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Original Article

Association between polymorphisms in MDM2 gene and oral cancer risk: a meta-analysis

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Abstract: This study aims to to systematically summarize the association between the polymorphisms of human homolog of mouse double minute 2 (MDM2) gene and oral cancer susceptibility. The relevant articles were searched from PubMed and Embase database. Studies were selected according to inclusion criteria and exclusion criteria. Seven studies were included in this meta-analysis. Seven data sets including 2108 cases and 2999 controls were about rs2279744 polymorphism; 801 cases and 1167 controls in 3 data sets were for rs937283 polymorphism. For MDM2 rs2279744 polymorphism, the individuals carrying TT genotype were more likely to develop oral cancer compared to those with GT or GG genotype (recessive model TT vs. GT+GG: OR=1.27, 95% CI=1.01-1.60, P=0.012 for heterogeneity). There were no significant associations between rs937283 polymorphism and oral cancer in any genetic model. In the stratified analysis by ethnicity, the associations between rs2279744 and oral cancer were significant among Caucasian population under the homogeneity model (TT versus GG: OR=1.57, 95% CI=1.12-2.21), the recessive model (TT versus GT+GG: OR=1.61, 95% CI=1.33-1.95) and the allelic model (T versus G: OR=1.34, 95% CI=1.13-1.58). However, the result among Asians was not statistically significant. There were not significant results in the stratified analysis by tumor type. Rs2279744 in MDM2 gene might be associated with susceptibility of oral cancer.

Keywords: Oral medicine, genetic susceptibility, human homolog of mouse double minute 2, single nucleotide polymorphism, systematic review

Introduction

Oral cancer is one kind of major malignancies which damage the health and lives of people, with an increasing incidence rate in last two decades worldwide. According to the statistical data of International Agency for Research on Cancer (IARC)'s Cancer Report 2008, there are approximately 274000 new cases and 145000 deaths from oral cancer annually [1]. Consequently, Oral cancer earns more and more attention from scientists and medical practitioners. The precancerous lesions such as oral leukoplakia generally precede oral cancer and almost 5%-10% of patients with oral leukoplakia will progress to malignancy.

There are multiple risk factors attributing to oral cancer, of which smoking and alcohol drinking are two major risk factors. Although environmental exposure is common in the patients of oral cancer, yet only a small fraction of them actually develop malignancies. It suggests that genetic susceptibility plays important role in the carcinogenesis. And there are many carcinogenic substances exist in occupational and living environment which can damage the DNA, such as the forming of DNA adduct. When the damage exceeds the ability of DNA repairing in the cells, the cells may transform to be unregulated proliferating malignancies. The tumor suppressor P53 play a highly conserved role in controlling several pathways, that protect cells from malignant transformation [2]. As we know, the p53 pathway plays important roles in most human cancers. And the study suggested that the p53 pathway can be regulated by the overexpression of the human homolog of mouse double minute 2 (MDM2) gene [3].

MDM2 gene, located in chromosome 12q13-14, is known as a principal regulator of p53 by encoding an ubiquitin protein ligase to inhibit the transcriptional activity of P53 [4]. The overexpression of MDM2 gene in tumor cells can lead to superabundant silencing of P53, which inhibit P53's tumor suppressor effect, and many studies reported its overexpression have associations with tumor invasiveness and poor prognosis in several kinds of malignancies [3, 5-7]. Moreover, overexpression of MDM2 gene has been reported in oral cancer [8-10] and overexpression of MDM2may substitute for inactivating p53 by mutation [11, 12], so MDM2 may play an important role in the development of oral cancer. Single nucleotide polymorphisms (SNP) are one type of the most important and widely studied variations of genes in recent years. The most studied SNPs of MDM2 were in its promoter region, MDM2-A2164G (rs937283) and MDM2-T2580G (rs2279744), which may change the transcription levels of MDM2 gene and alter the binding affinity of p53 and MDM2, in hence influencing the regulation of cell cycle [13].

There are studies reporting the association between rs937283 and rs2279744 in MDM2 gene and the susceptibility of oral cancer, [14-20] but their results were inconsistent. Until now, there was no meta-analysis on the relationship between the polymorphisms of MDM2 gene and the risk of oral cancer. The advantage of meta-analysis is that it could combine the published data together to reach a larger sample size in order to get more statistical power. So we conduct a meta-analysis to assess the associations between the polymorphisms (rs2279744 and rs937283) in MDM2 gene and the susceptibility of oral cancer.

Materials and methods

Data sources

Pubmed and Embase databases were the searching sources of the articles in the present study and we carried out the last search on April 2015. The systematic search subject terms or keyword were as follows: "mouse double minute 2 AND oral cancer", "mouse double minute 2 AND oral carcinoma", "MDM2 AND oral cancer", or "MDM2 AND oral carcinoma", SNP number "(rs937283 or rs2279744)AND (oral cancer or oral carcinoma)".

Study evaluation

The potential relevance of the articles was evaluated by reading the titles and abstracts of all the articles, of which that duplicate and unrelated articles were excluded at first. Two investigators independently evaluate the remaining articles to select the eligible articles. The inclusion criteria of the eligible studies were: (a) evaluating association between the rs279744 or rs937283 and risks of oral cancer or oral leukoplakia, (b) using a case-control study design, (c) odds ratios (ORs) with their 95% confidence intervals (95% CIs) were available or could be calculated for each study, (d) no restriction of country or ethnicity. The quality of each included study was evaluated by Newcastle-Ottawa method and the score of each study was between 6 to 7.

Data extraction

The following information was extracted for each included study: the name of the first author, year of publication, country, ethnicity, tumor type, SNP genotyping method, number of cases and controls, frequencies of each group with rs279744 and rs937283 genotypes. We couldn't extract information of environmental effects in the analyses because almost no studies presented the environmental effects.

Statistical methods

Hardy-Weinberg equilibrium was assessed by Chi-square test in control group of each included study. The associations between MDM2 SNPs and oral cancer risks were evaluated by calculating ORs and their 95% CIs from combinations of each study using heterozygote model (GT vs. GG for rs2279744; GA vs. AA for rs937283), homozygote model (TT vs. GG for rs2279744; GG vs. AA for rs937283), dominant model (TT+GT vs. GG for rs2279744; GG+GA vs. AA for rs937283), recessive model (TT vs. GT+GG for rs2279744; GG vs. GA+AA for rs937283) and allelic model (T vs. G for rs2279744; G vs. A for rs937283).

Cochran's Q test and I^2 test were conducted to assess between-study heterogeneity and the significant heterogeneity was considered as $P<0.05$ and/or $I^2 \geq 50\%$. If $P>0.05$ or $I^2<50\%$, the results of fixed-effect models were used. Otherwise, the results of random-effect models were used.

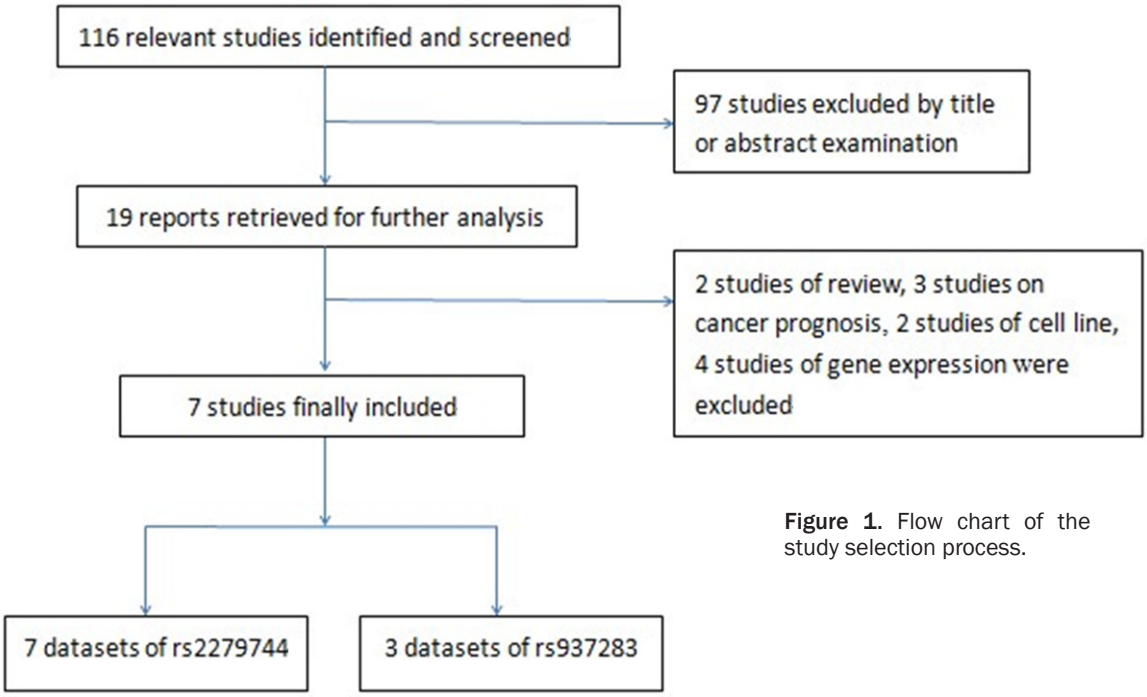

Figure 1. Flow chart of the study selection process.

Sensitivity analyses were also conducted. We excluded the studies in which genotype frequencies in controls derived from Hardy-Weinberg Equilibrium and assessed whether the results were in agreement with the findings from foregoing analysis. By sequentially deleting each single study involved in the meta-analysis, the potential influence of the individual data set to the pooled ORs was identified. The inverted funnel plots and the Egger's test were used to examine the publication bias. The subgroup analyses stratified by ethnicity and tumor type were conducted to estimate specific ORs for Asian population, for Caucasian population and for oral squamous cell carcinomas.

All of the statistical analyses were two-sided and performed using the Stata software version 11.0 (Stata Corp, College station, TX).

Results

Characteristics of included studies

A total of 116 studies were searched and identified. Examination of title and abstract excluded 97 studies. Among 19 articles eligible for further evaluation, 12 studies were excluded because there are reviews, studies about prognosis of oral cancer patients, or about cell line and gene expression. At last, 7 studies were included in quantitative synthesis for meta-analysis [11-17]. **Figure 1** showed the process of study selecting. These studies included 10 data sets of two SNPs. Seven data sets including 2108 cases and 2999 controls were about rs2279744 polymorphism and 801 cases and 1167 controls in 3 data sets were for rs937283 polymorphism. The characteristics of the selected studies are summarized in **Table 1**. Of the 7 included studies, with sample sizes ranged from 323 to 1623, 4 studies were on European population and 3 studies were on Asian population. Almost all of the cases were histologically confirmed and controls were mainly frequency matched by gender and age. The distribution of genotypes in the controls was mostly in Hardy-Weinberg equilibrium (HWE), except for one data sets of rs2279744 from which study was subjected to a sensitivity analysis.

The association between MDM2 rs2279744 and risks of oral cancer

Majority of ORs with their 95%CIs showed there were not statistically significant associations between rs2279744 and risk of oral cancer (TT vs. GG: OR=1.19 95% CI=0.93-1.44, P=0.145 for heterogeneity, I^2=39.1%; GT vs. GG: OR=0.99, 95% CI=0.85-1.17, P=0.999 for heterogeneity, I^2=0%; GT+TT vs. GG: OR=1.06, 95%

Table 1. Characteristics of all studies in meta-analysis

Author, year	Country	Ethnicity	CaseType	SNP	Genotyping method	No. (case/control)	Case			Control			HWE(P)
							TT/GG	GT/AG	GG/AA	TT/GG	GT/AG	GG/AA	
Jin L (2012)[14]	American	Caucasian	SGC	rs2279744	PCR-RFLP	156/511	67	61	28	170	232	109	0.075
Wang Z (2012)[15]	American	Caucasian	OC	rs2279744	PCR-RFLP	320/321	145	175*		106	215*		
Chen X (2010)[16]	American	Caucasian	OSCC	rs2279744	PCR-RFLP	325/335	146	132	47	112	165	58	0.835
Huanga SF (2009)[17]	China Taiwan	Asian	OSCC	rs2279744	MALDI-TOF	351/1272	274	653	345	80	176	95	0.930
Tua HF (2008)[18]	China Taiwan	Asian	All	rs2279744	Direct sequencing	259/116	57	129	73	29	55	32	0.582
			OSCC	rs2279744	Direct sequencing	189/116	44	93	52	29	55	32	
			OSF	rs2279744	Direct sequencing	70/116	13	36	21	29	55	32	
Hamida S (2008)[19]	Malaysia	Asian	OSCC	rs2279744	PCR-RFLP	207/116	48	104	55	30	58	28	0.997
Misra C (2009)[20]	Indian	Asian	All	rs2279744	PCR-RFLP	490/328	124	244	122	59	181	88	0.042
			OSCC	rs2279744	PCR-RFLP	297/328	70	147	80	59	181	88	
			leukoplakia	rs2279744	PCR-RFLP	193/328	54	97	42	59	181	88	
Jin L (2012)[14]	American	Caucasian	SGC	rs937283	PCR-RFLP	156/511	29	68	59	83	255	173	0.498
Wang Z (2012)[15]	American	Caucasian	OC	rs937283	PCR-RFLP	320/321		251*	69		210*	111	
Chen X (2010)[16]	American	Caucasian	OSCC	rs937283	PCR-RFLP	325/335	47	209	69	52	169	114	0.413

SGC: salivary gland carcinoma, OSCC: oral squamous cell carcinomas, OC: oropharyngeal cancer, OSF: oral submucous fibrosis. *represented the sum of GG+GT or GG+GA.

Table 2. Association between MDM2 polymorphisms with oral cancer risks

	Data set number	Fixed effect	Random effect	Phet	I-squared (%)
Rs2279744					
TT vs. GG	6	1.19 [0.99, 1.44]	1.19 [0.93, 1.53]	0.145	39.1
GT vs. GG	6	0.99 [0.85, 1.17]	0.99 [0.85, 1.17]	0.999	0.0
TT+GT vs. GG	6	1.06 [0.91, 1.24]	1.06 [0.91, 1.24]	0.869	0.0
TT vs. GT+GG	7	1.30 [1.14, 1.49]	1.27 [1.01, 1.60]*	0.012	63.3
T vs. G	6	1.11 [1.01, 1.22]	1.11 [0.97, 1.28]	0.063	52.2
rs937283					
GGvs. AA	2	1.25 [0.87, 1.78]	1.25 [0.86, 1.80]	0.302	6.3
GA vs. AA	2	1.33 [1.02, 1.73]	1.27 [0.50, 3.25]	0.000	91.8
GG+GA vs. AA	3	1.49 [1.22, 1.83]	1.46 [0.86, 2.48]	0.001	84.1
GG vs. GA+AA	2	1.03 [0.75, 1.41]	1.03 [0.75, 1.41]	0.445	0.0
G vs. A	2	1.13 [0.96, 1.34]	1.18 [0.86, 1.46]	0.114	59.9

Phet: *P* value for heterogeneity test. *significant results.

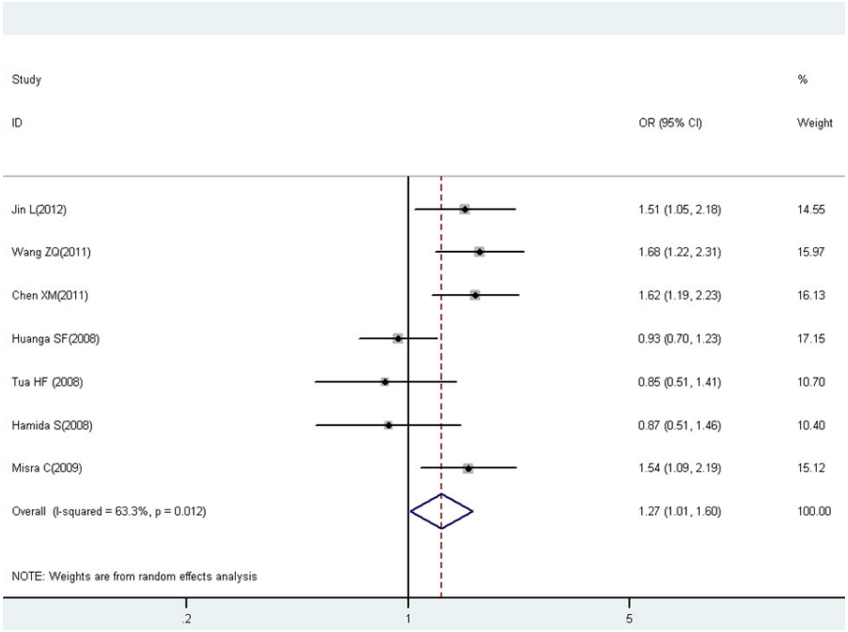

Figure 2. Meta-analysis of MDM2 polymorphism andoral cancer risk under the recessive model.

CI=0.91-1.24, P=0.869 for heterogeneity, I^2=0%; allele T vs. G: OR=1.11, 95% CI=1.01-1.22, P=0.063 for heterogeneity, I^2=52.2%) (**Table 2**). A significant result was observed in recessive model (TT vs. GT+GG: OR=1.27, 95% CI=1.01-1.60, P=0.012 for heterogeneity, I^2=63.3%) (**Figure 2**).

Subgroup analyses stratified by ethnicity and tumor type were conducted for rs2279744 polymorphism. In the stratified analysis by ethnicity, there were significant results in Caucasian population under the homogeneity model (TT versus GG: OR=1.57, 95% CI=1.12-2.21), the recsive mod-el (TT versus GT+GG: OR=1.61, 95% CI=1.33-1.95) and the allelic model (T versus G: OR=1.34, 95% CI=1.13-1.58). However, there were no statistically significant results in subgroup analysis of Asian group. In the stratified analysis by tumor type, no statistically significant results were observed between the risk of OSCC and rs2279744 polymorphism (GT vs. GG: OR=0.98, 95% CI=0.82-1.17; TT vs. GG: OR=1.01, 95% CI=0.90-1.36; dominant model TT +GT vs. GG: OR=1.02, 95% CI =0.86-1.21; recessive model TT vs. GT+GG: OR=1.14 95% CI=0.87-1.50; allele T vs. G: OR =1.06, 95% CI=0.96-1.18) (**Table 3**, **Figures 3-5**).

Results of sensitivity analysis suggested th at the pooled results of the metaanalysis were stable. When one study whose genotype frequencies in controls deviated from HWE wre excluded, the results did not change much. Each single study incl-uded in the meta-analysis was deleted each time and the pooled ORs didn't change, which supports the robustness of our findings. The results of inverted funnel plot and Egger's test showed that there was no publication bias.

MDM2 rs937283 SNP and oral cancer risks

For MDM2 rs937283 polymorphism, no significant associations were observed in all kinds of genetic models (GG vs. AA: OR=1.25, 95%

Table 3. Pooled ORs and 95% CIs for MDM2 rs2279744polymorphism of stratified meta-analysis

Subgroup	Genotype	No of studies	Test of association				Test of heterogeneity		
			OR (95% CI)	Z	*P*-value	Model	X^2	*P*-value	I^2 (%)
Asian	TT vs. GG	4	1.05 [0.84, 1.32]	0.46	0.644	F	4.42	0.220	32.1
	GT vs. GG	4	0.99 [0.82, 1.20]	0.06	0.949	F	0.16	0.984	0.0
TT+GT vs. GG		4	1.01 [0.84, 1.21]	0.12	0.903	F	0.61	0.893	0.0
TT vs. GT+GG		4	1.06 [0.85, 1.28]	0.62	0.532	F	6.64	0.084	54.8
Caucasian	T vs. G	4	1.03 [0.92, 1.15]	0.45	0.655	F	3.85	0.278	22.2
	TT vs. GG	2	1.57 [1.12, 2.21]	2.63	0.009	F	0.02	0.891	0.0
	GT vs. GG	2	1.00 [0.72, 1.40]	0.02	0.985	F	0.01	0.916	0.0
TT+GT vs. GG		2	1.24 [0.91, 1.69]	1.35	0.175	F	0.00	0.998	0.0
TT vs. GT+GG		3	1.61 [1.33, 1.95]	4.89	0.000	F	0.19	0.910	0.0
OSCC	T vs. G	2	1.34 [1.13, 1.58]	3.36	0.001	F	0.04	0.850	0.0
	TT vs. GG	5	1.01 [0.90, 1.36]	0.97	0.333	F	5.07	0.280	21.1
	GT vs. GG	5	0.98 [0.82, 1.17]	0.27	0.787	F	0.43	0.980	0.0
TT+GT vs. GG		5	1.02 [0.86, 1.21]	0.23	0.821	F	1.18	0.881	0.0
TT vs. GT+GG		5	1.14 [0.87, 1.50]	1.77	0.077	R	9.63	0.047	58.5
	T vs. G	5	1.06 [0.96, 1.18]	1.23	0.217	F	7.10	0.13	43.7

OR, odds ratio; vs, versus; R, random effect model; F, fixed effect model.

CI=0.87-1.78, P=0.302 for heterogeneity, I^2=6.3%; GA vs. AA: OR=1.27, 95% CI=0.50-3.24, P<0.000 for heterogeneity, I^2=91.8%; GG+GA vs. AA: OR=1.46, 95% CI=0.86-2.48, P=0.001 for heterogeneity, I^2=84.1%; GG vs. GA+AA OR=1.03, 95% CI=0.75-1.41, P=0.445 for heterogeneity, I^2=0.0%; G vs. A: OR=1.13, 95% CI=0.96-1.34, P=0.114 for heterogeneity, I^2=59.9%) (**Table 2**). Because there were only two to thr-ee studies in-cluded in the me-ta-analyses, so it's not suitable to conduct the stratified analyses for this polymorphism.

Sensitivity analysis suggested that the results were robust. Every one single study was deleted each time and the pooled ORs did not change. The results of inverted funnel plot and Egger's test showed that there was no publication bias.

Discussion

The genetic susceptibility may play important roles in the development of cancer. Single nucleotide polymorphisms of cancer-related genes may contribute to the disparity in the susceptibility to cancer betw-een individuals.

The p53 pathway is suggested to be the most important in regulating cellular proliferation and repair of DNA damage which is frequently observed to be dysfunctional in carcinogenesis of varieties of cancers. The studies reported that the mutation of p53 gene could happen in more than half of human cancers, suggesting that abnormal expression of p53may result in the deregulation of p53 pathway thus may promoting the development of cancers [2, 21]. It is worth noting that this pathway could be regulating not only by p53 but also by other gene such as MDM2 [22]. MDM2 has been suggested to be a negative regulator of the p53, affecting the translocation of p53 and regulating its transactivation activity. Therefore alteration in the expression level of MDM2 may influence the effect of the p53 pathway, and studies in vivo showed that MDM2 levels could affect p53-related tumor suppression as well as resulting the induction of tumors in mice [23, 24]. There were also evidence that MDM2 were up-regulated in many cancers, including lung, breast, sarcomas and oral carcinomas [8-10, 25-27].

The promoter region of MDM2 has a p53 responsive element that elevated level of p53 can induce the gene, providing an auto-regulatory feedback loop between MDM2 and p53 [28, 29]. The two SNPs in the promoter region, containing four p53-responsive elements, which are involved in the p53 feedback loop [30, 31]. The sequence variation increases the binding affinity of the transcriptional activator, resulting in higher level of MDM2 protein

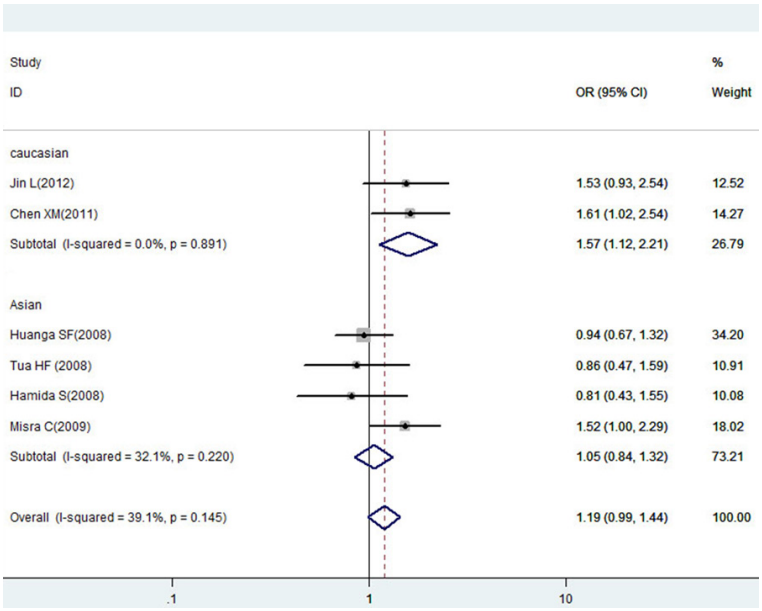

Figure 3. Stratified meta-analysisby ethnicity under the homogeneitymodel (TT versus GG).

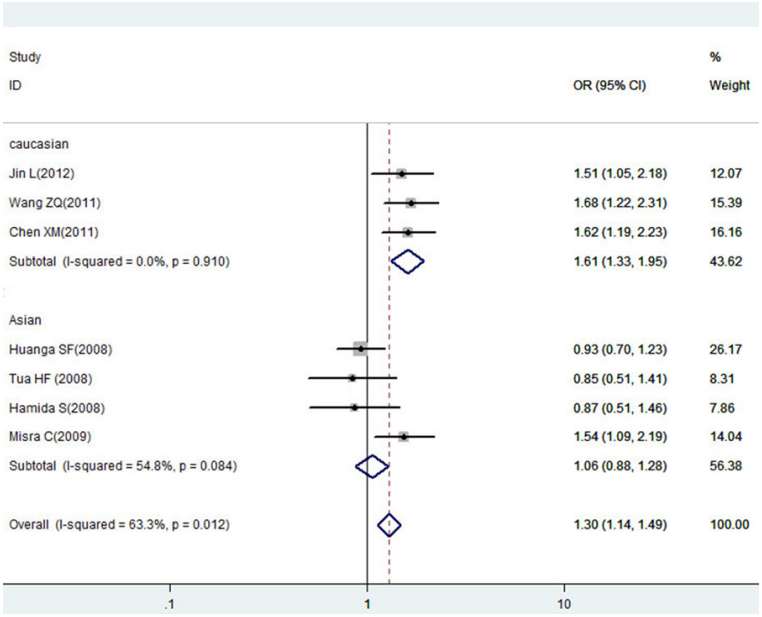

Figure 4. Stratified meta-analysisby ethnicity under the recessive model (TT versus GT+GG).

expression and the subsequent attenuation of the p53 pathway [32]. The alteration of the p53 pathway by the SNP resulting in earlier tumor onset indicate that the promoter polymorphism may act as a cancer susceptibly factor [32].

The rs2279744 termed SNP309 309G>T polymorphism in MDM2 gene has also been studied in many cancer types. However, the results remain conflicting. A meta-analysis of 36 studies with breast, colorectal and lung cancer has suggested that the SNP 309 variant does not have an impact on the risk of breast and colorectal cancers, but is associated with the risk of lung cancer which suggests that the effects of MDM2 SNP309 may vary in different tumor types [33]. Growing number of studies have been done to investigate the relationship between this SNP and the risks of oral cancer, but the results are inconclusive [14-20]. For rs937283 polymorphism, there are only three studies reporting on its association of oral cancer with conflicting results [14-16]. For the relationship of the two SNPs with cancer risk, the negative findings may result from the low statistical power of limited studies now. To better understand the association between these two polymorphisms and oral cancer risk, a meta-analysis with larger sample size and subgroup analysis is necessary. In the present meta-analysis, the statistical power was enlarged by combining the results of seven included studies. The results from this meta-analysis suggested that there was a significant association between rs2-279744 polymorphism in MDM2 gene and risk of oral cancer, which provided new evidence for the genetic susceptibility and etiology of oral cancer.

As we know, the incidence of most genetic polymorphisms could vary between populations of different ethnicity. In the stratified analysis by ethnicity, the significant associations were found among Caucasian under the homogeneity model, the recessive model and the allelic model. However, the result was not statistically significant in Asian population which suggested

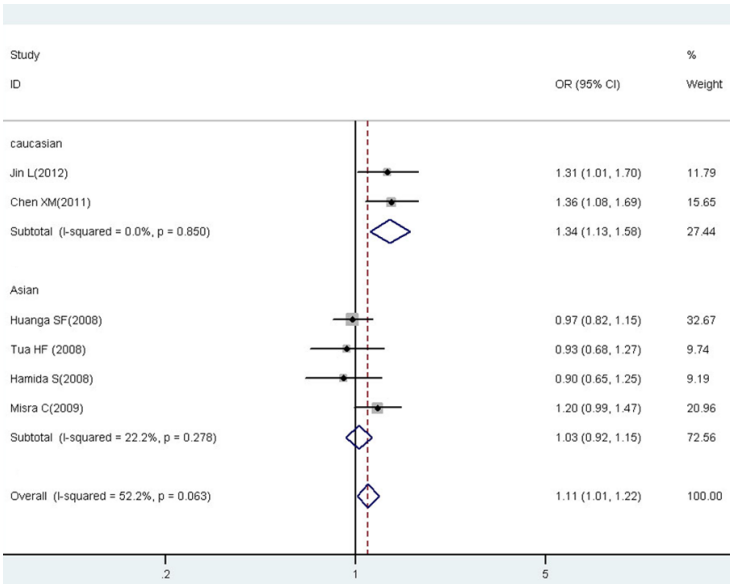

Figure 5. Stratified meta-analysisby ethnicity under the allelicmodel (T versus G).

that there may be ethnicity difference for association between two SNPs and cancer risks.

The current study is the first meta-analysis investigating the relationship of MDM2 rs2279744 and rs937283 polymorphisms with the risk of oral cancer. This meta-analysis suggested that rs2279744 (SNP309) might be associated with oral cancer risk. The SNP309 in the MDM2 results in higher expression of MDM2 mRNA and protein and subsequent attenuation of the p53 pathway which may promote the development of oral cancer [32]. The study reported that the mean age of onset for male OSCC patients with the MDM2 SNP 309 GG genotype was earlier than those with the MDM2 SNP 309 TT genotype and the patients harboring GG genotype could have attenuated p53 pathway and impaired genomic repair ability [32]. These results suggested that MDM2 rs2279744 polymorphism could result in over expression of MDM2 and attenuation of the p53 pathway that may be responsible for increased susceptibility of oral cancer.

Despite we try our best to perform a comprehensive analysis, some limitations exist in our meta-analysis should be noted. First, although the results for publication bias in our study were not statistically significant, we search for articles only in English databases, some local databases in Chinese were not included in our search, which could cause publication bias. Second, lack of the original data of available studies limited our further evaluation of potential interactions, such as age, gender, family history, environmental factors and lifestyle. Third, after stratified analysis, the numbers of the included studies are too small to get statistical significant results, so more approximate research data are needed for further study. Fourth, there may be genotyping errors or bias in primary studies, but we could not correct them. Therefore, more studies are needed to provide more evidence on the association between MDM2 polymorphisms and oral cancerin different ethnic populations.

In conclusion, our meta-analysis supported that the rs2279744 polymorphism in MDM2 gene is associated with the risk of oral cancer. Future well-designed and larger population studies are of great value to confirm these findings. Moreover, combination of genetic factors together with environmental exposures should also be considered.

Conclusion

Rs2279744 in MDM2 gene might be associated with oral cancer risk.

Acknowledgements

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Disclosure of conflict of interest

None.

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