accumulation of genetic and epigenetic changes in genome.[5] The association of genetic factors (especially genetic variants) and human cancers has attracted a lot of attention. Accumulating evidence supports the correlation between the alteration in protein structural/functional behavior/abnormal expression and genetic variants within relative genes.[6] Interestingly, the rs937283 is such a genetic variant that significantly enhances the transcription activity of the MDM2 gene and thereby increases the messenger RNA (mRNA) and protein expression levels of MDM2.[7] Until now, there has been no report investigating the association of this genetic variant with susceptibility to breast cancer, cervical cancer, liver cancer, colon cancer, or rectal cancer. To determine the role of MDM2 rs937283 variant in these cancers, we in this study analyzed the distribution of rs937283 and assessed the association of MDM2 with susceptibility to breast cancer, cervical cancer, liver cancer, colon cancer, and rectal cancer in a central Chinese population.

Several studies have investigated the association between rs937283 and susceptibility to multiple cancers.[7-15] However, the results remain conflicting rather than conclusive. To solve the discrepancies and the problem of inadequate statistical strength among previous studies, we further performed a meta-analysis, integrating the data from previous literatures and our present study, to get a more precise and reliable assessment of the association between MDM2 rs937283 variant and cancer susceptibility.

Materials and Methods

Participants

A total of 1058 healthy controls (558 males and 500 females), 480 patients with breast cancer, 384 patients with cervical cancer, 480 patients with liver cancer, 426 patients with colon cancer, and 361 patients with rectal cancer were enrolled in this study. The patients with cancer were confirmed histopathologically and volunteers were recruited from Hubei Cancer Hospital and Wuhan Xinzhou District People's Hospital between January 2015 and December 2016. The healthy controls were selected from cancer-free individuals who visited Wuhan Xinzhou District People's Hospital for regular physical examinations between September 2014 and December 2016 or who volunteered to participate in the epidemiology survey during the same period. Importantly, the controls were frequency matched to the cases by age (± 5 years), gender, smoking status, and drinking status. The response rate of the eligible controls was approximately 85%. All participants were biologically unrelated Han Chinese living in central China (Hubei province). This study was approved by the ethical committees of Wuhan University of Technology and written informed consent for the genetics analysis was obtained from all participants or their guardians.

The Genotyping of MDM2 rs937283 Variant

The peripheral blood samples (5 mL per participant) were collected into blood vacuum tubes containing EDTA and stored at 4°C. Genomic DNA was extracted from blood samples using the TIANamp Blood DNA Kit (DP348; TianGen Biotech, Beijing, China), according to the manufacturer's instructions, and stored at −20°C before use. The A to G substitution at rs937283 creates an *AvaII* restriction site; thus, genotyping of MDM2 rs937283 variant was subsequently performed via polymerase chain reaction (PCR) restriction fragment length polymorphism technique. Briefly, a 175 bp DNA fragment containing the polymorphism of interest was amplified with the primers (forward: 5′-GCGACCCCTCTGACCGA-3′ and reverse: 5′-CCTCAAGACTCCCCAGTTTC-3′). The PCR products were then digested with 10-unit *AvaII* restriction enzymes following the manufacturer's instructions (Takara, Bio Inc, Shiga, Japan). Digested fragments were separated by electrophoresis on 3% agarose gel and visualized under ultraviolet light with GelRed staining. The rs937283 G allele was identified by the presence of 2 bands (107 and 68 bp), whereas the A allele was identified by the presence of 1 band (175 bp). Genotyping analysis was repeated twice for all participants, and the results were 100% concordant. Next, 20% randomly selected PCR-amplified DNA samples were examined by DNA sequencing, and the results were also 100% concordant.

Statistical Analysis

All statistical analyses were performed with the Statistical Program for Social Sciences (SPSS, version 15.0, Chicago, Illinois). Two-sided χ^2 test was used to compare the differences in age, gender, smoking status, and alcohol status between patients with cancer and healthy controls. Genotypic frequency of rs937283 in healthy controls was tested for departure from Hardy-Weinberg equilibrium (HWE). Logistic regression analysis was used to estimate the association between rs937283 and cancer susceptibility. $P < .05$ was considered as statistically significant, and the Bonferroni correction for multiple testing was applied.

Meta-Analysis

A comprehensive literature search updated to April of 2018 was carried out in PubMed, EMBASE, ISI Web of Science, and CNKI and Wanfang databases without language restriction. The search terms used were as follows: mouse double minute 2 homolog, proto-oncogene proteins c-mdm2, MDM2, MDM2 proto-oncogene, E3 ubiquitin protein ligase, human homolog of mouse double minute 2, murine double minute 2, polymorphism, variant, mutation, SNP, single nucleotide polymorphism, rs937283, cancer, tumor, carcinoma. References listed in retrieved articles were also checked for missing information. Next, studies were eligible for inclusion in the meta-analysis if they met the following criteria: (1) studies on humans, (2) investigation of the MDM2 rs937283 variant and

Table 1. Demographic Characteristics of Patients With Breast Cancer, Patients With Cervical Cancer, and Healthy Females.

Variable		Patients With Breast Cancer (n = 480)	Patients With Cervical Cancer (n = 384)	Healthy Females (n = 500)	*P* Value[a]	
Age	≤60 years	274 (57.1%)[b]	204 (53.1%)	292 (58.4%)	.677	.117
	>60 years	206 (42.9%)	180 (46.9%)	208 (41.6%)		
Smoking status	Ever	137 (28.5%)	112 (29.2%)	137 (27.4%)	.691	.563
	Never	343 (71.5%)	272 (70.8%)	363 (72.6%)		
Drinking status	Ever	143 (29.8%)	116 (30.2%)	141 (28.2%)	.583	.515
	Never	337 (70.2%)	268 (69.8%)	359 (71.8%)		

[a]Two-sided χ^2 test for the distributions of age, smoking status, and drinking status between patients with breast cancer and healthy females (left column), as well as between patients with cervical cancer and healthy females (right column).
[b]Numbers in parentheses, percentage.

Table 2. Demographic Characteristics of Patients With Liver Cancer, Patients With Colorectal Cancer, and Healthy Controls.

Variables		Patients With Liver Cancer (n = 480)	Patients With Colon Cancer (n = 426)	Patients With Rectal Cancer (n = 361)	Healthy Controls (n = 800)	*P* Value[a]		
Age	≤60 years	280 (58.3%)[b]	245 (57.5%)	210 (58.2%)	434 (54.3%)	.154	.274	.213
	>60 years	200 (41.7%)	181 (42.5%)	151 (41.8%)	366 (45.7%)			
Gender	Male	343 (71.5%)	309 (72.5%)	246 (68.1%)	558 (69.7%)	.517	.308	.583
	Female	137 (28.5%)	117 (27.5%)	115 (31.9%)	242 (30.3%)			
Smoking status	Ever	140 (29.2%)	128 (30.0%)	100 (27.7%)	209 (26.1%)	.237	.143	.574
	Never	340 (70.8%)	298 (70.0%)	261 (72.3%)	591 (73.9%)			
Drinking status	Ever	158 (32.9%)	135 (31.7%)	122 (33.8%)	237 (29.6%)	.217	.454	.155
	Never	322 (67.1%)	291 (68.3%)	239 (66.2%)	563 (70.4%)			

[a]Two-sided χ^2 test for the distributions of age, smoking status, and drinking status between patients with liver cancer and healthy controls (left column), between patients with colon cancer and healthy controls (middle column), as well as between patients with rectal cancer and healthy controls (right column).
[b]Numbers in parentheses, percentage.

cancer susceptibility, (3) case–control study design, (4) valid data were accessible to estimate the OR and its 95% CI, and (5) HWE equilibrium should be established in control groups. Different ethnicity descents were categorized as Asian and Caucasian. All statistical analyses were conducted with the STATA 14.0 (StataCorp, College Station, Texas). The heterogeneity of included studies was assessed by the Cochran Q test and I^2.[16] If the P value of Q test is ≥ 0.1, the fixed-effect model was applied to calculate the combined OR[17]; otherwise, random-effects model was conducted.[18] The significance of combined OR was determined by the Z test. A P value $< .05$ was considered significant, and the Bonferroni correction for multiple testing was applied. Moreover, potential publication bias was assessed by Begg test and Egger test in this meta-analysis (significance at 5% level).

Results

The demographic characteristics of patients with cancer and healthy controls are presented in Tables 1 and 2. There were no significant differences in the distributions between patients with cancer and healthy controls relating to age, gender, smoking status, and drinking status. These results suggested that patients with cancer and healthy controls were well matched in the present case–control study.

Five types of patients with cancer (breast cancer, cervical cancer, liver cancer, colon cancer, and rectal cancer) were included in this study, and the MDM2 rs937283 variant was successfully genotyped in a total of 3189 participants. Table 3 showed us the allele/genotype distributions of rs937283 and their association with cancer susceptibility. The genotype frequencies of rs937283 among controls were in accordance with HWE ($P = .871$ and .344, respectively), indicating that the included control participants were representative. No significant association was identified for rs937283 with the susceptibility to cervical cancer, colon cancer, rectal cancer, or combined colorectal cancer. In contrast, rs937283 was shown to significantly associate with the susceptibility to breast and liver cancers. The allele/genotype distributions of rs937283 were significantly different between patients with breast cancer and healthy females ($P = .003$ and .008, respectively), as well as between patients with liver cancer and healthy controls ($P = .001$ and .004, respectively). Furthermore, logistic regression analysis was applied to estimate the association of rs937283 with susceptibility to breast and liver cancer. After Bonferroni correction for multiple testing ($0.05/5 = 0.01$), it was still found that the G allele and GG genotype of rs937283 were associated with an increased susceptibility to breast cancer than the A allele and AG/AA genotypes, respectively (G vs A, GG vs AA, and GG vs AG + AA). Similarly, the G allele and G variant genotypes of rs937283 significantly

Table 3. Genotype and Allele Distributions of MDM2 rs937283 Variant and Its Association With Cancer Susceptibility.

Group	rs937283	Cases	Controls	*P* Value[a]	Logistic Regression, *P* Value, OR (95% C])[b]		HWE Test[c]
Breast cancer	A	759 (79.1%)[d]	842 (84.2%)	.003	G vs A	.003, 1.41 (1.12-1.78)	
	G	201 (20.9%)	158 (15.8%)		GG vs AA	.005, 2.70 (1.34-5.38)	
	AA	307 (64.0%)	354 (70.8%)	.008	AG vs AA	.122, 1.25 (0.95-1.64)	0.871
	AG	145 (30.2%)	134 (26.8%)		GG + AG vs AA	.022, 1.36 (1.03-1.80)	
	GG	28 (5.8%)	12 (2.4%)		GG vs AG + AA	.009, 2.50 (1.27-5.00)	
Cervical cancer	A	630 (82.0%)	842 (84.2%)	.226	G vs A	.226, 1.17 (0.91-1.50)	
	G	138 (18.0%)	158 (15.8%)		GG vs AA	.745, 1.13 (0.50-2.70)	
	AA	256 (66.7%)	354 (70.8%)	.417	AG vs AA	.191, 1.20 (0.93-1.60)	0.871
	AG	118 (30.7%)	134 (26.8%)		GG + AG vs AA	.188, 1.19 (0.90-1.65)	
	GG	10 (2.6%)	12 (2.4%)		GG vs AG + AA	.847, 1.10 (0.46-2.50)	
Liver cancer	A	783 (81.6%)	1382 (86.4%)	.001	G vs A	.001, 1.43 (1.15-1.78)	
	G	177 (18.4%)	218 (13.6%)		GG vs AA	.005, 2.44 (1.30-4.56)	
	AA	327 (68.1%)	600 (75.0%)	.004	AG vs AA	.050, 1.30 (1.00-1.66)	0.344
	AG	129 (26.9%)	182 (22.8%)		GG + AG vs AA	.007, 1.38 (1.10-1.78)	
	GG	24 (5.0%)	18 (2.2%)		GG vs AG + AA	.009, 2.29 (1.20-4.25)	
Colon cancer	A	720 (84.5%)	1382 (86.4%)	.208	G vs A	.208, 1.16 (0.92-1.47)	
	G	132 (15.5%)	218 (13.6%)		GG vs AA	.818, 1.09 (0.51-2.40)	
	AA	304 (71.4%)	600 (75.0%)	.375	AG vs AA	.163, 1.21 (0.90-1.58)	0.344
	AG	112 (26.3%)	182 (22.8%)		GG + AG vs AA	.168, 1.19 (0.92-1.55)	
	GG	10 (2.3%)	18 (2.2%)		GG vs AG + AA	.913, 1.02 (0.45-2.80)	
Rectal cancer	A	605 (83.8%)	1382 (86.4%)	.101	G vs A	.101, 1.23 (0.96-1.57)	
	G	117 (16.2%)	218 (13.6%)		GG vs AA	.681, 1.17 (0.53-2.65)	
	AA	253 (70.1%)	600 (75.0%)	.209	AG vs AA	.080, 1.28 (0.96-1.70)	0.344
	AG	99 (27.4%)	182 (22.8%)		GG + AG vs AA	.079, 1.26 (0.95-1.69)	
	GG	9 (2.5%)	18 (2.2%)		GG vs AG + AA	.799, 1.09 (0.50-2.49)	
Colorectal cancer	A	1325 (84.2%)	1382 (86.4%)	.081	G vs A	.081, 1.19 (0.98-1.45)	
	G	249 (15.8%)	218 (13.6%)		GG vs AA	.701, 1.15 (0.60-2.20)	
	AA	557 (70.8%)	600 (75.0%)	.161	AG vs AA	.058, 1.24 (1.00-1.55)	0.344
	AG	211 (26.8%)	182 (22.8%)		GG + AG vs AA	.059, 1.20 (0.99-1.53)	
	GG	19 (2.4%)	18 (2.2%)		GG vs AG + AA	.828, 1.05 (0.50-2.05)	

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds ratio.
[a]Allele/genotype frequencies in cases and controls were compared using 2-sided χ^2 test.
[b]OR (95% CI) was estimated by logistic regression analysis and adjusted for age, sex, smoking status, and alcohol use.
[c]Genotypic frequency of rs937283 in controls was tested for departure from HWE using 2-sided χ^2 test.
[d]Numbers in parentheses, percentage.

increased the susceptibility to liver cancer (G vs A, GG vs AA, GG vs AG + AA, and GG + AG vs AA).

According to the inclusion criteria, we finally retrieved 9 relevant literatures. The characteristics of included studies in this meta-analysis are summarized in Table 4. The genotype frequencies of rs937283 among controls were in accordance with HWE in each study ($P > .05$). Of note, the adjusted *P* value (<.01, .05/5) using Bonferroni correction was also applied. As shown in Table 5, the meta-analysis revealed a significant association between rs937283 and cancer susceptibility in 2 genetic models (G vs A, odds ratio [OR] = 1.17, 95% confidence interval [CI] = 1.06-1.30, $P = .003$; GG + AG vs AA, OR = 1.21, 95% CI = 1.06-1.38, $P = .004$). In the further ethnicity-stratified analysis, no association was found for rs937283 with cancer susceptibility in Caucasian population, whereas rs937283 was significantly associated with cancer susceptibility in Asian population in 3 genetic models (G vs A, OR = 1.30, 95% CI = 1.13-1.49, $P < .001$; AG vs AA, OR = 1.26, 95% CI = 1.13-1.41, $P < .001$; GG + AG vs AA, OR = 1.30, 95% CI = 1.17-1.44, $P < 0.001$). In addition, the results of Begg test and Egger test demonstrated that the occurrence of publication bias was excluded under all genetic models (Table 5, all $P > .05$), suggesting that our statistical results were credible.

Discussion

Cancer has been a global health problem and a threat to human health and development. Among both men and women, the majority of deaths worldwide are due to cancers.[19] Liver cancer, colorectal cancer (colon and rectal cancers), and 2 female-specific cancers (breast and cervical cancer) are the most common cancer types and cause lots of cancer-related deaths in China.[4] Despite tremendous progress in the treatment of human cancers in recent decades, the prognosis remains unsatisfactory, especially in advanced stage tumors with distant metastasis.[20] Therefore, identification of the inherited variants associated with cancer susceptibility would be useful in making early diagnosis and risk prediction.

Table 4. Characteristics of the Present and Previous Studies.

References (Author, Year)	Ethnicity	Cancer Type	Genotyping Assay	Case, Control (*n*)			HWE Test[a]
				Total	G/A	GG/AG/AA	
Li et al[8]	Caucasian	Lung cancer	PCR-RFLP	1026, 1145	844/1208, 935/1355	175/494/357, 181/573/391	0.227
Chen et al[15]	Caucasian	Oral squamous cell carcinoma	PCR-RFLP	325, 335	303/347, 273/397	47/209/69, 52/169/114	0.715
Jin et al[9]	Caucasian	Salivary gland carcinoma	PCR-RFLP	156, 511	126/186, 421/601	29/68/59, 83/255/173	0.795
de Oliveira Reis et al[10]	Caucasian	Retinoblastoma	PCR-RFLP	104, 104	83/125, 70/138	16/51/37, 11/48/45	0.943
Yu et al[11]	Caucasian	Squamous cell carcinoma of the head and neck	TaqMan assay	1078, 1089	896/1260, 939/1239	187/522/369, 205/529/355	0.749
Zhang et al[12]	Caucasian	Differentiated thyroid carcinoma	PCR-RFLP	303, 511	251/355, 427/595	52/147/104, 89/249/173	0.971
Yang et al[13]	Asian	Esophageal squamous cell carcinoma	TaqMan assay	307, 311	162/452, 174/448	18/126/163, 24/126/161	0.924
Wang et al[14]	Asian	Laryngeal carcinoma	PCR-RFLP	126, 120	79/173, 47/193	18/43/65, 7/33/80	0.381
Jiao et al[7]	Asian	Retinoblastoma	TaqMan assay	137, 150	95/179, 70/230	18/59/60, 11/48/91	0.196
This study	Asian	Breast cancer	PCR-RFLP	480, 500	201/759, 158/842	28/145/307, 12/134/354	0.871
This study	Asian	Cervical cancer	PCR-RFLP	384, 500	138/630, 158/842	10/118/256, 12/134/354	0.871
This study	Asian	Liver cancer	PCR-RFLP	480, 800	177/783, 218/1382	24/129/327, 18/182/600	0.344
This study	Asian	Colon cancer	PCR-RFLP	426, 800	132/720, 218/1382	10/112/304, 18/182/600	0.344
This study	Asian	Rectal cancer	PCR-RFLP	361, 800	117/605, 218/1382	9/99/253, 18/182/600	0.344

Abbreviations: HWE, Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism.
[a]Genotypic frequency of −283T > C in normal controls was tested for departure from HWE using the χ^2 test.

Table 5. Meta-Analysis of the Association Between MDM2 rs937283 Variant and Cancer Susceptibility.

Genetic Model	Heterogeneity Test			Summary OR (95% CI)	Hypothesis Test		Begg Test		Egger Test		Studies (n)
	Q	*P*	I^2		*Z*	*P*	*z*	*P*	*T*	*P*	
rs937283 and cancer susceptibility											
G vs A	38.7	$<1 \times 10^{-3}$	66%	1.17 (1.06-1.30)	3.00	.003	1.16	.246	1.75	.222	14
GG vs AA	28.9	.007	55%	1.30 (1.04-1.62)	2.34	.019	1.77	.077	2.15	.054	14
AG vs AA	30.2	.004	57%	1.18 (1.04-1.34)	2.55	.011	0.55	.583	1.62	.134	14
GG + AG vs AA	36.2	.001	64%	1.21 (1.06-1.38)	2.84	.004	0.43	.669	2.03	.067	14
GG vs AG + AA	22.7	.045	43%	1.18 (0.99-1.42)	1.82	.069	1.65	.100	2.05	.064	14
rs937283 and cancer susceptibility in Asian											
G vs A	15.6	.029	55%	1.30 (1.13-1.49)	3.65	$<1 \times 10^{-3}$	0.12	.902	1.42	.206	8
GG vs AA	14.5	.044	52%	1.64 (1.12-2.42)	2.51	.012	0.37	.711	0.28	.792	8
AG vs AA	5.37	.615	0%	1.26 (1.13-1.41)	4.04	$<1 \times 10^{-3}$	0.37	.711	1.76	.130	8
GG + AG vs AA	9.91	.194	29%	1.30 (1.17-1.44)	4.81	$<1 \times 10^{-3}$	0.12	.902	1.58	.165	8
GG vs AG + AA	12.5	.085	44%	1.51 (1.06-2.15)	2.27	.023	−0.12	1.000	0.14	.897	8
rs937283 and cancer susceptibility in Caucasian											
G vs A	7.46	.189	33%	1.01 (0.94-1.09)	0.32	.748	0.75	.452	1.53	.201	6
GG vs AA	5.35	.375	6.5%	1.02 (0.88-1.18)	0.30	.765	1.13	.260	2.01	.114	6
AG vs AA	17.8	.003	72%	1.08 (0.86-1.35)	0.63	.529	0.75	.452	0.91	.414	6
GG + AG vs AA	16.1	.007	69%	1.08(0.88-1.33)	0.73	.468	0.75	.452	1.17	.309	6
GG vs AG + AA	3.08	.688	0%	1.01 (0.89-1.15)	0.12	.904	1.13	.260	1.19	.301	6

Abbreviations: CI, confidence interval; OR, odds ratio.

Increasing evidence has indicated that MDM2-TP53 pathway plays an important role in tumor development and progression.[21] The dysregulation of MDM2 would impair the MDM2-TP53 pathway and thereby might affect individual susceptibility to cancer.[22] The rs937283 variant was a novel functional variant identified in MDM2 gene promoter. Jiao *et al* proved that the transition of A to G at rs937283 significantly enhanced the transcription activity of the MDM2 gene *in vitro*.[7]

Therefore, rs937283 variant was a potential risk factor for cancer susceptibility. Indeed, we here identified that MDM2 rs937283 variant significantly increased the susceptibility to breast and liver cancer in a central Chinese population. However, inconsistent results were observed when exploring the association between rs937283 and susceptibility to cervical and colorectal cancer. So far 9 studies have been investigated the association between rs937283 and cancer susceptibility, including lung cancer (LuC),[8] oral squamous cell carcinoma (OSCC),[15] salivary gland carcinoma (SGC),[9] retinoblastoma (RB),[7,10] squamous cell carcinoma of the head and neck (SCCHN),[11] differentiated thyroid carcinoma (DTC),[12] esophageal squamous cell carcinoma (ESCC),[13] and laryngeal carcinoma (LaC).[14] Similarly, the results remain conflicting rather than conclusive. Specifically, MDM2 rs937283 was shown to be associated with the susceptibility to OSCC, LaC, and RB (in Asian), but not to LuC, SGC, SCCHN, DTC, ESCC, or RB (in Caucasian). One possibility for these discrepancies may be attributed to the different cancer types. The regulation of MDM2 expression is complex in normal cells, and the regulation of rs937283 variant on MDM2 expression may vary from cell types. Admittedly, different environments, lifestyles, and genetic backgrounds among different ethnic populations and small sample size may also contribute to the differences in the association of rs937283 and susceptibility to different types of cancers.

Currently, the meta-analysis is a statistical tool for combining the results from different studies on the same topic to increase the statistical strength and precision in estimating effects.[23] Therefore, a meta-analysis was further performed to estimate the real effect of rs937283 on cancer susceptibility. Interestingly, we found a positive association between rs937283 variant and increased cancer susceptibility in the overall population and Asian population. The explanation for this observation may be that the G allele of rs937283 variant in the MDM2 promoter region is closely linked to the high expression levels ofMDM2 mRNA and protein, which enhances the degradation of TP53 and thereby increases the cancer susceptibility. However, no significant association between rs937283 and cancer susceptibility was present in the Caucasian-stratified analysis, suggesting differences in genetic background may be a possible reflection of rs937283 on cancer susceptibility. Therefore, larger studies performed in different ethnicities are warranted to validate or further reinforce our present findings.

Genetic testing can identify individuals with an increased risk for human diseases such as cancer. The present findings in liver and breast cancer may be applied in clinical practice. Early identification of at-risk patients with liver/breast cancer may slow the progression of the disease through individualized treatment. Additionally, environmental risk factors can be identified and lifestyle modifications can be made to reduce the risk for developing liver/breast cancer. However, it should be noted that our study contained several limitations. First, we used a hospital-based case–control study design. Therefore, the potential for selection bias should be considered. Second, it cannot rule out the possibility that the MDM2 rs937283 variant may not be the causal loci but rather be in linkage disequilibrium with the causal loci. Third, the effect of rs937283 variant on MDM2 expression was not assessed in liver/breast cancer tissues from individuals with different rs937283 genotypes, which should be analyzed in further confirmatory study. Fourth, the underlying molecular mechanism for the regulation of rs937283 on MDM2 transcription activity remains unclear, which needs to be addressed in future functional studies. Finally, our current observations only involved Han Chinese population; thus, further confirmatory studies are demanded in other ethnic groups.

Conclusion

Our study provided statistical evidence that MDM2 rs937283 variant significantly increases the susceptibility to breast and liver cancer, but not cervical cancer, colon cancer, or rectal cancer in a central Chinese population. We further demonstrated that MDM2 rs937283 variant is more likely to confer an increased genetic susceptibility to cancer susceptibility in Asian (Chinese) population, but not in Caucasian population. MDM2 rs937283 variant may serve as a valuable risk factor or diagnostic biomarker among Chinese patients with cancer and needs more supporting evidence.

Authors' Note

This study was approved by the Ethical Committees of Wuhan University of Technology (approval no: WUT02720171123), and written informed consent for the genetics analysis was obtained from all participants or their guardians. Bifeng Chen and Jingdong Wang contributed equally to this work.

Declaration of Conflicting Interests

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ORCID iD

Bifeng Chen, PhD http://orcid.org/0000-0001-5482-1910

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