

## Original Article

# TP53 codon 72 polymorphism and susceptibility to cervical cancer in the Chinese population: an update meta-analysis

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**Abstract:** Background: Although many epidemiologic studies investigated the TP53 codon 72 polymorphism and its association with cervical cancer (CC), definite conclusions cannot be drawn. Aim of the study: To evaluate the association between TP53 codon 72 polymorphism and risk of cervical cancer in the Chinese population. Methods: A computerized literature search was carried out in PubMed, Springer Link, Ovid, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang Database to collect relevant articles. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. Results: A total of 16 studies including 1684 CC cases and 1178 controls were involved in this meta-analysis. Overall, significant increased association was found between the Pro/Pro carriers and CC risk when all studies in Chinese population pooled into the meta-analysis (heterozygous model: OR = 1.22, 95% CI: 1.01-1.46). In subgroup analyses stratified by ethnicity and source of controls, the same results were observed in Han and in hospital-based studies. Conclusion: Our results suggest that the TP53 codon 72 polymorphism may be potential biomarkers for CC risk in the Chinese population, especially for Han Chinese, and studies with wider spectrum of population are required for definite conclusions.

**Keywords:** Meta-analysis, TP53, Codon 72, polymorphism, cervical cancer

## Introduction

Cervical cancer (CC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008 [1]. More than 85% of these cases and deaths occur in developing countries [1]. In 2005, there were approximately 58,000 new cervical cancer cases and about 20,000 deaths in China [2]. Cervical cancer has been studied since the 19<sup>th</sup> century and the etiological factors were unknown until early 90s, when it was established that the persistent infection by the oncogenic types of the human papillomavirus (HPV) was the main etiological factor for its development [3-5]. Human papillomavirus are a necessary but insufficient cause of cervical

cancer, most HPV-infected women do not develop cervical cancer [6], and epidemiological studies have consistently associated the development of cervical cancer with the genetic factors such as TP53.

TP53 is one of the most extensively studied genes as a tumor suppressor. It has been thought to play a pivotal role in modulating cell growth, division, and apoptosis. Mutant TP53 may contribute to increased cell proliferation, loss of ability to undergo apoptosis, and increasing genetic instability [7]. An important TP53 polymorphism is the restriction fragment length polymorphism in codon 72 of exon 4 coding for proline (72Pro: CCC) or arginine (72Arg: CGC) [8]. The both structural forms have been shown to have some different biochemical and biological properties [9], such as different binding to components of the transcriptional machinery

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**Table 1.** Characteristics of studies included in the meta-analysis

References	Source of controls	Area	Ethnicity	Case/Control	Case			Control			HWE a	
					Arg/Arg	Pro/Pro	Pro/Arg	Arg/Arg	Pro/Pro	Pro/Arg	$\chi^2$	P
Zheng et al [19]	HB	Xinjiang	Han	120/122	24	41	55	32	22	68	1.82	0.177
Zheng et al [19]	HB	Xinjiang	Uigur	152/110	70	20	62	33	16	61	2.04	0.153
Zhou et al [20]	PB	Jiangsu	Han	404/404	75	123	206	88	118	198	0.08	0.773
Yao et al [21]	HB	Guizhou	Not stated	61/45	30	9	22	16	5	24	0.81	0.367
Li et al [22]	HB	Guangdong	Not stated	46/84	26	10	10	60	7	17	9.01	0.003*
Qie et al [23]	PB	Sichuan	Not stated	15/20	12	1	2	8	1	11	1.29	0.257
Hou et al [24]	PB	Sichuan	Not stated	99/60	57	12	30	14	22	24	2.07	0.151
Wu et al [25]	PB	Taiwan	Not stated	99/193	27	15	57	67	34	92	0.06	0.803
Wang et al [26]	HB	Xinjiang	Han	38/34	8	15	15	13	5	16	0.0004	0.983
Wang et al [26]	HB	Xinjiang	Uigur	73/26	35	15	23	8	5	13	0.005	0.945
Ngan et al [27]	HB	Hong Kong	Not stated	102/68	31	21	50	15	8	45	7.76	0.005*
Yang et al [28]	HB	Taiwan	Not stated	128/88	50	29	49	25	20	43	0.03	0.854
Jiang et al [29]	PB	Hunan	Han	105/140	55	15	35	50	21	69	0.13	0.723
Chen et al [30]	HB	Hubei	Han	156/72	22	51	83	22	16	34	0.17	0.678
Li et al [31]	PB	Shanxi	Han	33/51	11	5	17	11	9	31	2.41	0.120
Yang et al [32]	HB	Inner Mongolia	Mongolian	53/65	11	9	33	13	12	40	3.47	0.062

HB, hospital-based; PB, population-based. aHWE in controls; \*Not conformed to HWE.

and different activation of transcription [10]. These observations have provided the rationale for a large number of genetic association studies investigating TP53 Arg72Pro as a risk factor for various human malignancies [11]. Nevertheless, most studies published to date have had small sample sizes, rendering them underpowered to detect small genetic effect sizes, and often have produced controversial or inconclusive results. Moreover, several studies have shown that this TP53 polymorphism is segregated differentially among different ethnic populations, the Arg allele being more common in Caucasian than in African or Asiatic populations [12-18]. These findings require profound analysis to provide explanations for the differential susceptibility to cervical cancer development based on the genetic background of populations. Therefore, we conducted an update meta-analysis to more precisely define the effect of TP53 codon 72 polymorphism on risk for cervical cancer in the Chinese population.

## Materials and methods

### Search strategy and selection criteria

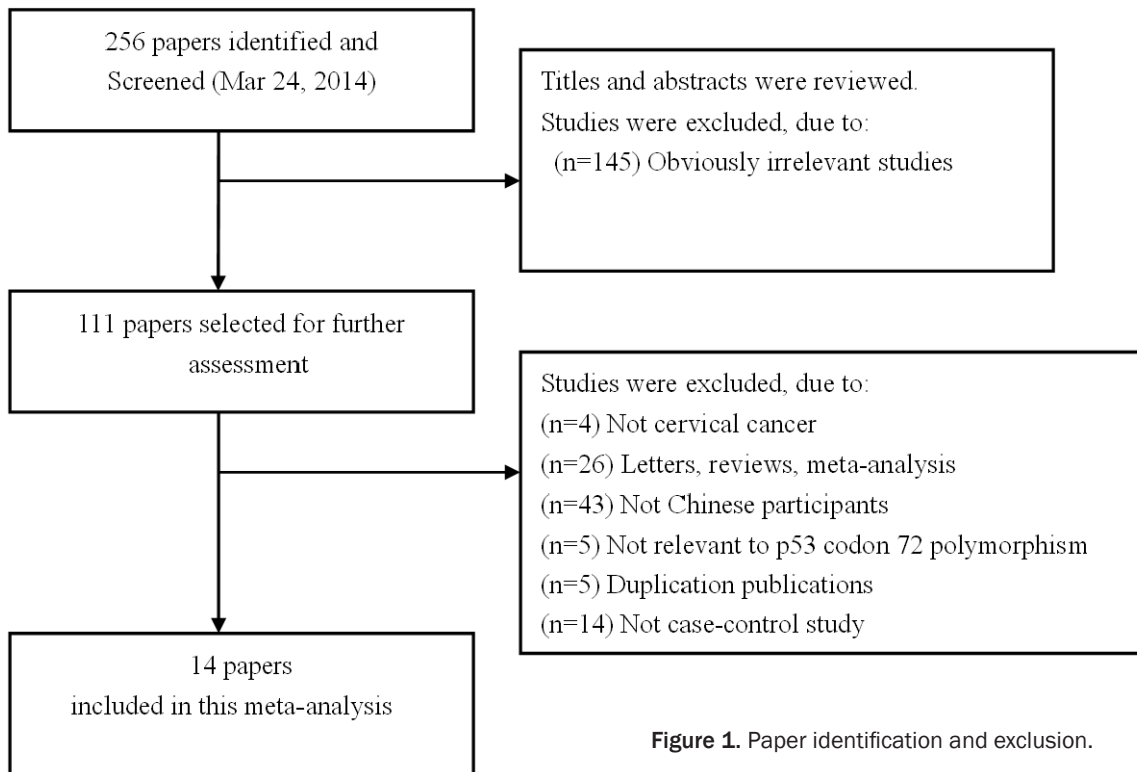
We systematically searched PubMed, Springer Link, Ovid, Chinese biomedical database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang Database

for studies reported before March 2014, without language restriction, using the search terms: TP53, P53, polymorphism, and cervical cancer. Review articles and bibliographies of relevant literatures were manually scanned to identify eligible studies. Studies were selected according to the following criteria: (a) The study used a case-control study design; (b) the report had available genotype frequency, in the case of the literature without genotype frequency reported, we contact with the author for unavailable genotype frequency; (c) in the case of duplication with multiple articles publishing data on the same population, the most complete data set was included; (d) all participants were Chinese. Review papers, letters, case reports, or editorial articles were excluded.

### Data extraction

Two investigators independently extracted data using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by all reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. We extracted standardized data sets from studies of TP53 codon 72 polymorphism and cervical cancer. The following information was sought from each publi-

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**Figure 1.** Paper identification and exclusion.

cation: authors, years of publication, geographical location of participants, source of controls, numbers of cases and controls, genotype frequencies and Hardy-Weinberg equilibrium (HWE) test. The categorization of ethnicity comprised Han, Uigur and other ethnic Chinese. For articles including different ethnicities, data were extracted separately (**Table 1**).

### Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. We calculated pooled ORs and 95% CIs for all studies combined. Furthermore, subgroup analyses were performed by ethnic groups and sources of controls. HWE in the control group for all studies was evaluated using the Chi-square test. Statistical heterogeneity among studies was estimated by use of the  $Q$  and  $I^2$  statistic.  $P$ -value greater than 0.10 for the  $Q$  test indicates a lack of heterogeneity among studies. Dependent on the results of heterogeneity test among individual studies, the fixed effect model (Mantel-Haenszel) or random effect model (DerSimonian and Laird) was selected to summarize the pooled OR. A sensitivity analysis was performed to illustrate

the accuracy and stability of the analytic results using both fixed effect model and random effect model. Publication bias was investigated with the funnel plot, in which the standard error (SE) of log OR of each study was plotted against its OR. Funnel-plot asymmetry was further assessed by the method of Egger's linear regression test. All the  $P$  values were two sided.  $P$  value less than 0.05 was considered statistically significant. All statistical analysis was conducted by using Stata version 10.0 (Stata Corp, College Station, Texas, USA).

### Results

#### Description of included studies

According to the inclusion criteria, 16 case-control studies (14 articles) [19-32] were included and 242 articles were excluded. The publication year of involved studies ranged from 1999 to 2012. The flow chart of study selection is shown in **Figure 1**. In total, 1684 cervical cancer cases and 1178 controls were involved in this meta-analysis, which evaluated the relationship between TP53 codon 72 polymorphism and cervical cancer risk. Among these studies, six were population based; eight

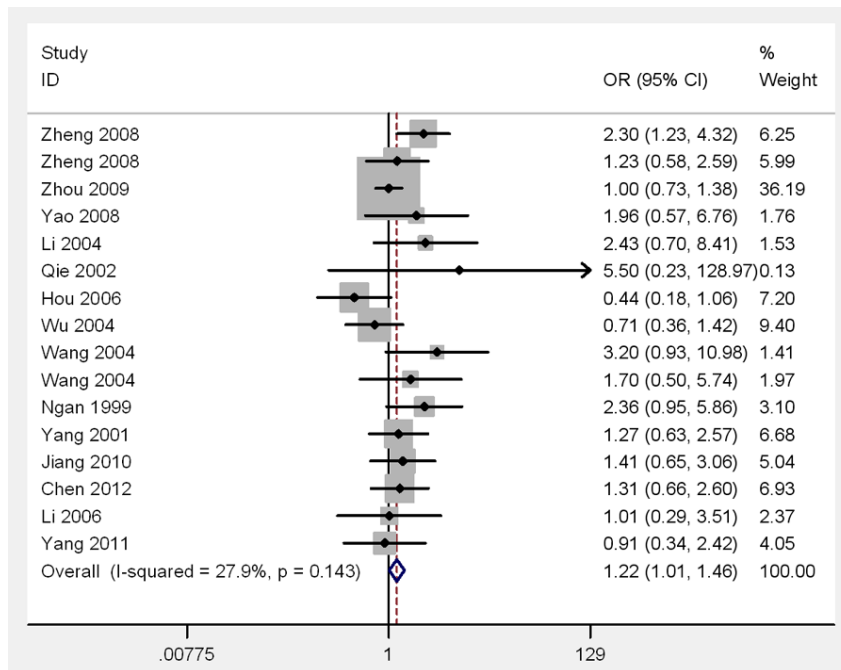
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**Table 2.** Main results in the total and subgroup analysis

Subgroups	Pro vs. Arg (Allele model)		Pro/Pro + Arg/Pro vs. Arg/Arg (Dominant model)		Pro/Pro vs. Arg/Arg + Arg/Pro (Recessive model)		Pro/Pro vs. Arg/Arg (Homozygous model)		Pro/Pro vs. Arg/Pro (Heterozygous model)	
	OR (95% CI)	<i>P</i> <sup>h</sup>	OR (95% CI)	<i>P</i> <sup>h</sup>	OR (95% CI)	<i>P</i> <sup>h</sup>	OR (95% CI)	<i>P</i> <sup>h</sup>	OR (95% CI)	<i>P</i> <sup>h</sup>
Overall	0.95 (0.75-1.20) <sup>R</sup>	< 0.001	0.81 (0.58-1.14) <sup>R</sup>	< 0.001	1.17 (0.87-1.58) <sup>R</sup>	0.004	1.05 (0.70-1.58) <sup>R</sup>	< 0.001	1.22 (1.01-1.46)	0.143
Source of control										
PB	0.68 (0.44-1.05) <sup>R</sup>	< 0.001	0.59 (0.31-1.10) <sup>R</sup>	< 0.001	0.75 (0.46-1.21) <sup>R</sup>	0.036	0.62 (0.30-1.27) <sup>R</sup>	0.001	0.93 (0.73-1.20)	0.314
HB	1.14 (0.86-1.50) <sup>R</sup>	< 0.001	0.97 (0.64-1.47) <sup>R</sup>	0.001	1.55 (1.20-1.99)	0.215	1.43 (0.88-2.31) <sup>R</sup>	0.009	1.65 (1.26-2.16)	0.717
Ethnicity										
Han	1.21 (0.88-1.67) <sup>R</sup>	0.001	1.18 (0.71-1.97) <sup>R</sup>	0.001	1.31 (1.05-1.63) <sup>R</sup>	0.054	1.57 (0.88-2.81) <sup>R</sup>	0.008	1.27 (1.00-1.61)	0.160
Uigur	0.70 (0.51-0.95)	0.913	0.50 (0.32-0.78)	0.943	0.94 (0.52-1.71)	0.770	0.61 (0.32-1.19)	0.842	1.35 (0.71-2.54)	0.660
Not stated	0.80 (0.51-1.26) <sup>R</sup>	< 0.001	0.64 (0.36-1.16) <sup>R</sup>	< 0.001	1.04 (0.55-1.97) <sup>R</sup>	0.003	0.84 (0.39-1.81) <sup>R</sup>	0.001	1.13 (0.80-1.58)	0.062
Sensitivity analyses for overall analysis	0.98 (0.89-1.09)	< 0.001	0.86 (0.74-1.00)	< 0.001	1.14 (0.96-1.36)	0.004	1.07 (0.87-1.31)	< 0.001	1.28 (1.00-1.63) <sup>R</sup>	0.143

PB, population-based; HB, hospital-based. *P*<sup>h</sup>, *P* value of heterogeneity test; <sup>R</sup>, Random-effects model were performed.

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**Figure 2.** Forest plots for the overall association between p53 Codon 72 Polymorphism and cervical cancer risk under the heterozygous model (Pro/Pro vs. Arg/Pro).

studies reported the same race (6 for Chinese Han, 2 for Uigur) and seven studies did not mention the ethnicity. The characteristics of the included studies are summarized in **Table 1**.

### Quantitative data synthesis

The main results of this meta-analysis and the heterogeneity test were shown in **Table 2**. The Pro/Pro genotype was significantly related to cervical cancer risk under the heterozygous model (Pro/Pro vs. Arg/Pro: OR = 1.22, 95% CI: 1.01-1.46) (Figure 2). However, no statistically significant associations were found under other four genetic models (Pro vs. Arg: OR = 0.95, 95% CI: 0.75-1.20; Pro/Pro + Arg/Pro vs. Arg/Arg: OR = 0.81, 95% CI: 0.58-1.14; Pro/Pro vs. Arg/Arg + Arg/Pro: OR = 1.17, 95% CI: 0.87-1.58; Pro/Pro vs. Arg/Arg: OR = 1.05, 95% CI: 0.70-1.58; respectively).

In the subgroup analysis based on source of controls, the results showed that the Pro/Pro carriers were significantly related to cervical cancer risk among hospital-based population (Pro/Pro vs. Arg/Pro + Arg/Arg: OR = 1.55, 95% CI: 1.20-1.99; Pro/Pro vs. Arg/Pro: OR = 1.65, 95% CI: 1.26-2.16; respectively), but not among

population-based studies (**Table 2**). Further subgroup analysis by ethnicity, the pooled results showed that there was significant association between TP53 codon 72 polymorphism and cervical cancer risk among Chinese Han and Uigur (Han, Pro/Pro vs. Arg/Arg + Arg/Pro: OR = 1.31, 95% CI: 1.05-1.63 Pro/Pro vs. Arg/Pro: OR = 1.27, 95% CI: 1.00-1.61. Uigur, Pro vs. Arg: OR = 0.70, 95% CI: 0.51-0.95; Pro/Pro + Arg/Pro vs. Arg/Arg: OR = 0.50, 95% CI: 0.32-0.78) (**Table 2**).

### Sensitive analysis

Sensitivity analyses were performed using both fixed effect model and random effect model, and the pooled ORs were not materially altered among overall analysis, indicating that the results were relatively stable and credible (**Table 2**). Sensitivity analyses could not be done because of the small sample size in the subgroup analyses.

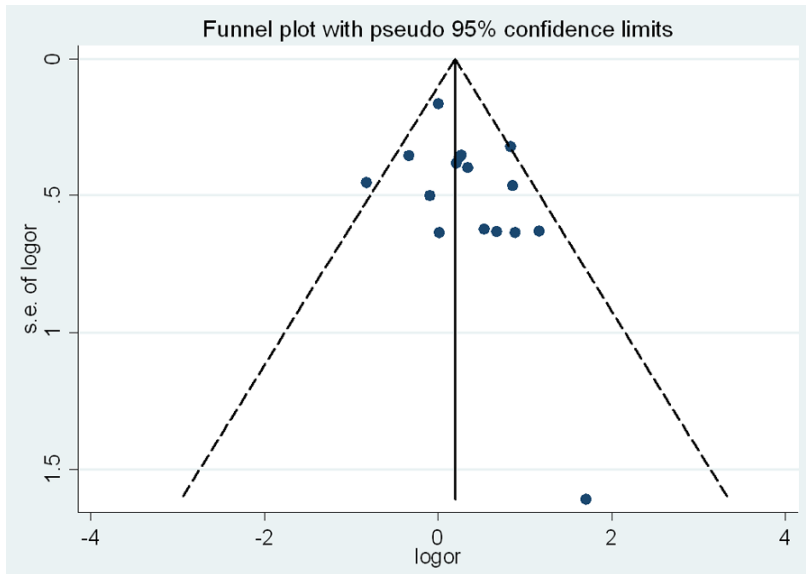
### Bias diagnosis

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. As showed in **Figure 3**, the shape of the funnel plot did not reveal any evidence of obvious asymmetry under heterozygous genetic model in overall analysis. Egger's test also showed that there was no significantly statistical evidence of publication bias for any of the genetic models (all  $P > 0.05$ , **Figure 4** for heterozygous genetic model in overall analysis).

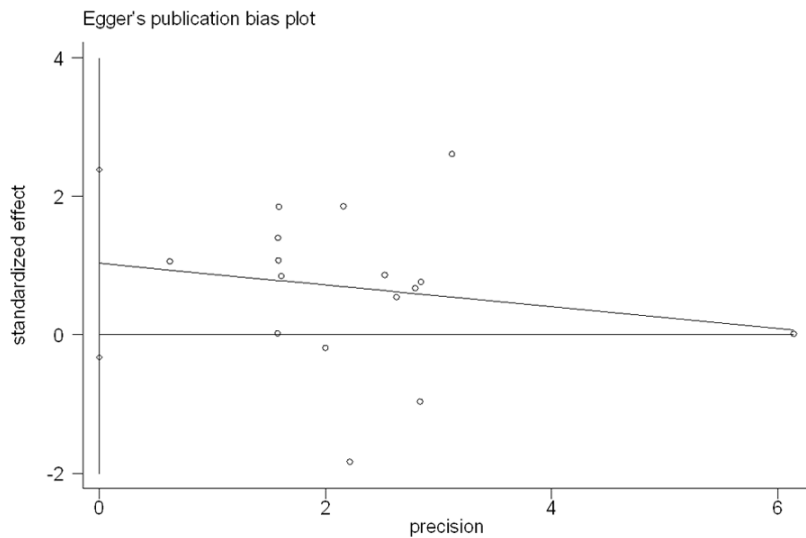
### Discussion

Due to the central role of TP53 in the development of cervical cancer and the different function between the Arg72 and the Pro72 allele, it has been hypothesized that Arg72Pro polymorphism is associated with risk of cervical cancer.

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**Figure 3.** The Funnel plot of selected studies on the association between p53 Codon 72 Polymorphism and cervical cancer risk among overall Chinese populations under the heterozygous model (Pro/Pro vs. Arg/Pro).



**Figure 4.** Egger's linear regression test for publication bias of selected studies on the association between p53 Codon 72 Polymorphism and cervical cancer risk among overall Chinese populations under the heterozygous model (Pro/Pro vs. Arg/Pro).

Many reports have been published but no clear consensus has been reached, perhaps because of racial difference, small sample sizes or other design features. In order to lessen the impact of different genetic background, we performed the present meta-analysis, which could quantitate the synthesis of all the available data and might help us to explore a more

robust estimate of the role of this polymorphism with cervical carcinogenesis in the Chinese population. Finally, 16 case-control studies were included and comprised a total of 1684 cervical cancer cases and 1178 controls. Meta-analysis results showed that the Pro/Pro genotype of TP53 codon 72 polymorphism significantly increased cervical cancer risk compared with Arg/Pro among Chinese population, suggested that the Pro/Pro genotype may be a risk factor. Our results were inconsistent with the previously published meta-analysis by Zhou et al. [33], which did not show significant associations with increased risk of cervical cancer among Chinese. In comparison, the previously published meta-analyses only included a smaller number of studies which were conducted in Chinese population, and most did not calculate pooled ORs for all studies in Chinese population.

When we performed the subgroup analyses by ethnicity and source of controls, significantly increased association with cervical cancer was found both in Chinese Han people and hospital-based studies under recessive and heterozygous modes, whereas

significantly decreased association was found in Uigur under allele and dominant models. These can be influenced by some factors. First, the relationship between genes and cervical cancer might be susceptible in different ethnicity. In addition, gene-environmental interaction might play an important role in susceptibility to cervical cancer. This controversy might

be plausible that TP53 codon 72 polymorphism has a distinct geographical distribution and therefore act differently as a genetic susceptibility marker [13]. Such evidence on the functionality of TP53 codon 72 polymorphism may lead to a better understanding of cervical cancer biology and behavior. It was also a strong rationale for the development of novel anti-cancer drugs interfering with TP53 protein production in cervical carcinogenesis.

The pathways of carcinogen metabolism are complex, mediated by the activity of multiple enzymes. Furthermore, environmental determinants and HPV status are crucial to progress to cervical cancer. The effect of any single gene might have a limited impact on cervical cancer risk than have so far been anticipated. Many controversial data are present in literature. Positive associations were found in certain populations and not confirmed in others. In addition to an expected interethnic variability in allele frequencies, variability has also been found within an ethnic group, resulting in heterogeneity in association studies. Gene-environment interactions and HPV status could be confounding factors in these studies, with controversial findings on cervical cancer risk. So, further studies with gene-gene and gene-environment interactions are required, especially regarding HPV. Such studies may eventually lead to have a better, comprehensive understanding of the association between the TP53 Arg72Pro polymorphism and cervical cancer risk.

This study has some limitations. Firstly, we did not perform subgroup analysis on smoking status and HPV infection status, because of the lack of sufficient data. Another potential limitation was that our results were based on unadjusted estimates. More precise analyses can be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, location, race and other factors. Third, in the subgroup analysis by ethnicity, the number of the included studies was limited and their sample sizes were small as for Uigur. It may have insufficient statistical power to explore the real association among Uigur. Finally, only published studies were included in this study, and publication bias may have occurred, even though it was not found in statistical tests. In spite of these limitations, our meta-analysis still had some advan-

tages. Most of all, we obeyed the inclusion and exclusion criteria strictly to reduce selection bias. Besides, our inclusion of non-English language reports, were important in minimizing a major potential threat to the validity of any meta-analysis-publication bias and the related threat of a language bias. Last but not the least, there was no evidence of publication bias in this meta-analysis and the sensitivity analysis had confirmed the reliability and stability of the results. Therefore, the 16 studies would appear to be comparable in all respects relevant to our meta-analysis.

In conclusion, this meta-analysis supports that TP53 codon 72 polymorphism may be associated with cervical cancer in Chinese population, especially for Han Chinese. As studies among other ethnic populations are currently limited, it is of great essentiality to conduct large-sample studies with wider spectrum of subjects to investigate the relationship between TP53 Arg72Pro polymorphism and cervical cancer risk, which would greatly help summarize the results from published papers.

### Disclosure of conflict of interest

None.

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