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Review Article

The TP53 codon 72 Pro/Pro genotype may be associated with an increased lung cancer risk in North China: an updated meta-analysis

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Abstract: Background: The polymorphism of TP53 codon 72, a transversion of G to C (Arg to Pro), has been demonstrated to be associated with the risk for lung cancer. However, individual studies conducted in Chinese have provided conflicting and inconclusive findings. Thus, we performed a meta-analysis by pooling all currently available case-control studies to estimate the effect of TP53 codon 72 Arg/Pro polymorphism on the development of lung cancer in the Chinese population. Material/Methods: Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 10 October 2014. Pooled ORs and 95% CIs were used to assess the strength of the associations. Results: A total of 12 case-control studies including 3681 lung cancer cases and 4358 controls were involved in this meta-analysis. Overall, no significant association was found between TP53 codon 72 variation and lung cancer risk when all studies in the Chinese population pooled into this meta-analysis. However, in the subgroup analysis by geographical locations, significantly increased risk was found in the population from North China under all genetic models (Allele model, OR=1.22, 95% CI: 1.04-1.43; Dominant model, OR=1.13, 95% CI: 1.01-1.25; Recessive model, OR=1.41, 95% CI: 1.07-1.87; Homozygous model, OR=1.47, 95% CI: 1.09-1.99; Heterozygous model, OR=1.40, 95% CI: 1.04-1.89). Conclusions: This meta-analysis provides the evidence that TP53 codon 72 polymorphism may contribute to the lung cancer development in North China and studies with large sample size and gene-gene (gene-environment) interactions are warranted to verify this finding.

Keywords: Meta-analysis, TP53 codon 72, polymorphism, lung cancer, Chinese

Introduction

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death in males globally, with 1.6 million newly confirmed cases and 1.4 million deaths from lung cancer annually [1]. In China, It was estimated that 605946 lung cancer cases were diagnosed in 2010, with a crude incidence rate of 46.08/100000, and 486 555 patients died from lung cancer, with a crude mortality rate of 37.00/100000 [2]. Although tobacco smoking has been established as the most important etiological factor of lung cancer, not all lung cancers are due to smoking, and increasing evidence for the association between genetic factors and lung cancer risk has been identified by hundreds of studies [3, 4], suggesting that the genetic factors may play a very important role in the development of lung cancer. In recent years, several common low-penetrance genes have been identified as potential lung cancer susceptibility genes. An important one is TP53 (p53), locating on chromosome 17p13 and encoding a 53-kDa nuclear phosphoprotein, which plays a pivotal role in modulating cell growth, division, and apoptosis [5]. At least 13 variants in TP53 have been identified [6, 7]. The most important one at codon 72 of exon 4, which encodes proline (Pro) or arginine (Arg), has been reported to affect the risks of many types of cancer especially of lung cancer. An association between p53 codon 72 polymorphism and lung cancer was first reported by

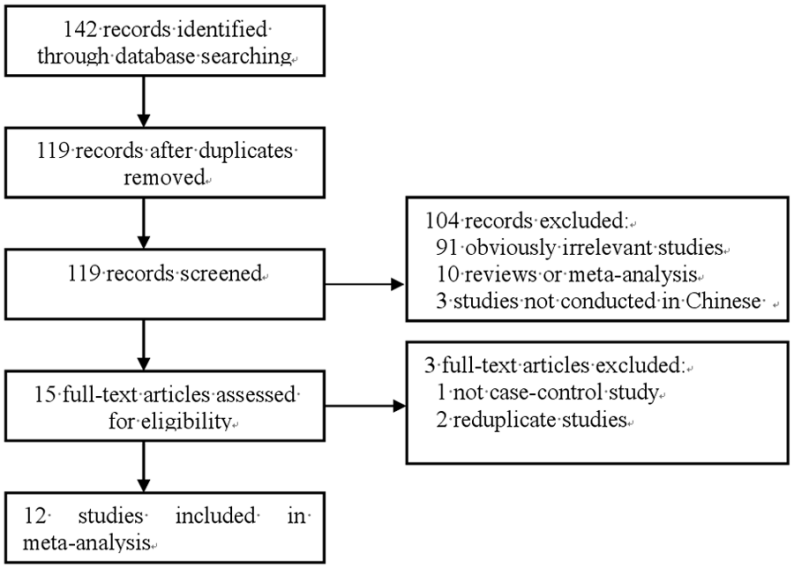

Figure 1. Flow diagram of the literature search.

Weston and co-workers in 1992 among U.S. populations [8], after which many studies analyzed the influence of p53 codon 72 polymorphism on lung cancer risk; no clear consensus, however, was reached. Moreover, three recent meta-analyses have reported conflicting results. Zhou C [9] found no statistically significant association between the p53 codon 72 polymorphism and lung cancer risk among Asians, Caucasians, Africans and the mixed population in 44 studies, in a meta-analysis performed by Qiao Q and Hu W [10] included 40 studies, the p53 codon 72 polymorphism did not correlate with lung cancer risk among Caucasians. Ye XH et al. [11], however, noted a significant risk of lung cancer for p53 codon 72 polymorphism carriers among Asians and Caucasians in 43 studies. Therefore, we conducted a meta-analysis to more precisely define the effect of TP53 codon 72 polymorphism on risk for lung cancer in only Chinese population.

Materials and methods

Search strategy and selection criteria

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 10 October 2014, using the following Mesh terms: (TP53 OR p53) AND lung cancer and polymorphism and (Chinese or China or Taiwan). The search was performed without any restrictions on language and focused on studies conducted in humans. Additional studies were identified by hand searching references in original articles and review articles. Studies were selected according to the following criteria: (a) The study used a case–control or cohort study design on association between the TP53 codon 72 polymorphism and lung cancer susceptibility; (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

Data were independently extracted by two reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by all the 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. The following information was collected from each study: first author's surname, year of publication, geographical location, ethnicity of subjects, source of controls, total numbers of cases and controls, genotype frequencies and HWE test. Ethnicities were categorized as Han and other ethnic Chinese.

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 10, STATA, College Station, TX). The distributions of genotypes in controls were tested by Hardy-Weinberg

Table 1. Characteristics of studies included the meta-analysis

Reference	Source of controls	Area	Ethnicity	Case no.	Control no.	Case			Control			HWE	
						Arg/Arg	Arg/Pro	Pro/Pro	Arg/Arg	Arg/Pro	Pro/Pro	χ^2	*P*
Wang 1999	Hospital-based	Taiwan	Not stated	194	152	68	74	52	47	75	30	0.02	0.994
Zhang 2003	Population-based	Hebei	Han	98	136	21	45	32	40	69	27	0.08	0.779
Shao 2005	Population-based	Jilin	Han	88	112	24	16	48	33	42	37	6.95	0.008
Zhang 2006	Population-based	Beijing	Han	1106	1420	321	506	279	425	731	264	2.62	0.105
Li 2009	Population-based	Guangdong	Han	125	101	50	58	17	37	42	22	2.26	0.133
Wang 2010	Population-based	Henan	Han	124	128	44	45	35	50	58	20	0.22	0.642
Chua 2010	Hospital-based	Singapore	Not stated	123	161	28	69	26	42	88	31	1.56	0.212
Yin 2010	Population-based	Jilin	Not stated	172	160	14	69	89	28	65	67	2.97	0.085
Liu 2013	Population-based	Heilongjiang	Han	360	360	144	137	79	126	115	119	46.88	0.000
Li 2013	Population-based	Shanxi	Not stated	363	446	118	146	99	161	196	89	4.24	0.039
Ren 2013	Population-based	Liaoning	Han	764	983	154	413	197	246	522	215	3.92	0.048
Yang 2013	Population-based	Hunan	Han	164	199	64	79	21	52	103	44	0.27	0.603

equilibrium (HWE) using the Chi-square test. Pooled ORs and 95% CIs were used to assess the strength of the associations. We calculated pooled ORs and 95% CIs for all studies combined. The heterogeneity was tested by the Q-statistics with *P*-values <0.1, and its possible sources of heterogeneity were assessed by subgroup analysis. 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 combined OR and their 95% CI. The significance of the pooled OR was determined by the z test. The sensitivity analysis was performed excluding the studies in which HWE was violated. 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. In addition, subgroup analysis stratified by ethnicity, source of controls and geographical location was also performed.

Results

Eligible studies

According to the inclusion criteria, 12 case-control studies [12-23] were included and 130 articles were excluded. The publication year of involved studies ranged from 1999 to 2013. The flow chart of study selection is shown in **Figure 1**. In total, 3681 lung cancer cases and 4358 controls were involved in this meta-analysis, which evaluated the relationship between TP53 codon 72 polymorphism and lung cancer risk. The source of controls was mainly based on a healthy population. Eight of these studies were conducted for Chinese Han population. The characteristics of the included studies are summarized in **Table 1**.

Quantitative synthesis

TP53 codon 72 variation was not associated with lung cancer risk under all genetic models in overall analyses (Allele model, OR=1.11, 95% CI: 0.96-1.28; Dominant model, OR=1.06, 95% CI: 0.90-1.25; Recessive model, OR=1.23, 95% CI: 0.96-1.58; Homozygous model, OR=1.23, 95% CI: 0.92-1.63; Heterozygous model, OR=1.25, 95% CI: 0.96-1.61; **Table 2**). In the subgroup analysis by ethnicity and source of controls, no significant associations were found in all models (**Table 2**). However, in the subgroup analysis by geographical locations, significantly increased risk was found in the population from North China under all genetic models (Allele model, OR=1.22, 95% CI: 1.04-1.43; Dominant model, OR=1.13, 95% CI: 1.01-1.25; Recessive model, OR=1.41, 95% CI: 1.07-1.87; Homozygous model, OR=1.47, 95% CI: 1.09-1.99; Heterozygous model, OR=1.40, 95% CI: 1.04-1.89; **Table 2**), whereas significantly decreased risk was found in the South under Allele and dominant models (Allele model, OR=0.81, 95% CI: 0.67-0.91; Dominant model, OR=0.72, 95% CI: 0.55-0.95; **Table 2**).

Sensitive analysis and bias diagnosis

Sensitivity analyses were performed by excluding the studies that were not in HWE, and the pooled OR were not materially altered under all

Table 2. Main results in the total and subgroup analysis

Study groups	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)	P^h	OR (95% CI)	P^h	OR (95% CI)	P^h	OR (95% CI)	P^h	OR (95% CI)	P^h
Overall	1.11 (0.96-1.28)^R	<0.001	1.06 (0.90-1.25)^R	0.012	1.23 (0.96-1.58)^R	<0.001	1.23 (0.92-1.63)^R	<0.001	1.25 (0.96-1.61)^R	<0.001
Overall in HWE	1.10 (0.91-1.34)^R	0.001	1.04 (0.81-1.34)^R	0.019	1.24 (0.92-1.68)^R	0.002	1.24 (0.83-1.84)^R	<0.001	1.27 (0.95-1.69)^R	0.013
Population-based	1.11 (0.94-1.32)^R	<0.001	1.07 (0.89-1.29)^R	0.006	1.22 (0.91-1.62)^R	<0.001	1.23 (0.88-1.70)^R	<0.001	1.22 (0.92-1.64)^R	<0.001
Hospital-based	1.08 (0.87-1.35)	0.844	0.96 (0.68-1.36)^R	0.312	1.32 (0.90-1.94)	0.477	1.15 (0.95-1.40)^R	0.006	1.41 (0.94-2.11)	0.237
Chinese Han	1.06 (0.86-1.29)^R	<0.001	1.00 (0.82-1.23)^R	0.018	1.15 (0.80-1.64)^R	<0.001	1.10 (0.75-1.61)^R	<0.001	1.19 (0.82-1.72)^R	<0.001
South China*	0.81 (0.67-0.91)	0.058	0.72 (0.55-0.95)	0.336	0.77 (0.38-1.58)^R	0.012	0.65 (0.32-1.31)^R	0.033	0.87 (0.41-1.84)^R	0.013
North China**	1.22 (1.04-1.43)^R	<0.001	1.13 (1.01-1.25)	0.071	1.41 (1.07-1.87)^R	<0.001	1.47 (1.09-1.99)^R	<0.001	1.40 (1.04-1.89)^R	<0.001

P^h, *P* value of heterogeneity test; ^{R}, Random-effects model were performed; *South China including Taiwan, Guangdong and Hunan; **North China including Beijing, Hebei, Jilin, Shanxi, Heilongjiang, Liaoning and Henan.

genetic models in overall analyses (**Table 2**), indicating that the results were relatively stable and credible. Sensitivity analyses could not be done because of the small sample size in the subgroup analyses.

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plots did not reveal obvious asymmetry (Figures not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The Egger's test indicated that there were no obvious publication bias under all genetic models in overall analyses (Allele model, t=-0.14, *P*=0.888; Dominant model, t=0.09, *P*=0.931; Recessive model, t=-0.31, *P*=0.763; Homozygous model, t=-0.24 *P*=0.815; Heterozygous model, t=-0.14 *P*=0.893).

Discussion

Although many studies analyzing the research results about the TP53 codon 72 polymorphism and their associations with lung cancer, definite conclusions cannot be drawn. 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 [24-28]. These findings require profound analysis to provide explanations for the differential susceptibility to lung 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 lung cancer in the Chinese population. This meta-analysis including information on 3681 lung cancer cases and 4358 controls indicated TP53 codon 72 polymorphism was not associated with lung cancer in the Chinese population when all the studies pooled into analysis. When we performed the subgroup analyses by the Han nationality and source of controls, the same results were found.

In addition, we performed subgroup analysis based on geographical locations. The results showed that the Pro/Pro and Pro carrier may be protective factors for lung cancer in the southern China whereas risk factors in the northern China, suggesting a possible role of geographical differences in the environment they lived in. There might be some reasons could be explained that. First, the relationship between genes and lung cancer might be susceptible in different ethnicity. In addition, gene-environmental interaction might play an important role in susceptibility to lung 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 [25]. Such evidence on the functionality of TP53 codon 72 polymorphism may lead to a better understanding of lung cancer biology and behavior.

The pathways of carcinogen metabolism are complex, mediated by the activities of multiple genes. Furthermore, environmental determinants are also crucial to progress to lung cancer. The effect of any single gene might have a limited impact on lung 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 [9-11]. 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 could be confounding factors in these studies, with controversial findings on lung cancer risk. So, further studies with gene-gene and gene-environment interactions are required. Such studies taking these factors into account may eventually lead to have a better, comprehensive understanding of the association between the TP53 Arg72Pro polymorphism and lung cancer risk.

Our meta-analysis has several strengths. First, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, a funnel plot and Egger's linear regression test were used to assess publication bias. Third, 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. Fourth, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Most of the important, impact of different genetic background was minimized by including the studies performed in Chinese populations only. In spite of these strengths, some limitations to this meta-analysis should be acknowledged. First, we didn't perform subgroup analy-

sis on smoking status and other exposure history, 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. Thirdly, the conclusion for the south China drawn from subgroup analyses might be limited because of the relevant small sample size.

In conclusion, our meta-analysis supports that TP53 codon 72 polymorphism might contribute to individual susceptibility to lung cancer in North China. Concerning lung cancer with multifactorial etiology, to further evaluate gene-gene and gene-environment interactions on TP53 Arg72Pro polymorphism and lung cancer, larger studies in the Chinese population with different environmental background or other risk factors are required to confirm our findings.

Disclosure of conflict of interest

None.

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