

Influence of *MDM2* polymorphisms on squamous cell carcinoma susceptibility: a meta-analysis

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Purpose: Controversial associations between single-nucleotide polymorphisms (rs2279744, rs937283, rs3730485) of the *MDM2* gene and the etiology of squamous cell carcinomas (SCCs) have been reported. This merits further comprehensive assessment.

Materials and methods: We systematically reviewed the available data and conducted an updated meta-analysis to evaluate the genetic effect of *MDM2* polymorphisms in SCC susceptibility, using Stata/SE 12.0 software.

Results: After screening, 7,987 SCC cases and 12,954 controls from 26 eligible case-control studies were enrolled. Overall, compared with the control group, a significantly increased SCC risk was observed for the *MDM2* rs2279744 polymorphism in the Asian population (test of association: odds ratio [OR] 1.12, $P=0.027$ for G vs T; OR 1.26, $P=0.016$ for GG vs TT; OR 1.25, $P<0.001$ for GG vs TT + TG; and OR 1.08, $P=0.023$ for carrier G vs T). In subgroup analysis by SCC type, a similarly increased esophageal SCC risk was detected (OR 1.19, $P<0.001$ for G vs T; OR 1.46, $P<0.001$ for GG vs TT; and OR 1.48, $P=0.005$ for GG vs TT + TG). Furthermore, *MDM2*-*TP53* double mutation was statistically associated with increased SCC susceptibility overall (OR 1.52, $P=0.001$), especially in the Asian population (OR 1.49, $P=0.022$). However, no significant difference between the control and case groups was obtained for *MDM2* rs937283 or rs3730485 under any genetic model (all $P>0.05$).

Conclusion: Our results highlight a positive association between the GG genotype of *MDM2* rs2279744 polymorphism and an increased risk of esophageal SCC in the Asian population, which needs to be clarified by more large-scale studies.

Keywords: *MDM2*, SCC, SNP, meta-analysis

Introduction

The *MDM2* gene maps to chromosome 12q14.3–q15.¹ The *MDM2* protein forms a complex with the p53 protein, attenuates the activity of p53, and promotes the subsequent degradation of p53 by acting as a ubiquitin E3 ligase for p53.^{2,3} The abnormal expression of the *MDM2/TP53* genes is linked to carcinogenesis or malignant transformation.^{2,4,5} Accumulating evidence supports the link between the alteration of protein structural/functional behavior and single-nucleotide polymorphisms (SNPs) within relative genes.^{6–11} Multiple prediction or detection techniques, such as structural biology, computational platform, and molecular dynamic simulation, contribute to the investigation of identification and function of disease-associated SNPs.^{6–11} The SNPs of rs2279744 (T309G or SNP309), rs3730485 (del1518^{+/-}) and rs937283 (A2164G), have been identified in the human *MDM2* gene.^{12,13} Previous reports have shown that *MDM2* polymorphisms are associated with susceptibility to various clinical diseases, such as bladder cancer,¹⁴ hepatocellular carcinoma,¹⁵ myelodysplastic syndromes,¹⁶ and leukemia.^{17,18}

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Keratinization of the epidermal cells often leads to the occurrence of squamous cell carcinoma (SCC), which behaves as the uncontrolled growth of outer abnormal squamous cells of the epidermis.^{19–21} Specific types of SCC, such as head and neck SCC (HNSCC), skin squamous cell carcinoma (SSCC), esophageal SCC (ESCC), oral SCC (OSCC), lung SCC (LSCC), and cervical squamous cell carcinoma (CSCC), have been described.^{19–23}

The different effects of the genetic mutations within *MDM2* have been reported to be related to the carcinogenesis of specific SCC types. For example, a lower plasma *MDM2* level was observed in laryngeal SCC patients with the GT genotype of *MDM2* rs2279744 than the TT genotype.²⁴ The prevalence of *MDM2* rs2279744 might be involved in OSCC onset, rather than increased OSCC risks.²⁵ Although several previous meta-analyses on the correlation between *MDM2* rs2279744 polymorphism and the risks of HNSCC, OSCC, or ESCC have been reported,^{26–28} another systematic evaluation with enlarged statistical power is still meaningful. Moreover, the meta-analyses of the association between *MDM2* rs937283 and rs3730485 polymorphisms and SCC risks, or between the *MDM2* rs2279744 polymorphism and other SCC types, such as SSCC and CSCC, have not been reported yet. It was thus worthwhile carrying out an updated systematic review and meta-analysis, in order to reassess the genetic relationship between common *MDM2* polymorphisms (rs2279744, rs937283, and rs3730485) and the overall risks of SCC.

Materials and methods

Article search

We searched for potentially relevant articles (up to May 7, 2016) from seven electronic databases: PubMed, Web of Science, Cochrane, Scopus, Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Weipu. The key terms 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; mutation; SNP; single nucleotide polymorphism; T309G; rs2279744; A2164G; rs937283; del1518; rs3730485; G285C; rs117039649; squamous cell carcinoma; carcinoma, squamous cell; and SCC.

Article screening and data extraction

With the help of EndNote X7 software, potential articles were screened for eligibility according to our strict inclusion/exclusion criteria. Exclusion criteria were duplicated articles, review or conference abstract, not human or clinical data,

not relevant to *MDM2*, not about SCC, meta-analysis, not relevant to mutation, lack of control data, and overlapped data. Eligible case-control studies needed to be linked to SCC risks and contain data on individual genotype numbers of *MDM2* rs2279744, rs937283, and rs3730485 polymorphisms. We independently extracted the following data: first author, year of publication, country, ethnicity, SNPs, sample sizes and genotype frequencies of case/control group, SCC type, source of control, genotyping assay, *P*-values of Hardy-Weinberg equilibrium (HWE), and test of control groups. A detailed discussion was required for the conflicting assessment.

Statistical analysis

Pooled odds ratios (ORs) with 95% confidence intervals (CIs) and *P*-values of associations based on Mantel-Haenszel statistics were calculated by Stata 12.0 software (StataCorp LP, College Station, TX, USA). *P*>0.05 was considered the exclusion of statistically significant difference between case and control groups. The *I*² test (0%–100%) and *Q*-statistic were adopted to evaluate the potential heterogeneities across case-control studies. *I*²>25% or *P*-value of *Q*-statistic <0.1 was considered significant heterogeneity, and statistical analysis under a random-effect model and sensitivity analysis were conducted. Six genetic (allele, homozygote, heterozygote, dominant, recessive, and carrier) models were employed. Subgroup analyses by ethnicity, source of controls, HWE or SCC types were also performed. In addition, potential publication bias was assessed by analysis of Begg's funnel plots (continuity-corrected) and Egger's publication-bias plots.

Results

Studies selected for meta-analysis

Figure 1 shows a flow diagram of our article-search strategy. A total of 545 potentially relevant articles were retrieved initially from the databases: PubMed (n=95), Web of Science (n=260), Cochrane (n=0), Scopus (n=73), CNKI (n=54), Wanfang (N=44), and Weipu (n=19). A total of 378 articles were obtained after duplicates had been removed by the EndNote software, and then 336 articles were excluded by screening titles and abstracts according to the exclusion criteria. Specific information is shown in Figure 1. Next, 42 full-text articles were assessed for eligibility; 16 articles were then excluded for lack of control data (n=10) and overlapped data (n=6). Finally, 26 independent articles with 7,987 SCC cases and 12,954 controls were selected for our meta-analysis.^{4,12,13,18,24,25,29–48} We then carefully extracted the data and summarized the characteristics (Table 1).

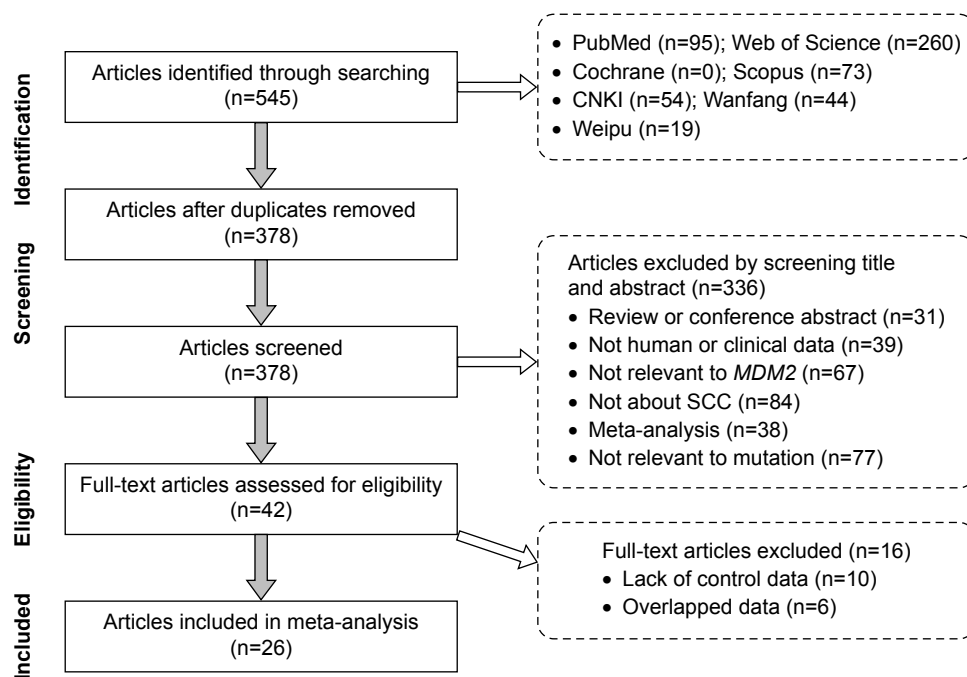


Figure 1 Flow diagram of article-search strategy for meta-analysis.
Abbreviation: SCC, squamous cell carcinoma.

Polymorphism rs2279744 of *MDM2* and SCC susceptibility

A total of 25 case-control studies^{4,12,13,18,24,25,30-48} were enrolled for the meta-analysis of *MDM2* rs2279744 and risks of SCC. As shown in Table 2, the results (G vs T, $I^2=70.0\%$, $P<0.001$; GG vs TT, $I^2=59.1\%$, $P<0.001$; TG vs TT, $I^2=72.9\%$, $P<0.001$; TG + GG vs TT, $I^2=73.7\%$, $P<0.001$; GG vs TT + TG, $I^2=36.3\%$, $P=0.04$; carrier G vs T, $I^2=31.5\%$, $P=0.068$) suggested that between-study heterogeneity existed for *MDM2* rs2279744. The random-effect model was thus applied for meta-analysis. The pooled results further showed that an increased SCC risk was observed under the allele model (Table 2, G vs T, OR 1.09, 95% CI 1–1.19; $P=0.041$), homozygote model (GG vs TT, OR 1.17, 95% CI 1.02–1.36; $P=0.03$), and recessive model (GG vs TT + TG, OR 1.18, 95% CI 1.07–1.30; $P=0.001$), but not other genetic models. Forest plots can be seen for meta-analysis of the allele (Figure 2A), homozygote (Figure 3A), heterozygote (Figure 4A), dominant (Figure 5A), and recessive (Figure 6A) models. These data revealed that the GG genotype of *MDM2* rs2279744 was statistically associated with increased SCC susceptibility.

Furthermore, subgroup analyses by ethnicity (Asian/Caucasian), HWE ($P>0.05/P<0.05$), source of control (population-based/hospital-based), and SCC type (HNSCC/

SSCC/ESCC/OSCC/CSCC/LSCC) were performed for all genetic models. As shown in Table 3, a significantly increased SCC risk was observed in the Asian population in four models (G vs T, OR 1.12, $P=0.027$; GG vs TT, OR 1.26, $P=0.016$; GG vs TT + TG, OR 1.25, $P<0.001$; carrier G vs T, OR 1.08, $P=0.023$). Similar results were obtained in the HWE $P>0.05$ group and the population-based group for the allele, homozygote, recessive, and carrier models (Table 3, all OR >1 , $P<0.05$). These data further indicated an association between the GG genotype of *MDM2* rs2279744 and increased SCC susceptibility in the Asian population. The results of stratified analyses by SCC type showed that a significantly increased ESCC risk was observed for three models (Table 4; G vs T, OR 1.19, $P<0.001$; GG vs TT, OR 1.46, $P<0.001$; GG vs TT + TG, OR 1.48, $P=0.005$). In addition, an increased SSCC risk was observed in the G vs T model (Table 4, OR 1.16, $P=0.022$) and the TG + GG vs TT model (OR 1.22, $P=0.028$), while an increased LSCC risk was only observed in the TG + GG vs TT model (Table 4, OR 1.18, $P=0.045$). In contrast, no significant difference was observed for OSCC and CSCC group in any genetic models (Table 4, test of association, all $P>0.05$). These data further suggested that patients with the GG genotype of *MDM2* rs2279744 appeared to be at a higher risk of developing ESCC in the Asian population.

Table 1 Characteristics of studies included for meta-analysis

Study	Country	Ethnicity	SNPs	Case		SCC type		Control		Source of control	Genotyping assay	HWE P-value
				Total	MM/Mm/mm	Total	MM/Mm/mm	Total	MM/Mm/mm			
Alhopuro et al ³¹	Finland	Caucasian	rs2279744	157	58/75/24	HNSCC	185	56/98/31	PB	PCR-RFLP and sequencing	0.28	
Almqvist et al ⁴	USA	Caucasian	rs2279744	559	234/261/64	SSCC	674	323/284/67	PB	Sequenom platform	0.69	
Cao et al ⁴³	People's Republic of China	Asian	rs2279744	351	50/170/131	ESCC	642	171/299/226	PB	PIRA-PCR	0.3	
Chen et al ¹³	USA	Caucasian	rs3730485	351	181/146/24	ESCC	642	310/285/47	HB	PCR-RFLP	0.09	
			rs2279744	325	146/132/47	OSCC	335	112/165/58	HB	PCR-RFLP	0.84	
Er et al ³⁰	People's Republic of China	Asian	rs937283	325	69/209/47	OSCC	335	114/169/52	HB	PCR-RFLP	0.41	
			rs2279744	121	47/31/43	ESCC	142	41/78/23	PB	PCR-RFLP	0.16	
Hamid et al ²⁵	Mixed	Asian	rs2279744	207	48/104/55	OSCC	116	30/58/28	PB	PCR-RFLP	1	
Hong et al ³³	People's Republic of China	Asian	rs2279744	758	203/348/207	ESCC	1,420	418/711/291	PB	PCR-RFLP	0.72	
Huang et al ⁴⁰	People's Republic of China	Asian	rs2279744	351	80/176/95	OSCC	1,272	274/653/345	PB	MALDI-TOF	0.29	
Jiang et al ³⁹	People's Republic of China	Asian	rs2279744	96	44/35/17	CSCC	140	30/84/26	PB	PCR-RFLP and sequencing	0.02	
Kohno et al ⁴⁴	Japan	Asian	rs2279744	377	68/183/26	LSCC	325	79/151/95	HB	Pyrosequencing	0.22	
Li et al ⁴⁶	People's Republic of China	Asian	rs2279744	132	37/70/25	ESCC	132	47/71/14	PB	PCR-RFLP	0.09	
Liu et al ³⁴	USA	Caucasian	rs2279744	423	178/186/59	LSCC	1,360	530/626/204	HB	TaqMan assay sequencing	0.39	
Loginov et al ³⁸	Russia	Caucasian	rs2279744	59	50/9/0	LSCC	160	156/4/0	PB	PCR-RFLP	0.87	
Ma et al ⁴²	People's Republic of China	Asian	rs2279744	226	49/119/58	ESCC	226	50/118/58	PB	PCR-RFLP	0.49	
Misra et al ¹⁸	India	Asian	rs3730485	226	120/91/15	ESCC	226	118/92/16	PB	PCR-RFLP	0.74	
			rs2279744	297	70/147/80	OSCC	328	59/181/88	PB	PCR-RFLP	0.04	
Nakashima et al ³⁷	Japan	Asian	rs2279744	103	29/46/28	HNSCC	120	37/50/33	PB	Sequencing and real-time PCR	0.07	
Nan et al ⁴⁷	USA	Caucasian	rs2279744	281	117/119/45	SSCC	851	380/356/115	PB	PCR-RFLP	0.03	
Park et al ³⁶	South Korea	Asian	rs2279744	270	57/128/85	LSCC	582	122/299/161	PB	PCR-RFLP	0.44	
Roszak et al ³²	Poland	Caucasian	rs2279744	379	139/169/71	CSCC	481	202/204/75	PB	PCR-RFLP and sequencing	0.05	
Singhal et al ⁴⁵	India	Asian	rs2279744	182	63/74/45	CSCC	182	108/52/22	PB	PCR-RFLP and sequencing	0.00	
Tu et al ³⁵	People's Republic of China	Asian	rs2279744	189	44/93/52	OSCC	116	29/55/32	PB	Sequencing	0.58	
Yang et al ²⁹	People's Republic of China	Asian	rs937283	307	163/126/18	ESCC	311	161/126/24	PB	TaqMan assay	0.92	
Yu et al ⁴¹	USA	Caucasian	rs2279744	1,083	463/486/134	HNSCC	1,090	488/472/130	PB	PCR-RFLP	0.33	
Zhang et al ¹²	People's Republic of China	Asian	rs937283	1,078	369/522/187	HNSCC	1,089	355/529/205	PB	TaqMan assay	0.75	
			rs2279744	132	37/70/25	ESCC	132	47/71/14	PB	PCR-RFLP	0.09	
Zhang et al ⁴⁸	People's Republic of China	Asian	rs3730485	132	17/59/56	ESCC	132	13/48/71	PB	PCR-RFLP	0.26	
			rs2279744	476	113/241/122	LSCC	1,420	418/711/291	PB	ARMS-PCR	0.72	
Zhou et al ²⁴	People's Republic of China	Asian	rs2279744	146	37/58/51	Laryngeal SCC	212	35/109/68	PB	Pyrosequencing	0.43	

Note: P<0.05 in bold.

Abbreviations: SNPs, single-nucleotide polymorphisms; M, major allele; m, minor allele; HNSCC, head and neck squamous cell carcinoma; SSCC, skin SCC; ESCC, esophageal SCC; OSCC, oral SCC; LSCC, lung SCC; CSCC, cervical SCC; PB, population-based; HB, hospital-based; PCR-RFLP, polymerase chain-reaction restriction fragment-length polymorphism; PIRA-PCR, primer-introduced restriction-analysis PCR; MALDI-TOF, matrix-assisted laser desorption/ionization time of flight; ARMS-PCR, amplification refractory mutation-system (tetra-primer) PCR; HWE, Hardy-Weinberg equilibrium.

Table 2 Meta analysis of the association between *MDM2* polymorphisms (rs2279744, rs937283, and rs3730485) and SCC susceptibility

SNP	Comparison	No of case-control studies	Case/control total sample size	Test of association			Heterogeneity		Model	Begg ^a		Egger	
				OR	95% CI	P-value	I ² (%)	P-value		z	P-value	t	P-value
rs2279744	G vs T	25	7,680/12,643	1.09	1–1.19	0.041	70	<0.001	R	0.05	0.963	0.43	0.671
rs2279744	GG vs TT	24	7,621/12,483	1.17	1.02–1.36	0.030	59.1	<0.001	R	0.05	0.96	–0.33	0.744
rs2279744	TG vs TT	25	7,680/12,643	1	0.87–1.15	0.975	72.9	<0.001	R	0.79	0.427	–0.48	0.637
rs2279744	TG + GG vs TT	25	7,680/12,643	1.06	0.92–1.21	0.422	73.7	<0.001	R	0.47	0.64	–0.18	0.861
rs2279744	GG vs TT + TG	24	7,621/12,483	1.18	1.07–1.3	0.001	36.3	0.04	R	0.74	0.457	0.52	0.607
rs2279744	carrier G vs T	25	7,680/12,643	1.06	1–1.13	0.064	31.5	0.068	R	0.09	0.926	0.78	0.446
rs937283	G vs A	3	1,710/1,735	1.02	0.84–1.24	0.803	67	0.048	R	0	1	0.57	0.668
rs937283	GG vs AA	3	1,710/1,735	0.99	0.69–1.43	0.957	52	0.124	R	0	1	0.33	0.795
rs937283	AG vs AA	3	1,710/1,735	1.22	0.78–1.9	0.377	85.7	0.001	R	1.04	0.296	1.05	0.485
rs937283	AG + GG vs AA	3	1,710/1,735	1.17	0.77–1.77	0.461	85.3	0.001	R	1.04	0.296	1.01	0.498
rs937283	GG vs AA + AG	3	1,710/1,735	0.89	0.74–1.08	0.231	0	0.84	F	1.04	0.296	–1.02	0.493
rs937283	carrier G vs A	3	1,710/1,735	1	0.89–1.12	0.992	9.8	0.33	F	0	1	0.59	0.659
rs3730485	– vs +	3	709/1,000	0.89	0.76–1.04	0.130	0	0.428	F	0	1	–0.81	0.567
rs3730485	–/– vs +/+	3	709/1,000	0.82	0.56–1.19	0.294	0	0.7	F	1.04	0.296	–0.69	0.614
rs3730485	+/- vs +/+	3	709/1,000	0.91	0.73–1.13	0.387	0	0.909	F	0	1	0.64	0.637
rs3730485	+/-, –/– vs +/+	3	709/1,000	0.89	0.73–1.1	0.275	0	0.809	F	0	1	–0.53	0.688
rs3730485	–/– vs +/+, +/-	3	709/1,000	0.79	0.58–1.09	0.146	0	0.5	F	0	1	0.62	0.648
rs3730485	Carrier – vs +	3	709/1,000	0.92	0.77–1.09	0.315	0	0.684	F	0	1	–0.81	0.566

Notes: ^aContinuity-corrected; significant *P*-values in bold.

Abbreviations: SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; F, fixed-effect model; R, random-effect model.

Polymorphisms rs937283 and rs3730485 of *MDM2* and SCC susceptibility

Next, pooled analysis for the association between the rs937283 and rs3730485 polymorphisms of *MDM2* and the risks of SCC was conducted (Table 2). A random-effect model was used for the comparison of G vs A, GG vs AA, AG vs AA, AG + GG vs AA, due to the presence of heterogeneity (all heterogeneity tests, $I^2 > 50\%$), whereas a fixed-effect model was used for others. No significant difference was observed for any genetic models (Table 2, test of association, all $P > 0.05$). The data failed to provide strong evidence regarding the association between the rs937283 and rs3730485 polymorphisms of *MDM2* and overall SCC susceptibility.

MDM2/TP53 mutations and SCC susceptibility

The *MDM2* rs2279744 polymorphism has been reported to suppress the p53 pathway via the modulation of *MDM2* expression.^{2,49} We also investigated the genetic relationship between SCC risks and *MDM2/TP53* mutations, including *MDM2*^{+/}/*TP53*[–], *MDM2*[–]/*TP53*⁺, and *MDM2*^{+/}/*TP53*⁺. Specific genotype information is shown in Table 5. A random-effect model was used. The data in Table 5 show significant differences for the *MDM2*^{+/}/*TP53*⁺ double mutation in the overall population (test of association, OR 1.52,

95% CI 1.19–1.95; $P = 0.001$) and the Asian population (test of association, OR 1.49, 95% CI 1.06–2.11; $P = 0.022$). However, no significant difference was observed for other mutations (test of association, all $P > 0.05$). According to our data, the combined effect of the *MDM2/TP53* double mutation may contribute to an increased SCC risk, especially in the Asian population.

Publication bias and sensitivity analysis

The results of Begg's funnel plots and Egger's publication-bias plots demonstrated that the occurrence of large publication bias was excluded under all genetic models (Tables 2 and 4, all $P > 0.05$), apart from the mutations of *MDM2*^{+/}/*TP53*[–] and *MDM2*^{+/}/*TP53*⁺ in the Caucasian group (Table 4, Egger's publication-bias plot, $P < 0.05$). Egger's funnel plots of publication bias for the allele (Figure 2B), homozygote (Figure 3B), heterozygote (Figure 4B), dominant (Figure 5B), and recessive (Figure 6B) models of *MDM2* rs2279744 polymorphism are shown. With regard to the sensitivity analysis, compared with overall meta-analysis data, no significant difference for the pooled OR value was observed when each study was omitted sequentially (Figure 2C for allele model of *MDM2* rs2279744; Figure 3C for homozygote model; Figure 4C for heterozygote model; Figure 5C for dominant model; Figure 6C for recessive

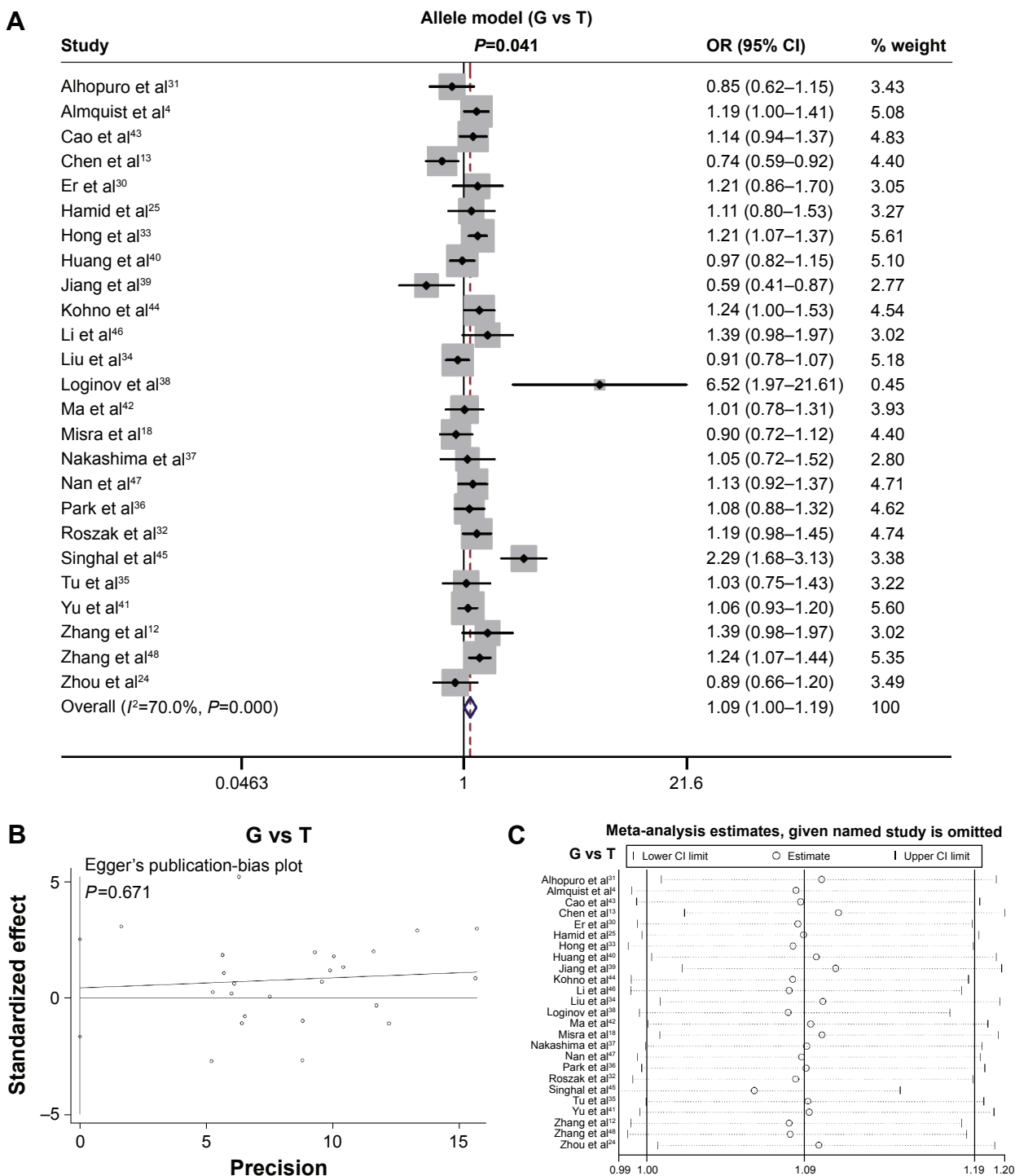


Figure 2 Meta-analysis of the association between *MDM2* rs2279744 and SCC susceptibility under the G vs T model.
Notes: (A) Forest plot; (B) Egger's funnel plot of publication-bias; (C) sensitivity analysis. Weights are from random-effect analysis.
Abbreviations: SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

model; data not shown for others). Consequently, these data suggested that our statistical results were credible.

Discussion

More and more studies on the possible role of the *MDM2* rs2279744 polymorphism in the onset and development

of cancer have been reported. Hu et al performed a meta-analysis based on 25 published case-control studies, and reported that *MDM2* rs2279744 seems to be associated with tumor susceptibility.⁵⁰ Chen et al reported that the *MDM2* rs2279744 polymorphism may be linked to an increased digestive tract cancer risk in the Asian population.⁵¹

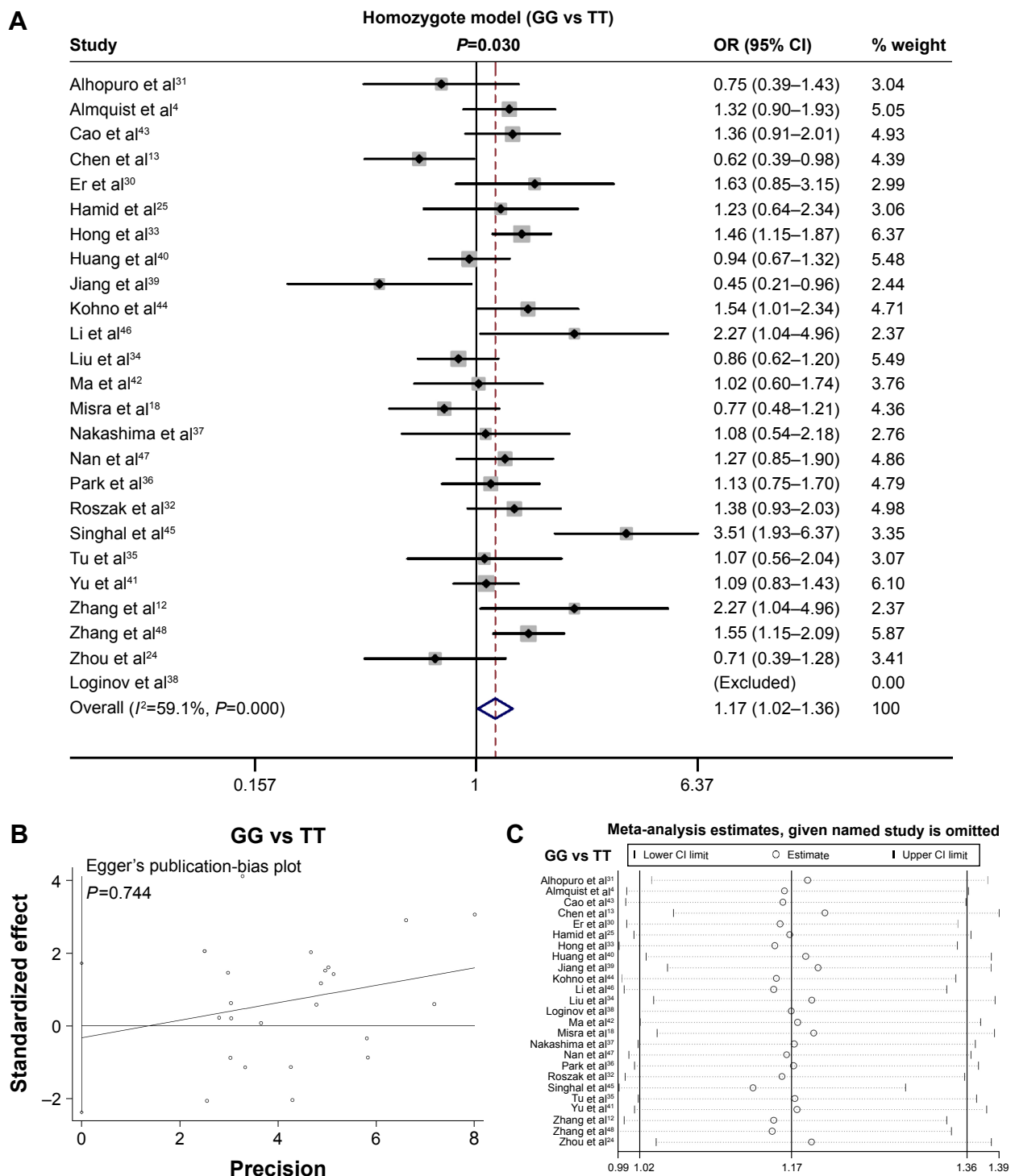


Figure 3 Meta-analysis of the association between *MDM2* rs2279744 and SCC susceptibility under the GG vs TT model.
Notes: (A) Forest plot; (B) Egger's funnel plot of publication-bias; (C) sensitivity analysis. Weights are from random-effect analysis.
Abbreviations: SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

Here, we further focused on the potential effect of *MDM2* rs2279744 in susceptibility to overall SCC and specific SCC types, including HNSCC, SSCC, ESCC, OSCC, CSCC, and LSCC.

Several SCC-related meta-analyses have been carried out previously. A meta-analysis by Liu et al based on seven

articles with 1,629 cases and 2,472 controls showed that the G allele of the *MDM2* rs2279744 polymorphism seemed to act as an important HNSCC protective factor in the Caucasian population, but not the Asian population.²⁶ However, in our meta-analysis, we were unable to observe a significant association between HNSCC susceptibility and *MDM2*

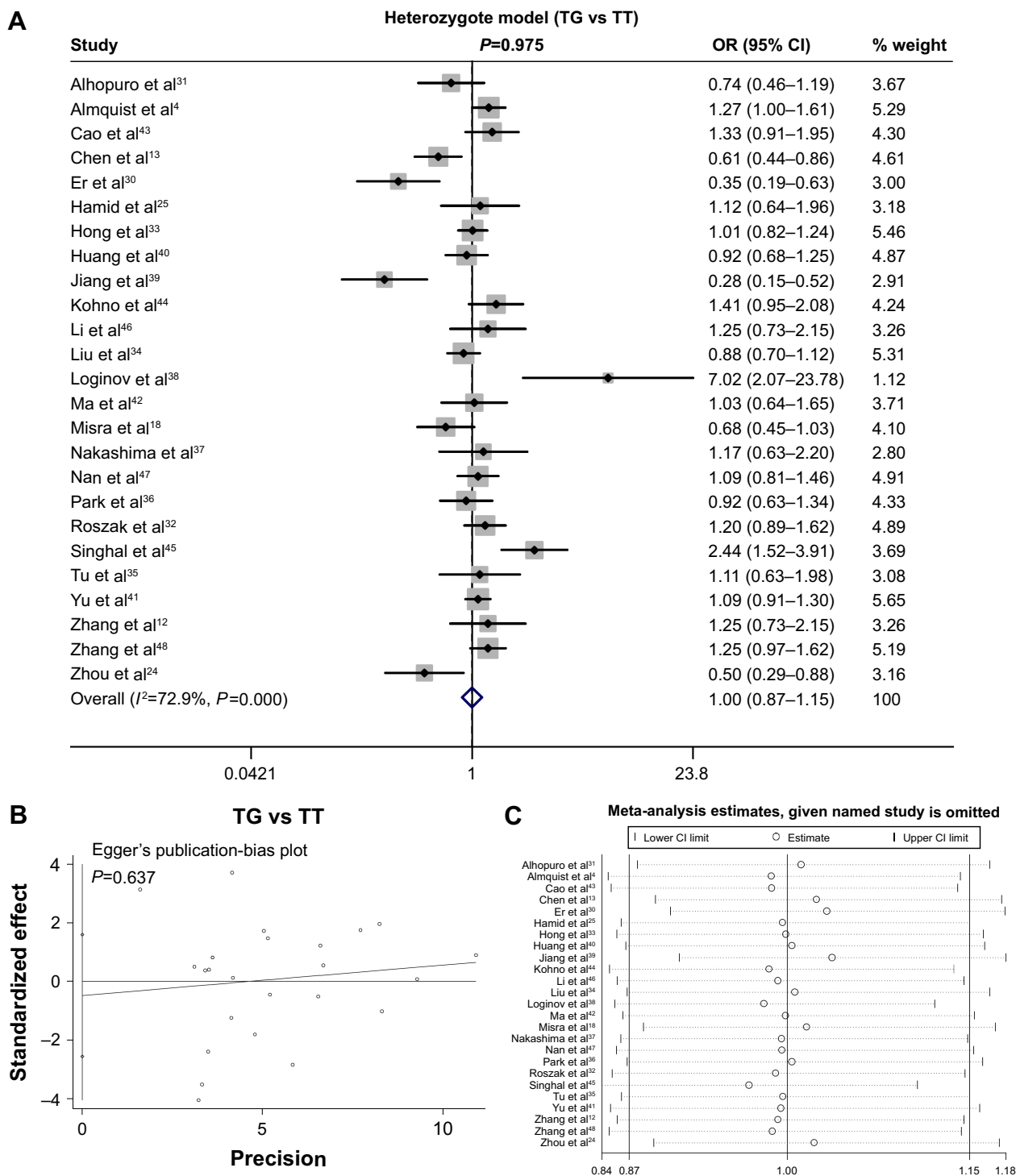


Figure 4 Meta-analysis of the association between *MDM2* rs2279744 and SCC susceptibility under the TG vs TT model.
Notes: (A) Forest plot; (B) Egger's funnel plot of publication-bias; (C) sensitivity analysis. Weights are from random-effect analysis.
Abbreviations: SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

rs2279744. How to explain this? Seven studies were enrolled in the meta-analysis of Liu et al.^{13,18,25,31,33,35,37} Also, data for OSCC in five studies^{13,18,25,33,35} were included as HNSCC. The disease in two studies^{31,37} was defined only as HNSCC. In our subgroup analysis, we tested the relationship between OSCC

risk and *MDM2* rs2279744. One new study⁴¹ was added in the new meta-analysis for HNSCC. We found that the *MDM2* rs2279744 polymorphism did not appear to be associated with OSCC susceptibility, which is partly consistent with the results of Xie et al.²⁷

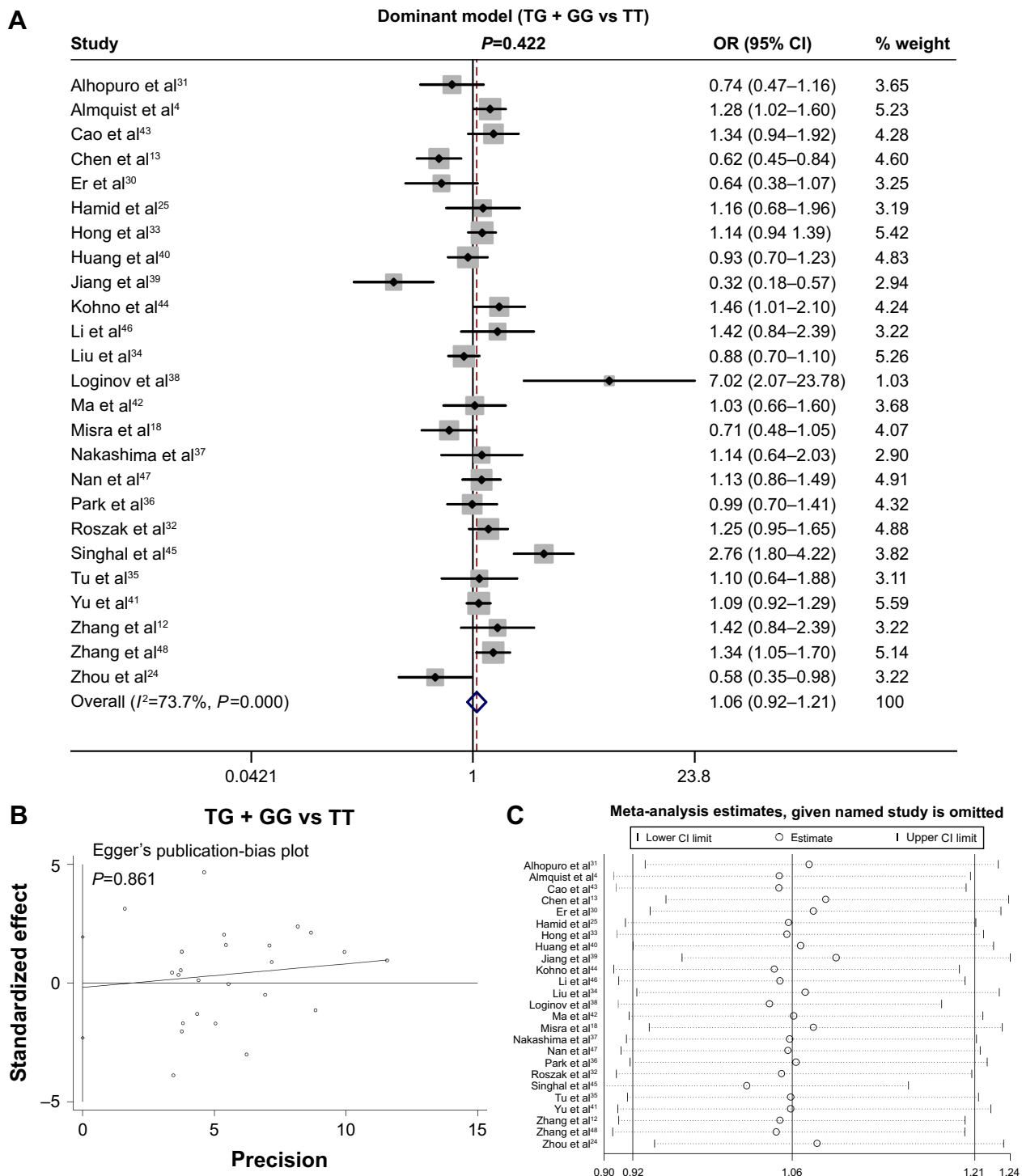


Figure 5 Meta-analysis of the association between *MDM2* rs2279744 and SCC susceptibility under the TG + GG vs TT model. **Notes:** (A) Forest plot; (B) Egger's funnel plot of publication-bias; (C) sensitivity analysis. Weights are from random-effect analysis. **Abbreviations:** SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

A meta-analysis by Chen et al based on six case-control studies, including 1,899 cases and 3,016 controls, showed that the *MDM2* rs2279744 polymorphism may be associated with increased risks of overall esophageal cancer, including SCC and adenocarcinoma, especially in the Asian population.²⁸

However, our meta-analysis only targeted the ESCCs. We thus removed one study on esophageal adenocarcinoma⁵² and added another new published case-control study.¹² All cases in six case-control studies were Chinese patients, with a mean age of >50 years and male:female ratio of >50%. The

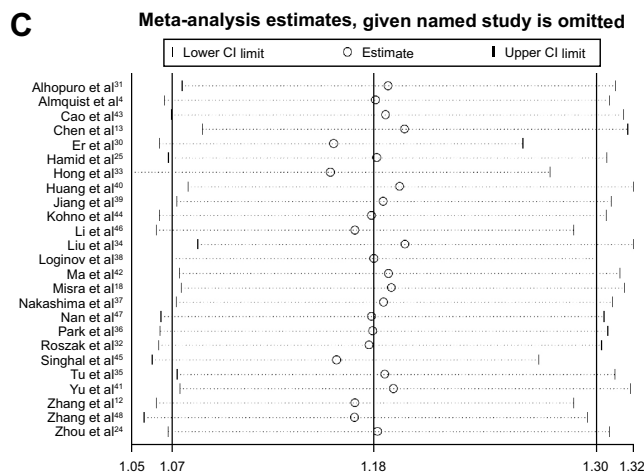
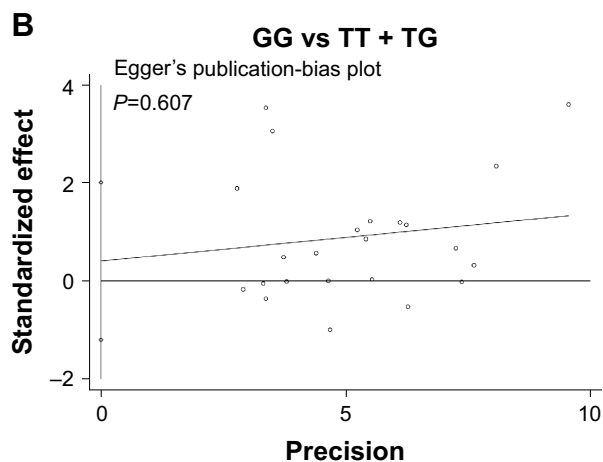
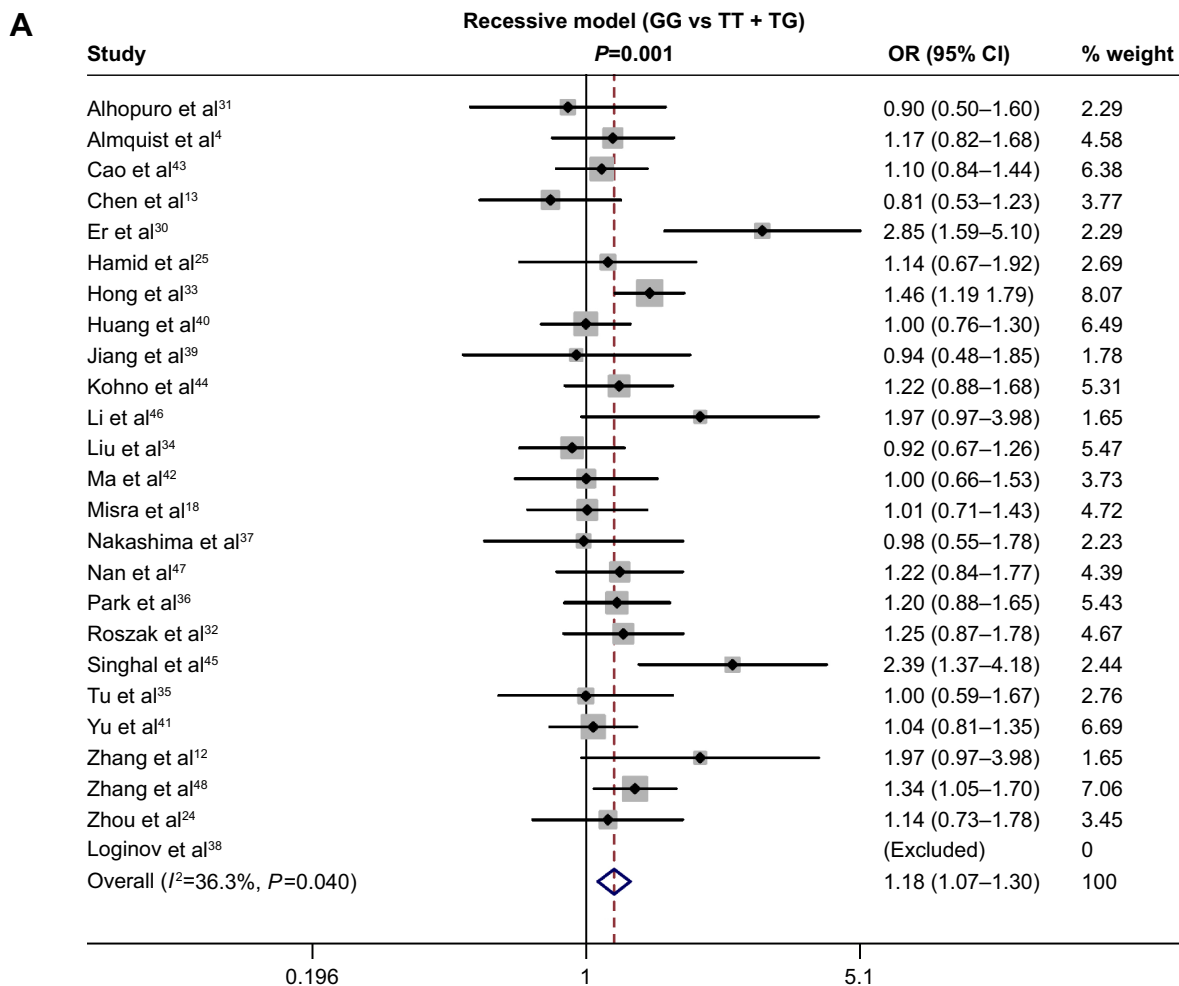


Figure 6 Meta-analysis of the association between *MDM2* rs2279744 and SCC susceptibility under the GG vs TT + TG model. **Notes:** (A) Forest plot; (B) Egger's funnel plot of publication-bias; (C) sensitivity analysis. Weights are from random-effect analysis. **Abbreviations:** SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval.

GG genotype of *MDM2* rs2279744 was likely to confer an increased susceptibility to ESCC in elderly male patients in People's Republic of China. The influence of habits and customs, such as drinking or smoking, should be considered.

Considering the close association between *MDM2* and p53,²⁻⁵ it is meaningful to investigate the role of gene-gene interaction between *MDM2* and *TP53* Arg72Pro polymorphism in SCC risks. In our meta-analysis, we observed a

Table 3 Subgroup analysis by ethnicity, source of controls, and HWE for association between *MDM2* rs2279744 and SCC susceptibility

Comparison	Ethnicity		HWE		Source of control	
	Asian	Caucasian	Y	N	PB	HB
G vs T						
No of case-control studies	17	8	21	4	22	3
Case/control total sample size	4,414/7,507	3,266/5,136	6,824/11,142	856/1,501	6,555/10,623	1,125/2,020
OR (95% CI)	1.12 (1.01–1.24)	1.03 (0.89–1.19)	1.09 (1.01–1.17)	1.09 (0.69–1.71)	1.12 (1.03–1.22)	0.94 (0.72–1.23)
P-value	0.027	0.669	0.026	0.711	0.011	0.662
GG vs TT						
No of case-control studies	17	7	20	4	21	3
Case/control total sample size	4,414/7,507	3,207/4,976	6,765/10,982	856/1,501	6,496/10,463	1,125/2,020
OR (95% CI)	1.26 (1.04–1.52)	1.03 (0.84–1.27)	1.18 (1.03–1.34)	1.13 (0.55–2.34)	1.22 (1.05–1.41)	0.94 (0.58–1.53)
P-value	0.016	0.755	0.015	0.74	0.008	0.805
TG vs TT						
No of case-control studies	17	8	21	4	22	3
Case/control total sample size	4,414/7,507	3,266/5,136	6,824/11,142	856/1,501	6,555/10,623	1,125/2,020
OR (95% CI)	0.97 (0.8–1.1)	0.97 (0.8–1.19)	1.02 (0.89–1.16)	0.87 (0.42–1.77)	1.01 (0.87–1.18)	0.9 (0.6–1.36)
P-value	0.781	0.805	0.818	0.691	0.857	0.629
TG + GG vs TT						
No of case-control studies	17	8	21	4	22	3
Case/control total sample size	4,414/7,507	3,266/5,136	6,824/11,142	856/1,501	6,555/10,623	1,125/2,020
OR (95% CI)	1.06 (0.88–1.28)	1.04 (0.84–1.28)	1.07 (0.95–1.2)	0.94 (0.45–1.94)	1.08 (0.94–1.25)	0.91 (0.6–1.4)
P-value	0.527	0.736	0.279	0.86	0.269	0.682
GG vs TT + TG						
No of case-control studies	17	7	20	4	21	3
Case/control total sample size	4,414/7,507	3,207/4,976	6,765/10,982	856/1,501	6,496/10,463	1,125/2,020
OR (95% CI)	1.25 (1.11–1.42)	1.05 (0.92–1.2)	1.17 (1.06–1.29)	1.27 (0.88–1.83)	1.22 (1.1–1.35)	0.99 (0.78–1.24)
P-value	<0.001	0.501	0.002	0.197	<0.001	0.911
Carrier G vs T						
No of case-control studies	17	8	21	4	22	3
Case/control total sample size	4,414/7,507	3,266/5,136	6,824/11,142	856/1,501	6,555/10,623	1,125/2,020
OR (95% CI)	1.08 (1.01–1.16)	1.03 (0.91–1.16)	1.06 (1.01–1.12)	1.07 (0.77–1.5)	1.08 (1.01–1.15)	1.06 (1–1.13)
P-value	0.023	0.672	0.031	0.676	0.018	0.618

Note: Significant P-values in bold.

Abbreviations: HWE, Hardy-Weinberg equilibrium; SCC, squamous cell carcinoma; PB, population-based; HB, hospital-based; Y, P-value of HWE >0.05; N, P-value of HWE <0.05; OR, odds ratio; CI, confidence interval.

positive association between *MDM2*^{+/}/*TP53*⁺ double mutation and SCC susceptibility in overall or Asian populations. The underlying molecular mechanism on the effect of *MDM2* genetic variation in the incidence of ESCC remains unclear. The rs2279744 SNP within the promoter region of *MDM2* can lead to a T–G substitution at the 309 nucleotide site, which is closely linked to the high expression of the *MDM2* protein via higher binding affinity with the transcriptional activator SP1, and thus enhances the degradation of p53.² It was possible that *MDM2* rs2279744 polymorphism is linked to the increased SCC risks, through influencing the role of p53 pathway in genomic stability and tumor prevention. Chen et al conducted a meta-analysis to investigate

the relationship between positive *MDM2* expression and clinicopathological characteristics of ESCC, and found that high *MDM2* expression was associated with early primary tumor stage and increased risk of regional lymph node metastasis, but not the risk of distant metastasis.⁵³ Vlatković et al reported that loss of MTBP expression seems to be associated with reduced survival in some patients with HNSCC.⁵⁴ In addition, several reported studies have estimated the role of the interaction between the *MDM2/TP53* gene and several environmental factors, including smoking exposure, alcohol consumption, or human papillomavirus infections in SCC susceptibility.^{13,29,38,40,41} For instance, rs2279744 and rs937283 of *MDM2* might be associated

Table 4 Subgroup analysis by disease type for association between *MDM2* rs2279744 and SCC susceptibility

Comparison	HNSCC	SSCC	ESCC	OSCC	CSCC	LSCC
G vs T						
No of case-control studies	3	2	6	5	3	5
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,605/3,847
OR (95% CI)	1.03 (0.92–1.15)	1.16 (1.02–1.32)	1.19 (1.09–1.3)	0.92 (0.81–1.05)	1.19 (0.62–2.25)	1.16 (0.95–1.42)
P-value	0.659	0.022	<0.001	0.223	0.603	0.153
GG vs TT						
No of case-control studies	3	2	6	5	3	4
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,546/3,687
OR (95% CI)	1.03 (0.82–1.31)	1.3 (0.98–1.71)	1.46 (1.23–1.74)	0.86 (0.7–1.07)	1.33 (0.5–3.52)	1.23 (0.92–1.65)
P-value	0.788	0.067	<0.001	0.173	0.569	0.161
TG vs TT						
No of case-control studies	3	2	6	5	3	5
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,605/3,847
OR (95% CI)	1.02 (0.83–1.26)	1.19 (0.99–1.43)	0.98 (0.72–1.34)	0.82 (0.65–1.04)	0.96 (0.35–0.62)	1.21 (0.88–1.67)
P-value	0.83	0.062	0.916	0.103	0.941	0.249
TG + GG vs TT						
No of case-control studies	3	2	6	5	3	5
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,605/3,847
OR (95% CI)	1.02 (0.82–1.26)	1.22 (1.02–1.45)	1.14 (0.94–1.38)	0.84 (0.66–1.06)	1.06 (0.39–2.85)	1.26 (0.91–1.75)
P-value	0.886	0.028	0.179	0.135	0.913	0.164
GG vs TT + TG						
No of case-control studies	3	2	6	5	3	4
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,546/3,687
OR (95% CI)	1.01 (0.81–1.26)	1.19 (0.92–1.55)	1.48 (1.12–1.94)	0.98 (0.83–1.16)	1.42 (0.88–2.31)	1.18 (1–1.38)
P-value	0.911	0.181	0.005	0.801	0.154	0.045
Carrier G vs T						
No of case-control studies	3	2	6	5	3	5
Case/control total sample size	1,186/1,210	840/1,525	1,720/2,694	1,369/2,167	657/803	1,605/3,847
OR (95% CI)	1.02 (0.9–1.16)	1.11 (0.96–1.29)	1.12 (1.01–1.24)	0.94 (0.84–1.06)	1.15 (0.71–1.86)	1.11 (0.92–1.34)
P-value	0.766	0.148	0.028	0.326	0.581	0.268

Note: Significant *P*-values in bold.

Abbreviations: HNSCC, head and neck squamous cell carcinoma; SSCC, skin SCC; ESCC, esophageal SCC; OSCC, oral SCC; CSCC, cervical SCC; LSCC, lung SCC; OR, odds ratio; CI, confidence interval.

with the occurrence of OSCC patients with HPV16 L1 seropositivity.¹³ However, due to the lack of sufficient data, we failed to carry out a subgroup analysis based on these environmental factors.

Our meta-analysis contained several limitations. Very few publications resulted in small sample sizes for the analysis of *MDM2* rs937283 and rs3730485. The possible effect of other unpublished studies on our negative conclusion should be taken into consideration. The same limitation of sample size existed in the meta-analysis of *MDM2/TP53* double mutation and several subgroup analyses of the *MDM2* rs2279744 polymorphism. Heterogeneity and potential publication bias may weaken our conclusion. Demographic features, lifestyle, or clinical characteristics were not considered, due to the lack of data. Larger and

independent studies are required to validate the association between *MDM2/TP53* mutations and susceptibility to different types of SCC.

Conclusion

Our updated meta-analysis demonstrated that there is a positive association between increased overall SCC risks and the *MDM2* rs2279744 polymorphism, rather than rs937283 or rs3730485. We further provided evidence that the GG genotype of *MDM2* rs2279744 is more likely to confer an increased genetic susceptibility to ESCC in the Asian population, particularly in Chinese. *MDM2* rs2279744 may be a valuable risk factor or diagnostic biomarker for patients with ESCC in People's Republic of China, and needs more supporting evidence.

Table 5 Meta-analysis of association between MDM2/TP53 mutations and SCC susceptibility

Mutation	Genotype	MDM2 rs2279744	TP53 Arg72Pro	No of case-control studies	Case/control total sample size	Test of association			Heterogeneity		Model		Begg ^a		Egger	
						OR	95% CI	P-value	I ² (%)	P-value	z	P-value	t	P-value		
MDM2+/TP53 ⁻	T/G or G/G		Arg/Arg	5	1,293/2,375	1.15	0.77–1.72	0.506	73.5	0.004	R	1.71	0.086	3.29	0.046	
MDM2-/TP53 ⁺	T/T		Arg/Pro or Pro/Pro	4	1,017/1,532	0.71	0.5–1	0.051	56.9	0.073	R	0.34	0.734	–1	0.424	
MDM2+/TP53 ⁺ , overall	T/G or G/G		Arg/Pro or Pro/Pro	9	2,474/4,319	1.52	1.19–1.95	0.001	43.1	0.08	R	0.1	0.917	0.11	0.918	
MDM2+/TP53 ⁺ , Asian	T/G or G/G		Arg/Pro or Pro/Pro	6	1,863/2,473	1.49	1.06–2.11	0.022	50	0.075	R	0	1	–0.75	0.541	
MDM2+/TP53 ⁺ , Caucasian	T/G or G/G		Arg/Pro or Pro/Pro	3	611/1,846	1.59	0.97–2.61	0.066	49.1	0.14	R	1.04	0.296	2.43	0.022	

Notes: ^aContinuity-corrected; significant P-values in bold.

Abbreviations: SCC, squamous cell carcinoma; OR, odds ratio; CI, confidence interval; R, random-effect model.

Disclosure

The authors report no conflicts of interest in this work.

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