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Review

Association of MDM2 gene SNP 309 polymorphism and human non-small cell lung cancer susceptibility: A meta-analysis

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ABSTRACT

This updated meta-analysis was performed to evaluate the relationship of a common polymorphism (T309 G, rs2279744 T > G) in the murine double minute 2 (MDM2) gene with susceptibility and prognosis of non-small cell lung cancer (NSCLC). The Cochrane Library, PubMed, Embase, CNKI, WanFang and CNKI databases were searched comprehensively for related study. Odds ratios (ORs) with their 95% confidence intervals (95% CI) were calculated. 11 articles with a total 6470 NSCLC patients and 8027 controls met the inclusion criteria were included. MDM2 T309 G polymorphism might be strongly correlated with an increased risk of NSCLC. The overall pooled analysis indicated that MDM2 309 T/G polymorphism was significantly associated with NSCLC susceptibility in the whole population under allelic (OR: 1.22, 95% CI: 1.08–1.38), recessive (OR: 1.37, 95% CI: 1.15–1.63), dominant (OR: 1.23, 95% CI: 1.04–1.45), and homozygous genetic models (OR: 1.49, 95% CI: 1.20–1.86). The subgroup analysis showed a significant association of MDM2 309 T/G polymorphism with NSCLC susceptibility in Asian population, but not in Caucasian population. Besides, a significant association was found again in the female population. The meta-analysis provides convincing evidence that the MDM2 T309 G polymorphism may contribute to NSCLC susceptibility, especially for Asians and women.

1. Introduction

Increasingly, non–small cell lung cancer (NSCLC) accounts for approximately 80 percent of lung cancer that is the most common cause of cancer- related death [1]. Most patients were diagnosed at the advanced stage disease and missed the best treatment time. Only small samples are available for accurate diagnosis and biological targeted testing. Substantial reports corroborated that NSCLC are based on the gene mutation rather than the histologic pathological types.

Mutations in the gene encoding murine double minute 2 (MDM2) which is an oncoprotein and a key negative regulator of p53 was an early event of lung cancer [2]. As we know, p53 is crucial for modulating DNA repair, cell growth and apoptosis [3,4]. Therefore, assurance of p53 activity is of great importance for anti-cancer effect [5]. Interestingly, epidermal growth factor receptor (EGFR) is down-regulated by p53 activation [6]. Moreover, upregulation of EGFR was commonly detected in lung cancer [7,8]. EGFR induces over-activation of downstream three main signaling pathways including Ras/MAPK, PI3K/Akt, and JAK/STAT, which leads to cells uncontrolled proliferation, and even oncogenesis [9,10]. Importantly, MDM2 was shown to catalyze the ubiquitination of DYRK1A which can phosphorylate p53 and augment its transcriptional activity [6,11]. Thus, it can be seen that MDM2-p53-EGFR axis is critical to the lung cancer. In previous meta-analysis on NSCLC, more attention on EGFR polymorphisms was paid. Although some positive evidence has shown that EGFR1 promoter polymorphism could be a risk factor associated with NSCLC [12], according to the above association analysis, we hope to shift attention on the polymorphism analysis of upstream regulatory gene MDM2. Because we speculated that its polymorphism regulates p53 activity and even ultimately affects the expression of EGFR.

When aberrant MDM2 binds to the N-terminal transcription of p53, it would be inhibited through mediating ubiquitination degradation [13]. So what is the source of anomalies in MDM2? Except for the change of expression level of MDM2 in various cancer, a common T to G polymorphism at nucleotide 309 (T309 G, rs2279744) in the promoter region of MDM2 has been widely taken into account. The polymorphism of MDM2 may accelerate cancer progression and it is very significative to reveal the characteristics and distribution of single nucleotide polymorphism.

With the advances in medical model, the rapid development of

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Table 1
The main characteristics of the included studies.

First author	Year	Country	Ethnicity	Genotyping method	Sample size (cases/controls)	Case			Controls			HWE		Quality score
						A1A1	A1A2	A2A2	A1A1	A1A2	A2A2	cases	control	
Lind	2006	Norway	Caucasian	TaqMan	341/412	130	156	55	161	207	44	0.477	0.059	7
Kohno	2011	Japan	Asian	RIPA-PCR	377/325	68	183	126	79	151	95	0.913	0.217	7
Mu	2006	China	Asian	PCR-SSCP	151/114	21	98	32	32	65	17	0	0.087	8
Mittelstrass	2008	Germany	Caucasian	MALDI-TOF	438/1294	183	205	50	547	598	149	0.514	0.453	7
Jun	2007	Korea	Asian	PCR-RFLP	485/582	89	234	162	122	299	161	0.78	0.438	8
Li	2017	China	Asian	TaqMan	186/196	32	96	58	51	101	44	0.471	0.655	8
Liu	2008	Canada	Caucasian	TaqMan	1787/1360	702	802	283	530	631	199	0.034	0.615	7
Zhang	2006	China	Asian	ARMS-PCR	837/1420	195	412	230	418	711	291	0.69	0.721	7
Li	2006	USA	Caucasian	PCR-RFLP	927/1145	382	415	130	408	574	163	0.312	0.086	8
Wang	2015	China	Asian	PCR-RFLP	177/196	28	56	93	51	101	44	0	0.655	8
Ren	2014	China	Asian	TaqMan	764/983	202	391	171	335	472	176	0.485	0.664	7

HWE, Hardy–Weinberg equilibrium; PCR-RFLP, PCR-restriction fragment length polymorphism; PIR A-PCR, Primer—introduced restriction analysis; PCR-SSCP, PCR-single-strand conformation polymorphism; ARMS-PC R, Amplification refractory mutation system-PCR; MALDI-TOFMS, Matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

molecular epidemiology makes us more and more aware of the importance of individual's own genetic factors and acquisitiveness on the risk of the regulation of disease. Thus, the ability to identify subgroup of patients more accurately may improve diagnosis and treatment level. Previous some of studies have demonstrated the polymorphism of single nucleotide in MDM2 was strongly related with the occurrence and development of malignant tumors [14]. More importantly, MDM2 polymorphisms on lung cancer susceptibility and prognosis generally focused on SNP309 (rs2079744), but the results were inconsistent. Thus, in this study, we intended to make a systematic review to analyze and update the relationship of MDM2 genetic polymorphism and susceptibility of NSCLC.

2. Methods

2.1. Literature search

Web of Science, PubMed, Embase, WanFang, and the China National Knowledge Infrastructure (CNKI) electronic databases were searched using the terms "SNP or mutation or genetic polymorphism or variation or variant or polymorphism or single nucleotide polymorphism" and "non-small cell lung cancer or NSCLC or lung cancer or non-small cell lung carcinoma'' and "murine double minute 2 or rs2279744 or T309 G or MDM2 or double minute 2 protein''. The last research was updated on Jun, 5th, 2019. Additionally, the relevant studies were also identified carefully through reviewed the references cited in the initial articles.

2.2. Inclusion and exclusion criteria

The studies were included according to the following criteria: (1) case-control studies and evaluated the association between MDM2 polymorphism and NSCLC susceptibility; (2) provided the complete data of allelic or genotypic frequencies of MDM2 polymorphism in all participants; (3) the control group genotype followed Hardy–Weinberg equilibrium (HWE). Studies were excluded according to the following reasons: (1) reviews, duplication, case reports or animal studies; (2) not case-control studies; (3) Reports with incomplete data.

2.3. Data extraction

The data were extracted by using a standardized protocol. Two investigators independently extracted data from each eligible literature, and disagreements was reconciled by third author. The following information was extracted: the first author's name, publication year, country, ethnicity, genotyping methods, the number of cases and control, genotype of cases and control, P value for Hardy-Weinberg equilibrium and NOS score [15].

2.4. Statistical analysis

In this meta-analysis, five allelic models as the Allele contrast, homozygous, heterozygous, dominant model, and recessive genetic model were examined. The pooled ORs with 95% confidence intervals (CIs) were used to evaluate the strength of the association. P value $<$ 0.05 was considered statistically significant. Hardy–Weinberg equilibrium (HWE) of the populations was tested by Fisher exact test, and the significance level was defined as $\alpha < 0.05$. The heterogeneity across studies were assessed by I^2 value and Cochran Q test and the significance was set at $P < 0.05$ level. If heterogeneity was detected, the random-effects model would be used. Otherwise, the fixed-effects model was adopted. Moreover, publication bias was assessed by funnel plot and Egger's regression test. In addition, the stability of the pooled results was evaluated by sensitivity analysis. All the above analyses were performed by Stata 12.0 software (StataCorp, College Station, TX, USA).

3. Results

3.1. Characteristics of studies

After the retrieval process, 12 articles [16–27] were included in this meta-analysis according to our inclusion criteria. Among the 12 retrieved studies, one study was excluded due to controls deviated from the HWE [26]. As shown in Table 1, there were 6470 NSCLC patients and 8027 controls were used to assess the relationship between MDM2 309 T/G polymorphism and NSCLC susceptibility. Patients were from China, USA, Korea, Norway, Japan, Germany, and Canada.

3.2. Quantitative synthesis

The overall pooled analysis indicated that MDM2 309 T/G polymorphism was significantly associated with NSCLC susceptibility in the whole population under allelic (OR: 1.22, 95% CI: 1.08–1.38), recessive (OR: 1.37, 95% CI: 1.15–1.63), dominant (OR: 1.23, 95% CI: 1.04–1.45), and homozygous genetic models (OR: 1.49, 95% CI: 1.20–1.86) (Figs. 1–6; Table 2). The subgroup analysis based on ethnicity showed a significant association of MDM2 309 T/G polymorphism with NSCLC susceptibility in Asian population under allelic (OR: 1.37, 95% CI: 1.21–1.56), recessive (OR: 1.56, 95% CI: 1.24–1.95), dominant (OR: 1.43, 95% CI: 1.28–1.61), homozygous (OR: 1.81, 95% CI: 1.47–2.23), and heterozygous genetic models (OR: 1.30, 95% CI:

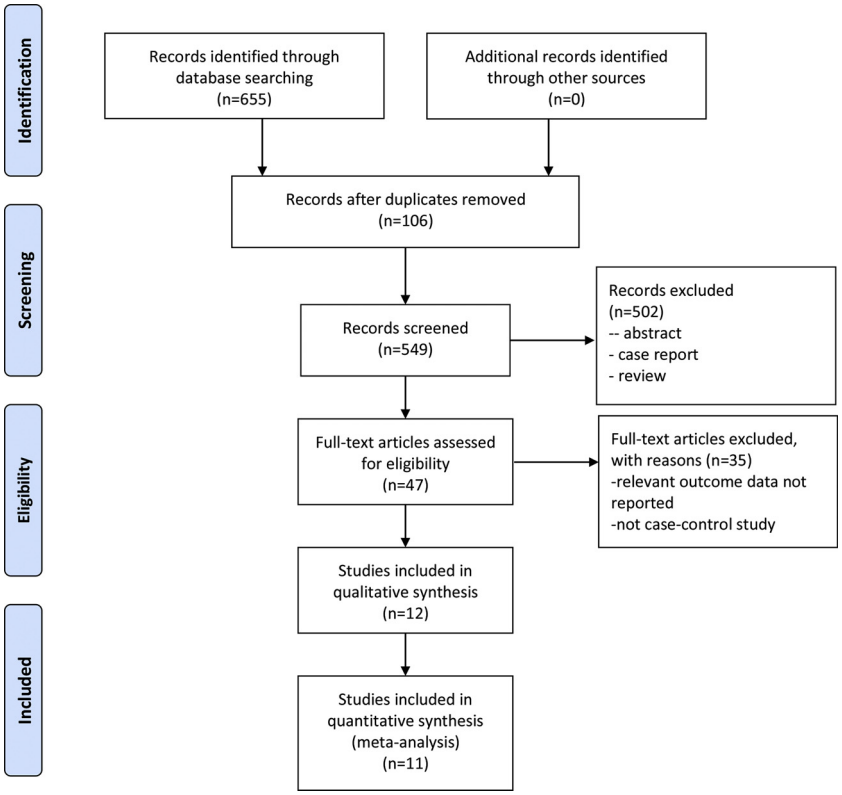

Fig. 1. Flow diagram of articles selection process.

1.15–1.47), but not in Caucasian population. Besides, the stratified analysis by gender showed that a significant association of MDM2 309 T/G polymorphism with NSCLC susceptibility under homozygous (OR: 1.38, 95% CI: 1.07–1.78) and recessive genetic model (OR: 1.42, 95% CI: 1.12, 1.80) in female population (Table 3). We conducted subgroup analysis by genotyping methods, result showed TaqMan method was significantly correlated with risks of NSCLC under homozygous, recessive genetic and allelic genetic model($P < 0.05$) (Table 4).

3.3. Sensitivity analysis and bias diagnostics

In the current meta-analysis, sensitivity analysis was conducted by removing a single study at a time and reanalyzing the pooled results.

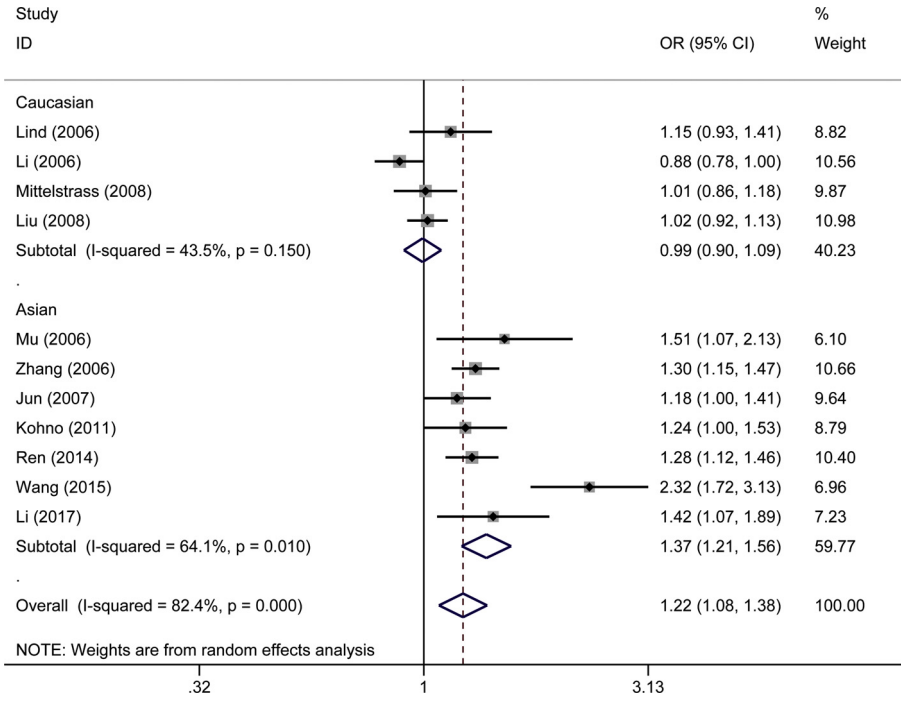

Fig. 2. Forest plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism under an Allele genetic model (G vs. T).

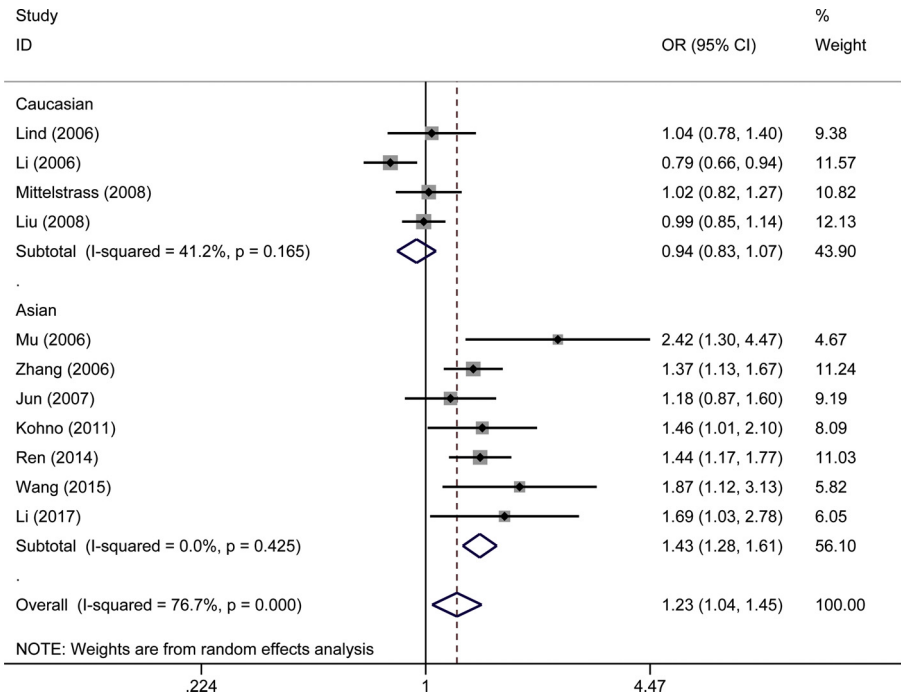

Fig. 3. Forest plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism under a Dominant genetic model (GG + GT vs. TT).

The results indicated that Removal of any one studies did not change the results from the original analysis. The results of the funnel plots and Egger's test did not show any significates publication bias in the current analysis, expect under dominant genetic model in ethnicity subgroup (Fig. 7; Table 2).

4. Discussion

MDM2 is regarded as a proto-oncogene that can be activated in different types of human tumors [28], and NSCLC is not an exception. The activation of MDM2 in human lung cancer cell line enhanced proliferation, colony-forming capacity, and tumorigenicity through promoting the ubiquitination and proteasome-dependent degradation of p53 which regulates DNA repair, cell cycle and angiogenesis, as well as other cellular pathways [29,30]. It was reported that MDM2 was modified by site-specific acetylation and ubiquitin, after that it could suppress the development of tumor [31]. Previous study has verified that abnormal expression of MDM2 mediated by genetic variants may contribute to subsequent attenuation of the p53 pathway, and accelerate the deterioration of the NSCLS [32]. Although meta-analysis of the relationship between MDM2 polymorphism an NSCLC has been done before, their conclusion only revealed that MDM2 T309 G

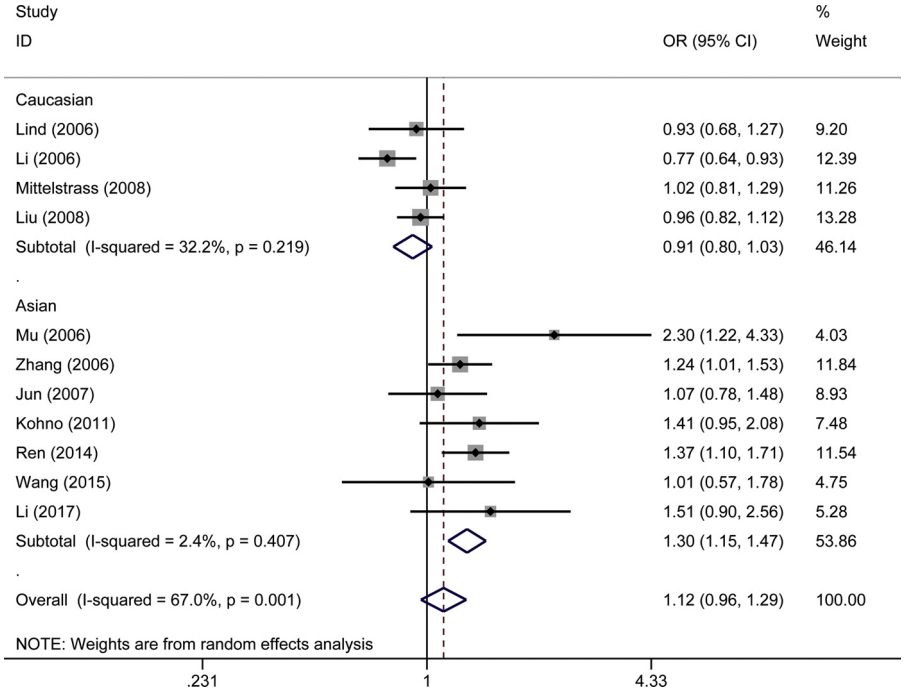

Fig. 4. Forest plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism under a Heterozygote genetic model (TG vs. TT).

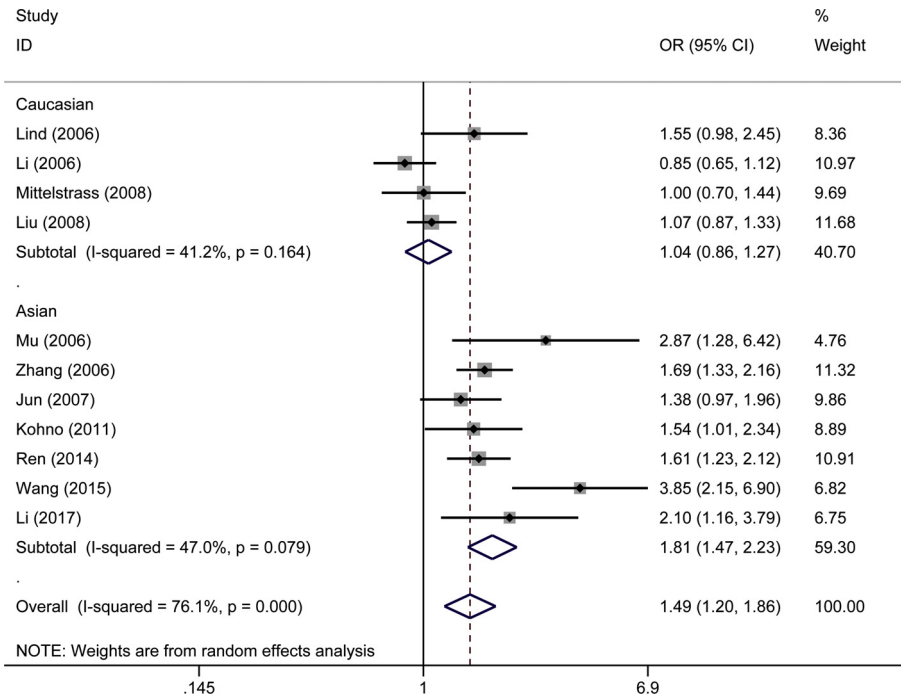

Fig. 5. Forest plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism under a Homozygote genetic model (GG vs. TT).

polymorphism may be a causative factor for the incidence of NSCLC and it may contribute to NSCLC susceptibility and prognosis [33]. Rather, in the present meta-analysis, in addition to confirming the previous points, we have also revealed that Asian and female population showed a hypersensitive association of MDM2 309 T/G polymorphism with NSCLC susceptibility in the subgroup analysis of the ethnicity and gender. Our results are more accurate.

So how does MDM2 polymorphism contribute to tumorigenesis in NSCLS? To summarize, SNP309 in the promoter of the MDM2 gene increases the binding affinity of the transcriptional activator Sp1, which leads to the high level of MDM2 [34]. The increased MDM2 further contributes to the attenuation of the p53 function. The homozygous G/G or heterozygous T/G genotypes have been shown to be associated with significantly higher levels of MDM2 expression, which signifies that gene polymorphism indeed has a crucial effect on expression of gene [35,36]. It is worth thinking about the effect of other polymorphism of MDM2 on its expression. It was reported that there is indeed another functional SNP(SNP285C) located 24 base pairs upstream of SNP309 [36]. However, SNP285 only regulates the effect of SNP309 to some degree. For example, SNP285C allele would antagonize the eff ;ect of SNP309 G, reducing the binding strength between Sp1 and the MDM2 promoter. In other words, the main effect is still

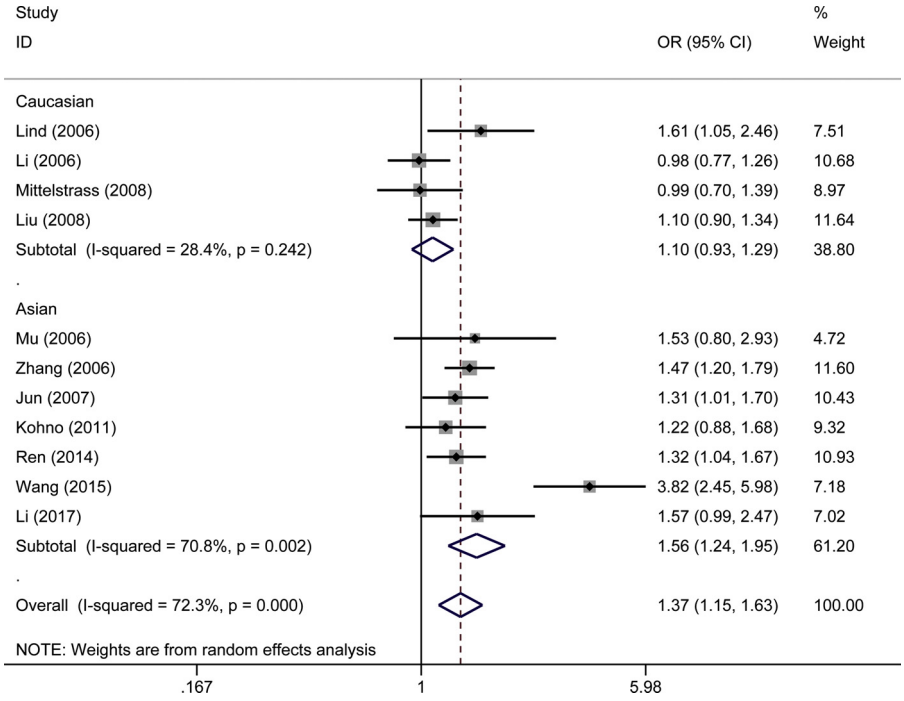

Fig. 6. Forest plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism under a Recessive genetic model (GG vs. GT + TT).

Table 2
Results of the association between MDM2 309 T/G polymorphism and NSCLC susceptibility risk by different ethnicities.

Comparison model	Studies	Overall effect			Heterogeneity		Publication bias	
		OR (95% CI)	Z-score	p-value	I^2 (%)	*p*-value	Begg's test	Egger's test
homozygous genetic model	11	1.49 (1.20,1.86)	3.58	0.000	76.1	0.000	0.131	0.036
Caucasian	4	1.04 (0.86,1.27)	0.42	0.673	41.2	0.164	0.497	0.530
Asian	7	1.81 (1.47,2.23)	5.54	0.000	47.0	0.079	0.176	0.107
heterozygous genetic model	11	1.12 (0.96, 1.29)	1.44	0.149	67.0	0.001	0.492	0.470
Caucasian	4	0.91 (0.80, 1.03)	1.44	0.150	32.2	0.219	1.000	0.907
Asian	7	1.30 (1.15, 1.47)	4.18	0.000	2.4	0.407	0.453	0.504
dominant genetic model	11	1.23 (1.04, 1.45)	2.47	0.013	76.7	0.000	0.039	0.029
Caucasian	4	0.94 (0.83, 1.07)	0.93	0.354	41.2	0.165	0.497	0.770
Asian	7	1.43 (1.28, 1.61)	6.24	0.000	0.0	0.425	0.011	0.083
recessive genetic model	11	1.37 (1.15, 1.63)	3.54	0.000	72.3	0.000	0.336	0.170
Caucasian	4	1.10 (0.93, 1.29)	1.08	0.282	28.4	0.242	0.497	0.492
Asian	7	1.56 (1.24, 1.95)	3.84	0.000	70.8	0.002	0.453	0.323
allelic genetic	11	1.22 (1.08, 1.38)	3.20	0.001	82.4	0.000	0.131	0.080
Caucasian	4	0.99 (0.90, 1.09)	0.13	0.899	43.5	0.150	0.497	0.595
Asian	7	1.37 (1.21, 1.56)	4.96	0.000	64.1	0.010	0.176	0.160

OR, odds ratio; CI, confidence interval.

Table 3
Results of the association between MDM2 309 T/G polymorphism and NSCLC susceptibility risk by gender.

Comparison model	Studies	Overall effect			Heterogeneity	
		OR (95% CI)	Z-score	p-value	I^2 (%)	*p*-value
homozygous genetic model	6	1.11 (0.94,1.32)	1.29	0.197	45.8	0.100
Male	3	0.95 (0.77,1.19)	0.43	0.665	0.0	0.366
Female	3	1.38 (1.07,1.78)	2.48	0.013	24.8	0.264
heterozygous genetic model	6	0.97 (0.87, 1.09)	0.51	0.610	0.0	0.554
Male	3	0.98 (0.84, 1.15)	0.21	0.833	0.0	0.445
Female	3	0.95 (0.80, 1.13)	0.53	0.594	12.1	0.321
dominant genetic model	6	1.00 (0.90, 1.12)	0.02	0.982	0.0	0.640
Male	3	0.98 (0.85, 1.13)	0.33	0.744	0.0	0.850
Female	3	1.03 (0.88, 1.22)	0.40	0.686	28.6	0.246
recessive genetic model	6	1.17 (0.91, 1.51)	1.21	0.213	55.4	0.047
Male	3	0.99 (0.73, 1.34)	0.07	0.944	50.2	0.134
Female	3	1.42 (1.12, 1.80)	2.86	0.004	0.0	0.494
allelic genetic	6	0.99 (0.92, 1.07)	0.26	0.798	0.0	0.573
Male	3	0.94 (0.85, 1.04)	1.21	0.225	0.0	0.689
Female	3	1.06 (0.94, 1.19)	0.99	0.321	0.0	0.705

OR, odds ratio; CI, confidence interval.

caused by SNP309. Of course, the secondary effect of SNP283 cannot be ignored. Unfortunately, few studies have published simultaneously the MDM2 polymorphism about the two sites at the same time, which made our meta-analysis more difficult to carry out. Moreover, it is reported that the effect of polymorphism of MDM2 on cancer risk, in general, are more dependent on tissue type, which implies that SNP309 variation in MDM2 occupies a decisive position but not SNP285 in NSCLC [37].

Thus, in our study, we just focus on the T309 G site, and we looked through other literature and evaluated the potential value of SNP309 for tumor to reveal the biological mechanisms that may be involved more fully. *Gansmo et al.* found that a different risk of endometrial but not for ovarian cancer applying a different model among individuals harboring the SNP309 TT genotype. In addition, *Gansmo* also demonstrated that del1518 is an indel polymorphism residing in the MDM2 promoter P1 and it was to be associated with increased risk of colon cancer [38]. In line with previous risk assessments, our study identified that MDM2 SNP309 may be a potential biomarker for NSCLC risk, particularly for Asian people and women. MDM2 SNP 309 G G enhanced SP1 binding ability, by combining the effect of estrogen, enabling the transcriptional activity of MDM2 and promoting the tumor formation [34]. Because women's estrogen levels are much higher than men's, interactions with estrogen may be one of the reasons for the increased risk of NSCLC in women.

The present study verified the stability of meta-analysis results through sensitivity analysis. Additionally, the Begg's test and Egger's test were also used to identify no publication bias. However, this study also exists in some limitations: the literature was just limited to English and Chinese; due to lack of original data, this meta-analysis was based on unadjusted estimates of OR and 95% CI, and multiple factors such as age, gender, tumor stage, smoking, and other risk factors should be taken into consideration; the racial subgroup lacks African population due to the lack of data; our study failed to obtain original data from the included studies, which may limit the further evaluation of the potential role of MDM2 T309 G polymorphism in the pathogenesis of NSCLC; NSCLC is a multi-factorial disease. Disease age, tumor stage, smoking, histology, or Gene–gene/gene–environment interactions may play important roles in the pathology of NSCLC, but most studies lack relative information to analysis association of MDM2 with NSCLC clinicopathological features according to these factors.

In summary, this meta-analysis suggests that MDM2 SNP309 polymorphism was significantly associated with an increased overall NSCLC risk with allelic, recessive, dominant and homozygous genetic models, especially for Asians and women. However, large and well-designed studies are needed to validate this finding. Moreover, further studies exploring the association between SNP283 and SNP309, may provide a more valuable and comprehensive understanding of MDM2 polymorphism and NSCLC risk. Whether or not estrogen influences the MDM2 expression remains to be fully elucidated.

Table 4
Results of the association between MDM2 309 T/G polymorphism and NSCLC susceptibility risk by different genotyping methods.

Comparison model	Studies	Overall effect			Heterogeneity	
		OR (95% CI)	Z-score	p-value	I^2 (%)	*p*-value
homozygous genetic model	11	1.49 (1.20,1.86)	3.58	0.000	76.1	0.000
TaqMan	4	1.45 (1.08,1.94)	2.50	0.012	64.6	0.037
RIPA-PCR	1	1.54 (1.01,2.34)	2.02	0.043	–	–
PCR-SSCP	1	2.87 (1.28,6.42)	2.56	0.010	–	–
MALDI-TOF	1	1.00 (0.70,1.44)	0.02	0.987	–	–
PCR-RFLP	3	1.58 (0.77,3.27)	1.24	0.216	91.0	0.000
ARMS-PCR	1	1.69 (1.33,2.16)	4.26	0.000	–	–
heterozygous genetic model	11	1.12 (0.96,1.29)	1.44	0.149	67.0	0.001
TaqMan	4	1.13 (0.89,1.42)	1.00	0.319	67.8	0.025
RIPA-PCR	1	1.41 (0.95,2.08)	1.72	0.085	–	–
PCR-SSCP	1	2.30 (1.22,4.33)	2.57	0.010	–	–
MALDI-TOF	1	1.03 (0.81,1.29)	0.21	0.836	–	–
PCR-RFLP	3	0.89 (0.70,1.13)	0.93	0.352	40.5	0.186
ARMS-PCR	1	1.24 (1.01,1.53)	2.03	0.042	–	–
dominant genetic model	11	1.23 (1.04,1.45)	2.47	0.013	73.6	0.010
TaqMan	4	1.21 (0.95,1.54)	1.51	0.131	64.6	0.037
RIPA-PCR	1	1.46 (1.01,2.10)	2.03	0.042	–	–
PCR-SSCP	1	2.42 (1.31,4.47)	2.81	0.005	–	–
MALDI-TOF	1	1.02 (0.82, 1.27)	0.18	0.857	–	–
PCR-RFLP	3	1.14 (0.73,1.79)	0.58	0.560	84.2	0.002
ARMS-PCR	1	1.37 (1.13,1.67)	3.16	0.002	–	–
recessive genetic model	11	1.37 (1.15,1.63)	3.54	0.000	72.3	0.000
TaqMan	4	1.29 (1.08,1.53)	2.86	0.004	28.0	0.244
RIPA-PCR	1	1.22 (0.88,1.68)	1.19	0.233	–	–
PCR-SSCP	1	1.53 (0.80,2.93)	1.30	0.194	–	–
MALDI-TOF	1	0.99 (0.71,1.39)	0.06	0.955	–	–
PCR-RFLP	3	1.66 (0.87,3.17)	1.52	0.128	92.6	0.000
ARMS-PCR	1	1.47 (1.21,1.79)	3.79	0.000	–	–
allelic genetic	11	1.22 (1.08,1.38)	3.20	0.001	82.4	0.000
TaqMan	4	1.18 (1.02,1.37)	2.17	0.030	68.8	0.022
RIPA-PCR	1	1.24 (1.00,1.53)	1.96	0.049	–	–
PCR-SSCP	1	1.51 (1.07,2.13)	2.33	0.020	–	–
MALDI-TOF	1	1.01 (0.86,1.19)	0.11	0.916	–	–
PCR-RFLP	3	1.32 (0.84,2.07)	1.20	0.232	94.4	0.000
ARMS-PCR	1	1.30 (1.15,1.47)	4.26	0.000	–	–

OR, odds ratio; CI, confidence interval; PCR-RFLP, PCR-restriction fragment length polymorphism; PIR A-PCR, Primer—introduced restriction analysis; PCR-SSCP, PCR-single-strand conformation polymorphism; ARMS-PC R, Amplification refractory mutation system-PCR; MALDI-TOFMS, Matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

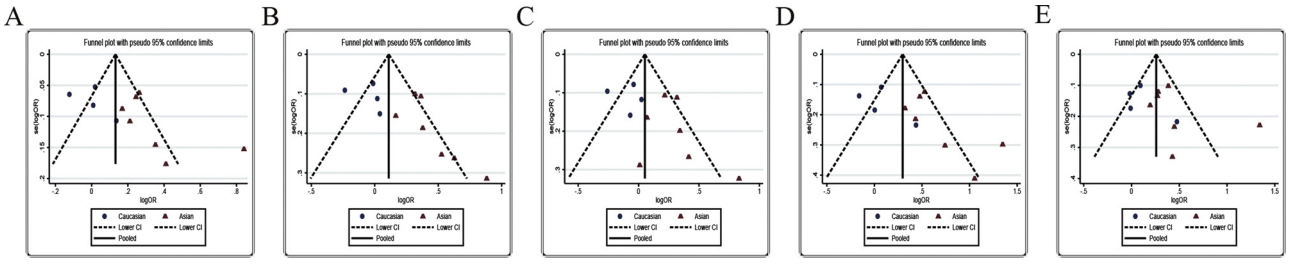

Fig. 7. Funnel plot of Non-small cell lung cancer (NSCLC) associated with MDM2 309 T/G gene polymorphism. (A–E) Indicates allele, dominant, heterozygote, homozygote, recessive model, respectively.

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