Int J Clin Exp Pathol 2023;16(12):357-367
www.ijcep.com /ISSN:1936-2625/IJCEP0138513

Original Article

Association between p73 RS2273953 to RS1801173 polymorphism and risk of lung cancer: a meta-analysis of 2,897 cases and 3,317 controls

Xu Li[1], Zaiqiang Guo[2], Chengwei Zhang[3], Ying Xiong[1], Chunxia Ding[4], Ke Wei[1], Xiaohong Dai[5], Hui Dai[6], Yonghuai Ma[7], Fangcai Lin[3,8]

[1]Department of Geriatrics, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China; [2]Department of Gastroenterology, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China; [3]Department of Thoracic Surgery, Capital Medical University Electric Power Teaching Hospital, Beijing 100073, China; [4]Department of Anesthesiology, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China; [5]Department of Pediatrics, Capital Medical University Electric Power Teaching Hospital, Beijing 100073, China; [6]Department of Respiratory, Capital Medical University Electric Power Teaching Hospital, Beijing 100073, China; [7]Department of Stomatology, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China; [8]Department of General Surgery, Capital Medical University Electric Power Teaching Hospital, Beijing 100073, China

Received August 23, 2021; Accepted July 12, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Background: Lung cancer is one of the most common and deadly cancers in humans. *P73*, a member of the *p53* family, is a vital gene for the carcinogenesis of lung cancer. Single nucleotide polymorphism (SNP) of *P73* gene may affect the risk of lung cancer. Therefore, we performed a meta-analysis of *p73* SNP and lung cancer risk using the most recent data. Methods: A total of 1407 articles from EMBASE, Web of science, PubMed and Chinese National Knowledge Infrastructure (CNKI) databases were identified initially from the search. A meta-analysis of the association between *P73* polymorphism and lung cancer risk was performed based on various genetic models and by type of lung cancer and race. Results: Seven articles published in either English or Chinese with English abstract were eventually selected for final analysis. The total pooled population included 6214 subjects (2,897 cases and 3,317 controls). The results showed that *p73* RS2273953 to RS1801173 polymorphism was associated with increased risk of lung cancer in Caucasians but not in Asians. Within Asians, those with *p73* GC/GC may have an increased risk for squamous carcinoma compared to those with GC/AT+AT/AT polymorphism. Conclusions: Our analysis suggested a lack of association between *p73* RS2273953 to RS1801173 polymorphism and risk of lung cancer overall. However, patients with GC/GC polymorphism showed an increased risk for squamous carcinoma in the lung compared to those with GC/AT+AT/AT in Asians.

Keywords: *P73*, polymorphism, lung cancer, meta-analysis, RS2273953 to RS1801173

Introduction

Lung cancer is one of the most common and deadly cancers in humans, accounting for one-third of the global cancer prevalence. In 2012, approximately 1.8 million people worldwide were newly diagnosed with lung cancer and 1.59 million died from lung cancer [1]. Environmental, social behavioral (smoking), and genetic factors are all important risk factors for lung cancer.

Evidence suggested that *p73* gene might be associated with the etiology of various cancers, including lung cancer. All *p73, p63,* and *p53* genes belong to the p53 family [2]. *P73* is a structural and functional homolog of p53, located at human chromosome 1p36.33 [3]. Studies have found that several important functional domains are coded by the human *p73* gene, including TA (transactivation), DBD (DNA-binding domain), OD (oligomerization domain), and SAM (sterile alpha-motif) domains, all belonging to the *P73* protein family [4]. Two functional *p73* isoforms have also been identified thus far. TA*p73* contains all four domains while Delta N*p73* (ΔN*p73*) misses the N-terminal transactivation domain, TA. A high level of TA*p73* expres-

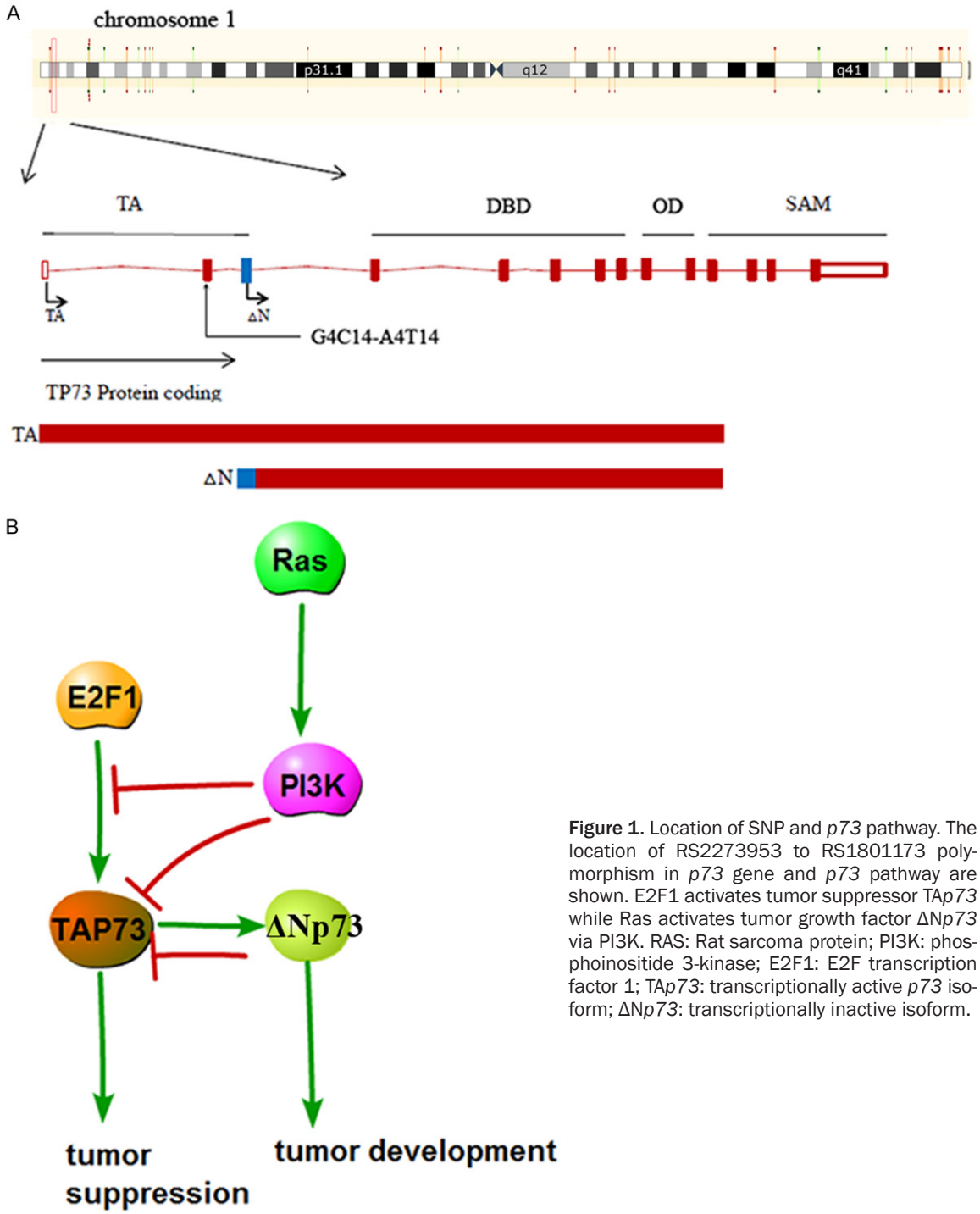

Figure 1. Location of SNP and *p73* pathway. The location of RS2273953 to RS1801173 polymorphism in *p73* gene and *p73* pathway are shown. E2F1 activates tumor suppressor TA*p73* while Ras activates tumor growth factor ΔN*p73* via PI3K. RAS: Rat sarcoma protein; PI3K: phosphoinositide 3-kinase; E2F1: E2F transcription factor 1; TA*p73*: transcriptionally active *p73* isoform; ΔN*p73*: transcriptionally inactive isoform.

sion suppresses tumor growth while ΔN*p73* was found up-regulated in cancer patients (**Figure 1**) [5]. Other studies also showed that ΔNp73α and E2F4/p130 suppressed the expression of genes (negative regulators of proliferation) in Papillomavirus 38 E6/E7-Transformed Keratinocytes [6, 7].

Due to its significant public health impact, it is important to understand the association between *p73* polymorphism and lung cancer, so that individuals with higher risk genotypes can be identified for targeted screening and prevention. Polymorphisms, for example, may turn out to be risk or protective factors, so they

may be valuable markers for the diagnosis, treatment, and prognosis of lung cancer. Among the *P73* polymorphisms, rs2273953 to rs1801173 (G4C14-A4T14) have been intensively studied. These two SNPs, located at upstream of the initiating AUG of exon 2 in position 4 and 14, are intronic SNPs and related. The relationship between these SNPs cancers varies by cancer types. Research has suggested that rs2273953 to rs1801173 might be associated with the risk of lung cancer, though the results were not consistent [8, 9]. A previous meta-analysis of five studies showed no association between rs2273953 to rs1801173 and lung cancer risk [10]. Since additional studies have been subsequently published, we chose to conduct an updated analysis by including the most recent data. In this study, we conducted a comprehensive systematic review of current literature on this issue and analyzed the associations between rs2273953 to rs1801173 and the risk of lung cancer overall, as well as the association with two major types of lung cancer separately.

Methods

Literature review

We first searched the EMBASE, Web of Science, PubMed and Chinese National Knowledge Infrastructure (CNKI) databases to identify scientific publications that reported the association between *p73* polymorphism and risk for lung cancer up until May, 2021. The key words used in the search were '*p73*, SNP, lung cancer', '*p73*, SNP, lung tumor', '*p73*, polymorphism, and lung cancer', or '*p73*, polymorphism, lung tumor'. Only the articles in English or Chinese with English abstract were selected for screening. After excluding duplicates, titles and abstracts of the articles were reviewed. Studies were selected using the following inclusion criteria: 1) case-control (patients with lung cancer vs controls) study, 2) genotype distribution data for *p73* were provided. The studies were excluded if they were: 1) review articles, cohort studies, in vitro studies, and animal studies; 2) not related to *p73* gene; 3) not a human study; or 4) not related to the association between lung cancer and host genetics. The study was approved by the Review Board of the Institute. The study selection is summarized in **Figure 2**. The study was carried out in accordance with PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) [11]. Firstly, the published articles were selected using the keywords in the preferred database (EMBASE, Web of Science, PubMed, and CNKI). Secondly, duplicate articles were excluded. Thirdly, the articles were screened by the title and abstract. Fourthly, the full-texts of articles were retrieved. Finally, selected articles were reviewed and data were extracted.

Data extraction

For each selected study, the authors, year of publication, country of origin, demographics of patients (age, race) and genotyping method were extracted independently by two experienced researchers, and any disagreement was adjudicated by the 3rd researcher. The final data are summarized in **Table 1**.

Genotype distribution in both cases and controls are summarized in **Table 2**.

Statistical analyses

Pearson's Chi-square test was used to check for Hardy-Weinberg Equilibrium (HWE) in each study. The heterogeneity between studies was tested with Z test and I^2 test. Random-effects model was used when it was significant (*P*-value <0.05) and fixed-effects model was used when heterogeneity was not significant [12]. The publication bias was also assessed using Begg's test and Egger's test [13, 14]. The association between the *p73* polymorphism and lung cancer risk was estimated by pooled odds ratio (OR) and 95% confidence intervals (CI). $P<0.05$ was considered significant. Statistical analyses were conducted with Stata 13.0 (College Station, TX, USA).

Results

Characteristics of selected studies

A total of 1407 articles were initially identified from the literature search. As shown in **Figure 2**, 52 abstracts were reviewed after the initial screening by excluding duplicates, conference articles, and books. GWAS (Genome-wide association study) studies were also excluded because of missing the genotype distribution information. A total of 11 articles that reported the association of human *p73* RS2273953 to

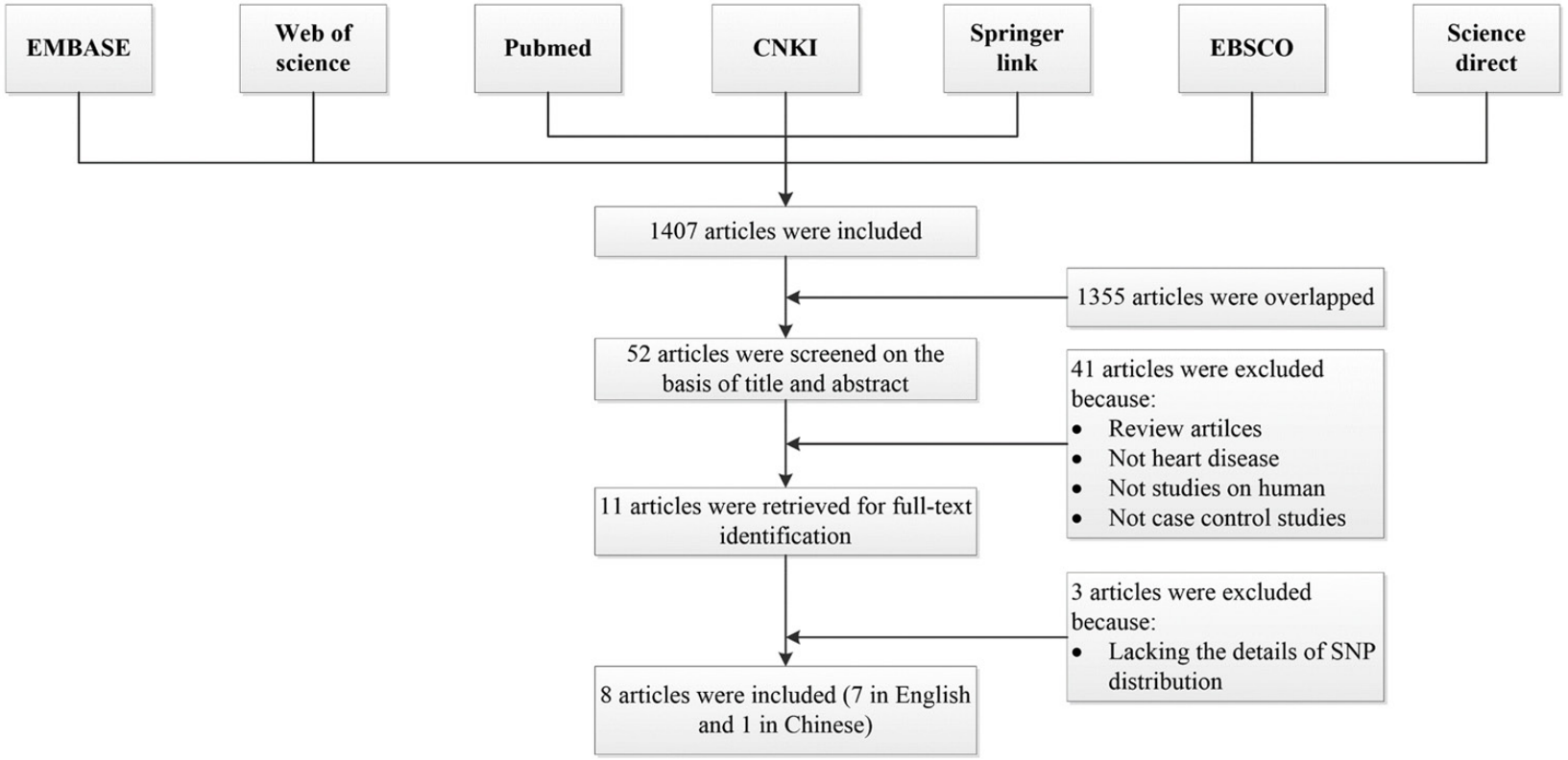

Figure 2. Flow chart showing the study selection procedure. CNKI: China National Knowledge Infrastructure.

Table 1. Characteristics of studies included in the analysis

Authors	Year of publication	Country	Host ethnicity	Age, years mean ± SD or mean (range)		Samples n		Genotyping method
				Cases	Controls	Cases	Controls	
Shuang-Shuang Wang et al.	2015	China	Han Chinese	49.9 ± 0.7	50.0 ± 0.5	186	198	PCR-CTPP
Shuang-Shuang Wang et al.	2014	China	Han Chinese	≤45 (79) >45 (89)	≤45 (94) >45 (101)	168	195	PCR-CTPP
Akio Hiraki et al.	2003	Japan	Japanese	61.0 (26-81)	56.8 (39-69)	189	235	PCR-CTPP
Zhibin Hu et al.	2005	China	Han Chinese	≤60 (247) >45 (178)	≤60 (349) >45 (239)	425	588	PCR-SSCP
Jin Eun Choi et al.	2006	Korea	Korean population	61.3 ± 9.4	60.2 ± 9.6	582	582	PCR-sequencing
Xiaoai Zhang et al.	2013	China	Han Chinese	≤50 (64) 51-60 (74) 61-70 (82) >70 (70)	≤50 (102) 51-60 (85) 61-70 (106) >70 (87)	293	380	PCR-RFLP
Guojun Li et al.	2004	America	American population	61.1 (32-87)	61.0 (32-91)	1054	1139	PCR-sequencing

SD: standard deviation; PCR: polymerase chain reaction; CTPP: confronting two-pair primers; RFLP: restriction fragment length polymorphism; SSCP: single strand conformation polymerase.

Table 2. Genotype and allele distribution of p73 polymorphisms in lung cancer patients and controls

Study	Case					Control					Total		HWE	Chi	*p*-value
	GC/GC	GC/AT	AT/AT	GC	AT	GC/GC	GC/AT	AT/AT	GC	AT					
Shuang-Shuang Wang (2015)	108	68	10	284	88	104	68	26	276	120	186	198	Chinese	6.92	0.01
Shuang-Shuang Wang (2014)	101	59	8	261	75	102	68	25	272	118	168	195	Chinese	5.9	0.02
Akio Hiraki et al.	109	68	12	286	92	130	95	10	355	115	189	235	Asian	2.06	0.15
Zhibin Hu et al.	255	149	21	659	191	295	248	45	838	338	425	588	Chinese	0.52	0.47
Jin Eun Choi et al.	320	221	41	861	303	338	212	32	888	276	582	582	Korean	0.03	0.87
Xiaoai Zhang et al.	163	116	14	442	144	247	120	13	614	146	293	380	Chinese	0.12	0.73
Guojun Li et al.	593	394	67	1580	528	721	365	53	1807	471	1054	1139	Caucasian	0.6	0.44

HWE: Hardy-Weinberg Equilibrium.

Table 3. Meta-analysis by genetic models for p73 polymorphism

SNP	Genetic model	Pools	OR (95% CI)	Z	P	I^2%	P_{het}	Effect model	Begg's test P>|z|	Egger's test P>|t|
RS2273953 to RS1801173	GC/GC vs GC/AT+AT/AT	6214	1.01 (0.80, 1.29)	0.11	0.912	80.1	0.000	Random	0.099	0.221
	AT/AT vs GC/AT+GC/GC	6214	0.88 (0.56, 1.36)	0.59	0.555	72.6	0.001	Random	0.176	0.249
	GC/GC vs AT/AT	3963	1.15 (0.70, 1.88)	0.54	0.592	77.6	0.000	Random	0.099	0.240
	GC/GC vs GC/AT	5837	0.98 (0.79, 1.21)	0.22	0.824	71.7	0.002	Random	0.293	0.337
	GC vs AT	12428	1.04 (0.84, 1.30)	0.37	0.711	84.4	0.000	Random	0.099	0.176

OR: odds ratio; CI: confidence interval; P_{het}: *P* value for heterogeneity.

RS1801173 polymorphisms, complete linkage disequilibrium polymorphisms, and lung cancer risk were selected for full-text review. Three of them were further excluded after reviewing the article due to missing necessary genetic distribution data. Also, two studies from South Korea were found to be from the same team. We selected the earlier article that was published in 2006. Finally, 7 studies (6 in English [8-10, 15-18] and 1 in Chinese [19]) were included in our meta-analysis. As summarized in **Table 1**, the race of study population included Chinese, Korean and Caucasian. The final pooled study population consisted of 6214 subjects (2897 cases and 3317 controls). The genotype and allele distribution of G4C14-A4T14 polymorphism were shown in **Table 2**. Based on the search of CNBI SNPs database, the locations of SNP were identified and shown in **Figure 1**. As for the cancer type, all studies focused on squamous carcinoma and adenocarcinoma; small cell carcinoma was included in six articles [8-10, 15, 18, 19]; and large cell carcinoma was reported only in Jin Eun Choi's study [18] although some of the articles had no information on genetic distribution.

Meta-analysis of p73 polymorphism

As summarized in **Table 2**, seven case-control studies (2879 cases and 3317 controls) reported a relationship between *p73* RS2273953 to RS1801173 polymorphism and the risk of lung cancer. Two studies deviated from Hardy-Weinberg equilibrium (S.S. Wang 2014, P= 0.02; S.S. Wang 2015, P=0.01) [10, 15]. The heterogeneity between studies was significant (*P*<0.001, I^2=81.8%), thus we used a random effect model to synthesize the pooled OR (**Table 3**). The overall OR of the Allele model (GC vs AT alleles) was 1.04 (95% CI: 0.84, 1.30, P=0.711) (**Table 3**; **Figure 3A**). Analyses of Heterozygote, Homozygote, Dominant and Recessive models did not identify a significant association either (**Table 3**). Subgroup analysis by allele comparison (GC vs AT) and by race were also performed (**Figure 3B**). The AT polymorphism was shown to be a significant risk factor for lung cancer in Caucasians [8]. However, there was no association between *p73* RS2273953 to RS1801173 polymorphism and lung cancer in Chinese. Chinese patients with an AT allele were shown to have a lower risk of lung cancer in three studies [10, 15, 19] but a higher risk in one study (Xiao'ai Zhang's study) [9] (**Figure 3**).

Four of the 7 articles contained the genetic distribution of two major types of lung cancer, squamous carcinoma and adenocarcinoma, but only two of them (both by Shuang-Shuang Wang [10, 15]) studied the intact genotype, and the other two [8, 19] compared the models GC/GC vs GC/AT+AT/AT. For squamous carcinoma, the overall OR was 1.07 (0.65, 1.74) and *p* value was 0.79 (**Table 4**).

Subgroup analysis by race was also shown in **Figure 4A**. Interestingly, compared to GC/AT+AT/AT, GC/GC was shown to be associated with a significantly increased risk for squamous carcinoma in Asians, but a decreased risk in Caucasians. For adenocarcinoma, the overall OR was 1.09 (0.80, 1.48) and *p* value was 0.58 (**Table 4**; **Figure 4B**). Subgroup analysis by race also did not find any significant association. The funnel plot is shown in **Figure 5**.

Discussion

We conducted a meta-analysis to evaluate the association between *p73* RS2273953 to RS1801173 polymorphism and lung cancer risk. Five different genetic models (Allele, Heterozygote, Homozygote, Dominant, and Recessive model) were analyzed. A subgroup analysis by race was also performed. Based on

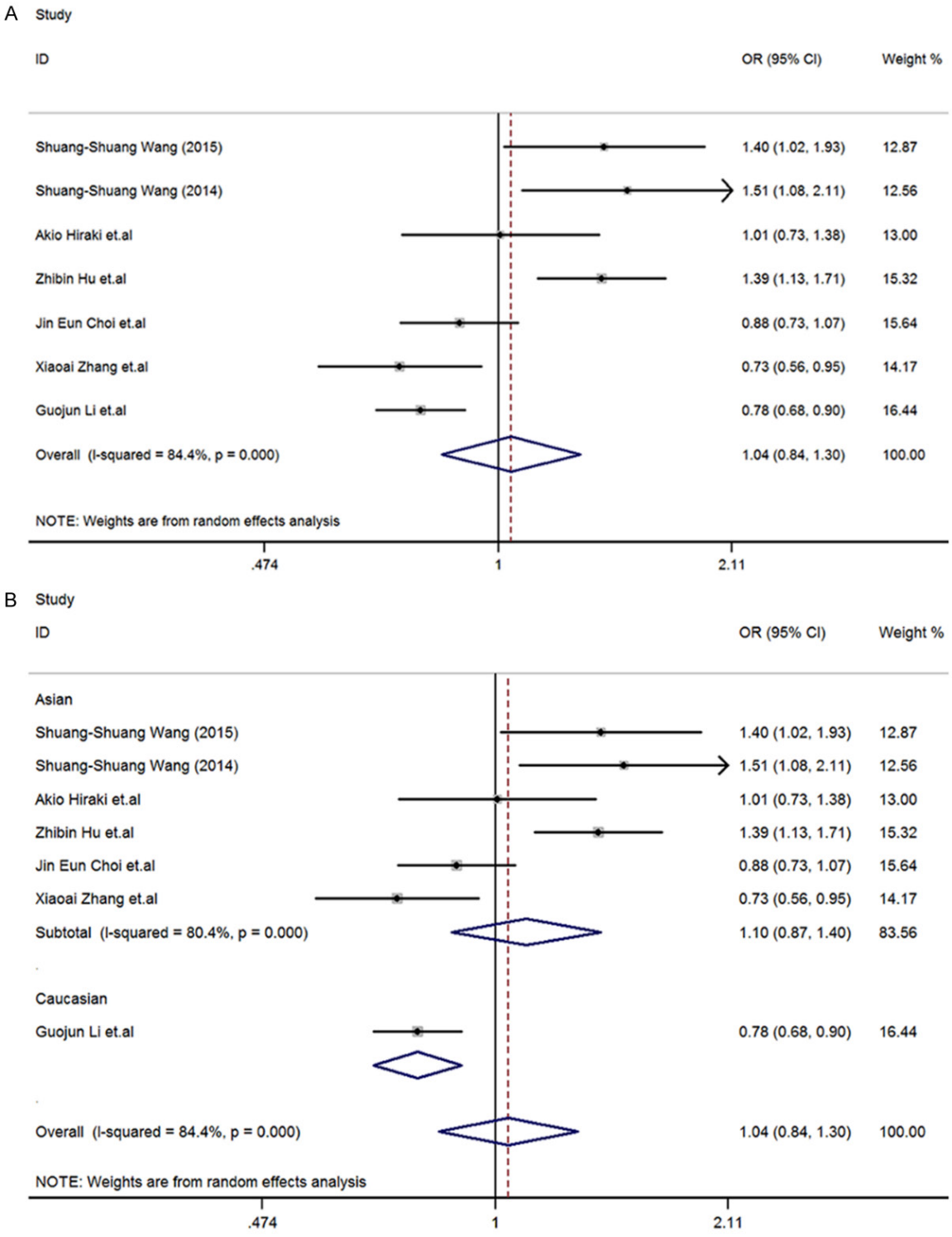

Figure 3. Forest plot of the association between RS2273953 to RS1801173 and lung cancer risk. A. The whole analysis was performed in the Allele model. There was a lack of association in the overall pool. B. Subgroup analysis was performed by ethnicity. A lack of association was found in the pollution excluding the Caucasians. OR: odds ratio; CI: confidence interval; df: degrees of freedom.

data from 6214 subjects (2897 cases and 3317 controls), RS2273953 to RS1801173 polymorphism in *p73* gene was not associated with a risk of lung cancer in the overall popula-

Table 4. Meta-analysis by GC/GC vs GC/AT+AT/AT model for p73 polymorphism stratified by histologic type

SNP	Genetic model	Pools	Types	OR (95% CI)	Z	P	I^2%	P_{het}	Effect model	Begg's test P>|z|	Egger's test P>|t|
RS2273953 to RS1801173	GC/GC vs GC/AT+AT/AT	2743	SC	1.07 (0.65, 1.74)	0.27	0.791	84.8	0.000	Random	1.000	0.382
		2858	AC	1.09 (0.80, 1.48)	0.55	0.580	54.0	0.089	Random	0.497	0.200

OR: odds ratio; CI: confidence interval; P_{het}: *P* value for heterogeneity; SC: squamous carcinoma; AC: adenocarcinoma.

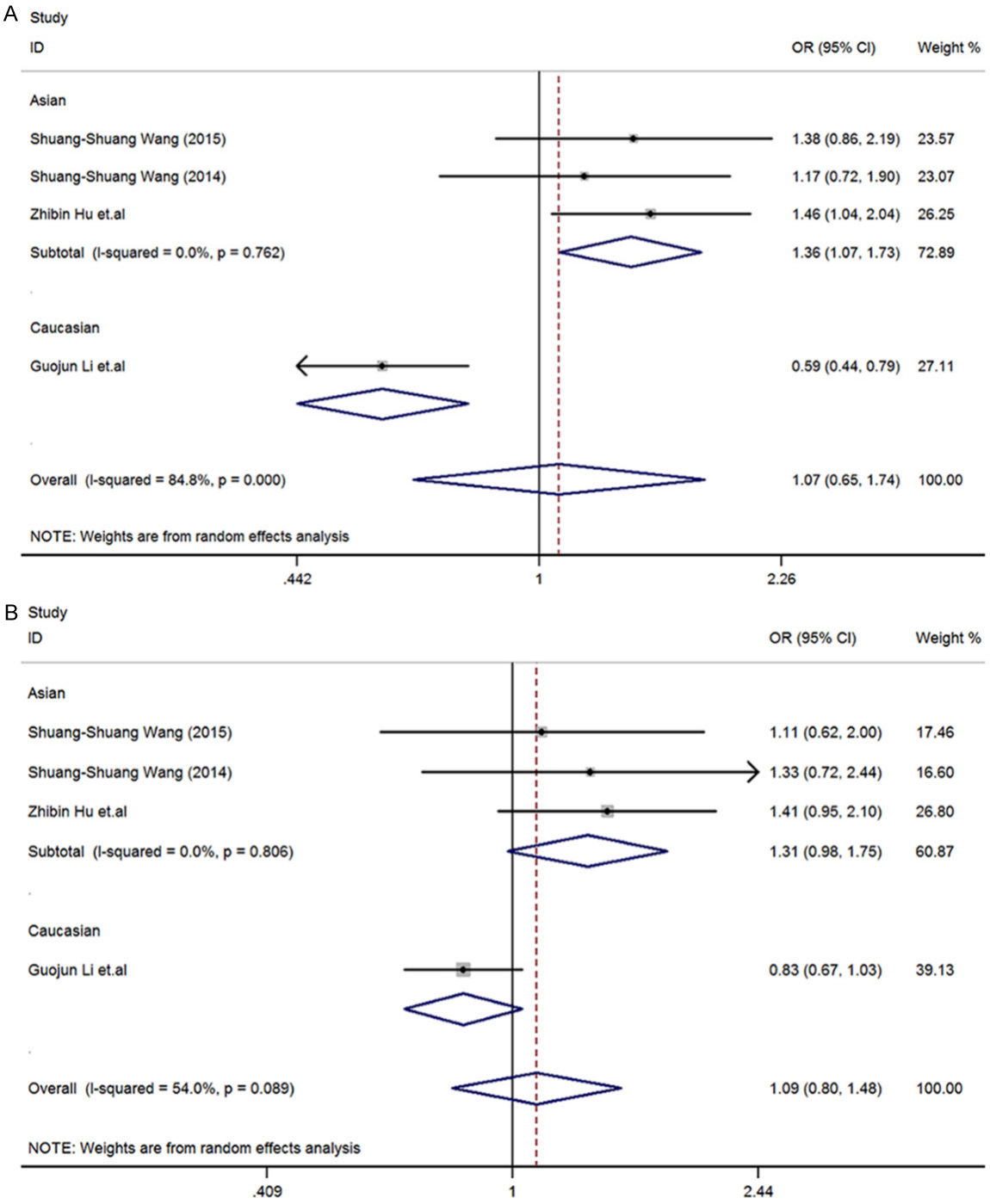

Figure 4. Forest plot of the association between RS2273953 to RS1801173 GC/GC vs GC/AT+AT/AT model and lung cancer risk by squamous carcinoma and adenocarcinoma. OR: odds ratio; CI: confidence interval; df: degree of freedom.

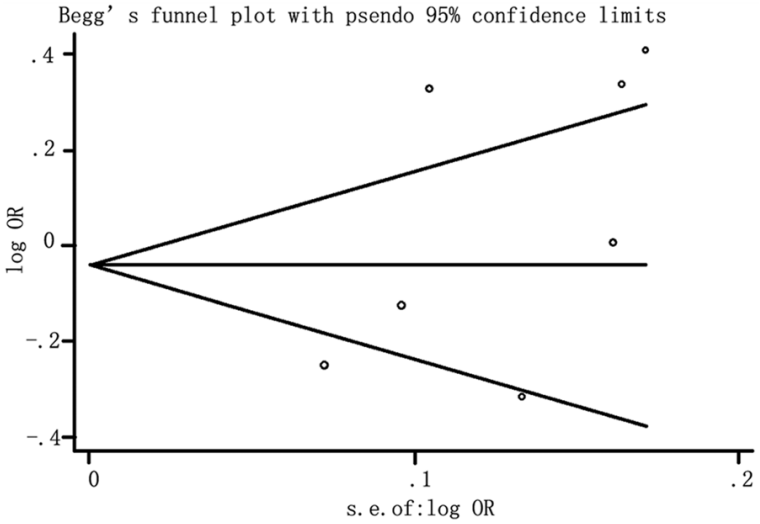

Figure 5. Funnel plot of studies included in the analysis.

tion. However, we found a significant association between *p73* RS2273953 to RS1801173 polymorphism and lung cancer risk in the Caucasian population, which was driven by a single study. More research in this population is needed to confirm this finding.

The process of cancer formation includes initiation, progression and evasion, with autonomous cell proliferation being the last step. These biologic processes are affected by genetic or epigenetic variations of the important genes [20]. *P73* gene maps at chromosome 1p36.33 and has similar structure and function to p53. It is well known that tumor protein 53 (p53) can accumulate in nucleus, leading to cell cycle arrest or apoptosis. However, whether the signal pathway induced by *p73* can affect tumor suppression in the same manner remains unclear [21]. The *p73* gene can be alternatively spliced and translated into transcriptionally active (TA*p73*) and inactive (ΔN*p73*) isoforms. The PI3K (phosphoinositide 3-kinase) activated by Ras (Rat sarcoma) protein down-regulates TA*p73* and decreases the TA*p73*/ΔN*p73* ratio [5]. The abundance of ΔN*p73* may be associated with many types of cancer [22, 23]. Specifically, the RS2273953 to RS1801173 polymorphism is located in the exon 2 which is part of TA*p73* transcript but not ΔN*p73*. The location of this polymorphism suggests the possibility of its influence on the function of TA*p73* or the translation of ΔN*p73*. Identifying the role of *p73* isoforms will provide further information to understand the mechanism of its tumor suppression. Several studies have investigated an association between *p73* polymorphism and lung cancer risk. Therefore, using lung cancer as an example, our analysis provided further information to extend the understanding of the mechanism of tumor suppression associated with p73 gene. In the earlier studies of this issue, conflicting results were reported related to the effects of different alleles. The reason may be related to the differences in regional and genomic background of the study population. One meta-analysis of five studies on this topic showed the same conclusion [10]. In this analysis, we included both previous and the most recent studies. However, we still did not find any significant association in all five genetic models, except GC polymorphisms in Caucasians.

The mechanism for lung cancer of AT allele of p73 remains unclear. Though the P3 (TP73 mRNA transcribed from 3rd promoter) could not affect the biologic mechanism [24], a study suggested that the AT allele has altered transcription start site which may affect the translation efficiency [25]. The above finding may explain the difference in role of *p73* RS2273953 to RS1801173 in different ethnic groups.

According to the principles of epigenetics, *p73* RS2273953 to RS1801173 polymorphism may interact with other well-known factors of lung cancer, such as individuals' age, sex, or smoking history [8]. Therefore, a systemic covariance analysis that accounts for the effects of environmental and behavioral factors should be considered to assess a direct association between *p73* RS2273953 to RS1801173 polymorphism and the lung cancer risk. However, such analysis is possible only with the original study data.

Limitations

In our analysis, the number of studies in each subgroup was different and there was only one

study in the Caucasian subgroup. Therefore, the generalizability of the results was limited. A study with more widely represented population and patient-level data should be considered to confirm the findings of this analysis.

Conclusion

Our analysis showed no association between *p73* RS2273953 to RS1801173 polymorphism and lung cancer risk in the overall population. However, GC polymorphism was associated with decreased risk in Caucasians. In Asians GC/GC polymorphism was associated with a significantly increased risk of squamous carcinoma of the lung when compared to GC/AT+ AT/AT. A larger study that includes broader patient population and collects environmental and behavioral data could be considered to confirm the findings.

Disclosure of conflict of interest

None.

Abbreviations

CI, confidence intervals; CNKI, Chinese National Knowledge Infrastructure; DBD, DNA-binding domain; HWE, Hardy-Weinberg Equilibrium; OD, oligomerization domain; OR, odds ratios; SAM, sterile alpha-motif; SNP, Single nucleotide polymorphism; TA, transactivation.

Address correspondence to: Dr. Xu Li, Department of Geriatrics, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China. E-mail: lixu_angel@sina.com; Yonghuai Ma, Department of Stomatology, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing 100072, China. E-mail: 13521430088@163.com; Fangcai Lin, Department of Thoracic Surgery, Capital Medical University Electric Power Teaching Hospital, Taipingxili Jia 1, Beijing 100073, China. E-mail: fc_lin@126.com

References

[1] Stewart BW and Wild CP. World cancer report 2014. IARC Press: International Agency for Research on Cancer; 2014.

[2] Xu Y, Yang X, Xiong Q, Han J and Zhu Q. The dual role of p63 in cancer. Front Oncol 2023; 13: 1116061.

[3] Nomoto S, Haruki N, Kondo M, Konishi H, Takahashi T, Takahashi T and Takahashi T. Search for mutations and examination of allelic expression imbalance of the p73 gene at 1p36.33 in human lung cancers. Cancer Res 1998; 58: 1380-1383.

[4] Peng CY, Tsai SL, Yeh CT, Hung SP, Chen MF, Chen TC, Chu CM and Liaw YF. Genetic alternations of p73 are infrequent but may occur in early stage hepatocellular carcinoma. Anticancer Res 2000; 20: 1487-1492.

[5] Oswald C and Stiewe T. In good times and bad: p73 in cancer. Cell Cycle 2008; 7: 1726-1731.

[6] Taverniti V, Krynska H, Venuti A, Straub ML, Sirand C, Lohmann E, Romero-Medina MC, Moro S, Robitaille A, Negroni L, Martinez-Zapien D, Masson M, Tommasino M and Zanier K. The E2F4/p130 repressor complex cooperates with oncogenic ΔNp73α to inhibit gene expression in human papillomavirus 38 E6/E7-transformed keratinocytes and in cancer cells. mSphere 2023; 8: e0005623.

[7] Heryanto YD and Imoto S. Identifying key regulators of keratinization in lung squamous cell cancer using integrated TCGA analysis. Cancers (Basel) 2023; 15: 2066.

[8] Li G, Wang LE, Chamberlain RM, Amos CI, Spitz MR and Wei Q. P73 G4C14-to-A4T14 polymorphism and risk of lung cancer. Cancer Res 2004; 64: 6863-6866.

[9] Zhang X, Li X, Wu Z, Lin F and Zhou H. The p73 G4C14-to-A4T14 polymorphism is associated with risk of lung cancer in the Han nationality of North China. Mol Carcinog 2013; 52: 387-391.

[10] Liu H, Liang Y, Liao H, Li L and Wang H. Association of p73 G4C14-to-A4T14 polymorphism with lung cancer risk. Tumour Biol 2014; 35: 9311-9316.

[11] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P and Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1.

[12] Kavvoura FK and Ioannidis JP. Methods for meta-analysis in genetic association studies: a review of their potential and pitfalls. Hum Genet 2008; 123: 1-14.

[13] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[14] Begg CB and Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst 1989; 81: 107-115.

[15] Wang SS, Zhu XQ, Yang SD, Dong LL, Li W and Tang J. Association of p73 G4C14-to-A4T14

polymorphism with non-small cell lung cancer risk. Oncol Lett 2015; 10: 995-999.
[16] Jun HJ, Park SH, Lee WK, Choi JE, Jang JS, Kim EJ, Cha SI, Kim DS, Kam S, Kim CH, Kang YM, Jung TH and Park JY. Combined effects of p73 and MDM2 polymorphisms on the risk of lung cancer. Mol Carcinog 2007; 46: 100-105.
[17] Hiraki A, Matsuo K, Hamajima N, Ito H, Hatooka S, Suyama M, Mitsudomi T and Tajima K. Different risk relations with smoking for non-small-cell lung cancer: comparison of TP53 and TP73 genotypes. Asian Pac J Cancer Prev 2003; 4: 107-112.
[18] Choi JE, Kang HG, Chae MH, Kim EJ, Lee WK, Cha SI, Kim CH, Jung TH and Park JY. No association between p73 G4C14-to-A4T14 polymorphism and the risk of lung cancer in a Korean population. Biochem Genet 2006; 44: 543-550.
[19] Hu ZB, Miao XP, Ma HX, Tan W, Niu JY, Lin DX and Shen HB. Association of two genetic polymorphisms in the 5' untranslated region of exon 2 of the p73 gene and risk of lung cancer. Zhonghua Liu Xing Bing Xue Za Zhi 2005; 26: 106-109.
[20] Tomasini R, Mak TW and Melino G. The impact of p53 and p73 on aneuploidy and cancer. Trends Cell Biol 2008; 18: 244-252.
[21] Wang L, He G, Zhang P, Wang X, Jiang M and Yu L. Interplay between MDM2, MDMX, Pirh2 and COP1: the negative regulators of p53. Mol Biol Rep 2011; 38: 229-236.
[22] Lucena-Araujo AR, Kim HT, Thome C, Jacomo RH, Melo RA, Bittencourt R, Pasquini R, Pagnano K, Gloria AB, Chauffaille Mde L, Athayde M, Chiattone CS, Mito I, Bendlin R, Souza C, Bortolheiro C, Coelho-Silva JL, Schrier SL, Tallman MS, Grimwade D, Ganser A, Berliner N, Ribeiro RC, Lo-Coco F, Lowenberg B, Sanz MA and Rego EM. High DeltaNp73/TAp73 ratio is associated with poor prognosis in acute promyelocytic leukemia. Blood 2015; 126: 2302-6.
[23] Orzol P, Holcakova J, Nekulova M, Nenutil R, Vojtesek B and Coates PJ. The diverse oncogenic and tumour suppressor roles of *p63* and p73 in cancer: a review by cancer site. Histol Histopathol 2015; 30: 503-521.
[24] Li Q, Athan ES, Wei M, Yuan E, Rice SL, Vonsattel JP, Mayeux RP and Tycko B. TP73 allelic expression in human brain and allele frequencies in Alzheimer's disease. BMC Med Genet 2004; 5: 14.
[25] Kaghad M, Bonnet H, Yang A, Creancier L, Biscan JC, Valent A, Minty A, Chalon P, Lelias JM, Dumont X, Ferrara P, McKeon F and Caput D. Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers. Cell 1997; 90: 809-819.