Journal of
Pulmonary & Respiratory Medicine

Cheng et al., J Pulm Respir Med 2018, 8:1
DOI: 10.4172/2161-105X.1000446

Research Article Open Access

Meta-Analysis of P73 Polymorphism and Risk of Non-Small Cell Lung Cancer

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Abstract

Background: The relationship between *p73* gene G4C14-to-A4T14 polymorphism and non-small cell lung cancer risk is unclear. Now we performed a meta-analysis to clarify the association of p73 polymorphism with non-small cell lung cancer.

Methods: To assess the association between p73 polymorphism and non-small cell lung cancer deeply, we searched Pubmed, Embase, CNKI, Wanfang and CBM databases. All analyses were done using RevMan 5.3 software which provided by the Cochrane Collaboration and Stata version 12.0. The statistical heterogeneity among studies was assessed with the chi-square-based Q test. We used the random effects model as well as the fixed effects model to calculate the pooled ORs.

Results: Our meta-analysis included 6 studies with a total of 1658 patients with non-small lung cancer and 2328 cancer-free control subjects. In all comparisons, we find none of genetic models shows significant relation with the risk of non-small lung cancer (recessive model: OR: 1.16, 95%CI: 0.94-1.43; dominant model: OR: 0.63, 95%CI: 0.37-1.06; co-dominant model: OR: 1.63, 95%CI: 0.94-2.83; allelic model: OR: 1.20, 95%CI: 0.98-1.48). However, when we proceeded to subgroup analysis according country, significantly increased risk was observed in a recessive models (OR: 1.35, 95%CI: 1.15-1.59), in a co-dominant model: (OR: 2.49, 95%CI: 1.76-3.53), in an allelic model (OR, 1.41, 95%CI, 1.24-1.61). Significantly decreased risk was observed in a dominant model (OR: 0.42, 95%CI: 0.30-0.59).

Conclusions: Our results indicate that *p73* gene G4C14-to-A4T14 polymorphism is associated with the risk of non-small cell lung cancer in China. However, a large gene-to-environment research is required to confirm this conclusion.

Keywords: p73 polymorphism; Non-small cell lung cancer; Meta analysis

Background

Non-small lung cancer (NSCLC) was a subtype for lung cancer, one of the most common malignancies of the world, especially in male [1]. The incidence of NSCLC is largely affected by tobacco smoking. However, not every NSCLC patient has the smoking history [2,3]. As we all know, genetic factors play an important role in lung cancer. The different individual genetic susceptibility to tumor [4-6]. Therefore, the research of genetic variants related to NSCLC may contribute to forecasting an individual's risk of suffering from this disease. Recently, *p73 gene* is identified a significant gene of tumorigenesis and lots of studies have demonstrated that the *p73* gene have a pivotal role in the occurrence of various types of cancer, including lung cancer [7-10]. However, there are very few reports of literature about NSCLC, and the results are not conclusive. Akio found p73 polymorphism was related with the decreased risk of NSCLC in Japanese population [11]. However, Wang found the opposite conclusion [12]. Therefore, to further explore the relationship between p73 polymorphism and NSCLC, we utilized a meta-analysis including data from all eligible case-control studies to summarize the currently published data.

Methods

Literatures collection and screening We searched several databases including the Pubmed, Embase, CNKI (China National Knowledge Infrastructure), Wanfang database and Chinese Biomedicine databases for all articles on the relation between p73 G4C14-A4T14 polymorphism and risk of non-small lung cancer (last search update 10th August 2017) by using keywords of 'p73', 'polymorphism', 'polymorphisms' and 'lung cancer' without any restriction on language or publication year. We also searched the other publications of references quoted in review and related meta-analysis by hand. The inclusion and exclusion criteria of literatures Studies would be considered for inclusion if:

1. Independently published case-control or cohort studies where the relation between p73 G4C14-to-A4T14 polymorphism and NSCLC susceptibility was investigated;
2. The publication published available genotype data for odds ratio (OR) or relative risk (RR) values and 95%CI (confidence interval) estimation and
3. If several studies were published on the basis of the same case population, we selected the most recent or the largest study.

The major exclusion criteria were:

1. Duplicate data,
2. There is not available relevant data
3. In the control population there is heterogeneity of gene polymorphism.

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Received February 02, 2018; **Accepted** February 07, 2018; **Published** February 13, 2018

Citation: Cheng X, Liu H, Song Y, An Y, Xuan W, et al. (2018) Meta-Analysis of P73 Polymorphism and Risk of Non-Small Cell Lung Cancer. J Pulm Respir Med 8: 445. doi: 10.4172/2161-105X.1000445

Quality assessment and data extraction

Two investigators extracted information from all eligible publication independently according to the inclusion criteria. Any disagreement was coordinated by referring to a third investigator. We assessed the methodological quality of the included studies with the Cochrane Handbook 5.2 quality evaluation criteria. The essential information from various studies included publication year, the first author, ethnicity, and country, sample size of cases and controls and genotype frequency for the present polymorphism.

Statistical analysis

All analyses were done using RevMan 5.3 software and Stata version 12.0. A statistical significance was considered when $P<0.05$. Assessment of the relation between p73 G4C14-to-A4T14 polymorphism and NSCLC susceptibility was performed by calculating ORs with 95% CIs. The pooled ORs were performed for allele model (AT *vs.* GC), the homozygote genotypes (AT/AT *vs.* GC/GC), the heterozygote genotypes (AT/GC *vs.* GC/GC), the dominant model(AT/AT+AT/GC *vs.* GC/GC), and the recessive model (AT/AT *vs.* AT/GC+GC/GC). Subgroup analysis was conducted by different countries. The statistical heterogeneity among studies was assessed with the chi-square-based Q test ($P<0.10$ was considered significant) [13]. If there was no obvious heterogeneity, the fixed-effects model derived from the Mantel-Haenszel method was used to estimate the summary OR [14]; otherwise, the random-effects model using the DerSimonian and Laird method was used [15]. Using the Pearson chi-square test, we checked the Hardy-Weinberg equilibrium (HWE) for the controls of all studies. Besides, we performed sensitivity analysis to check if any single data had a greater impact on the overall conclusion. Funnel plots was applied to diagnose the potential publication bias [16].

Results

Study identification

As shown in Figure 1, 47 English literatures were reviewed through database searching. A total of thirty seven literatures were excluded because of different gene/SNP/cancer, duplicate publication and review or meta-analysis. Six literatures were excluded because of unavailable genotype data. Finally, a total of 6 literatures [11,12,17-21] were included in the analysis with a total of 1658 patients with NSCLC and 2328 control subjects. Features included in this literature were shown in Table 1.

Quantitative synthesis

The main result of meta-analysis and heterogeneity are present in Figures 2 and 3. As significant heterogeneity was detected, we used the random effects model as well as the fixed effects model to calculate the pooled ORs. In overall comparisons, none of genetic models showed significant association with the risk of non-small lung cancer (recessive model: OR: 1.16, 95%CI: 0.94-1.43; dominant model: OR: 0.63, 95%CI: 0.37-1.06; co-dominant model: OR: 1.63, 95%CI: 0.94-2.83; allelic model: OR: 1.20, 95%CI: 0.98-1.48) (Figure 2). However, when we proceeded to subgroup analysis according country, significantly increased risk was observed in a recessive models (OR: 1.35, 95%CI: 1.15-1.59), in a co-dominant model: (OR: 2.49, 95%CI: 1.76-3.53), in a allelic model (OR: 1.41, 95%CI: 1.24-1.61). Significantly decreased risk was observed in a dominant model (OR: 0.42, 95%CI: 0.30-0.59) (Figure 3).

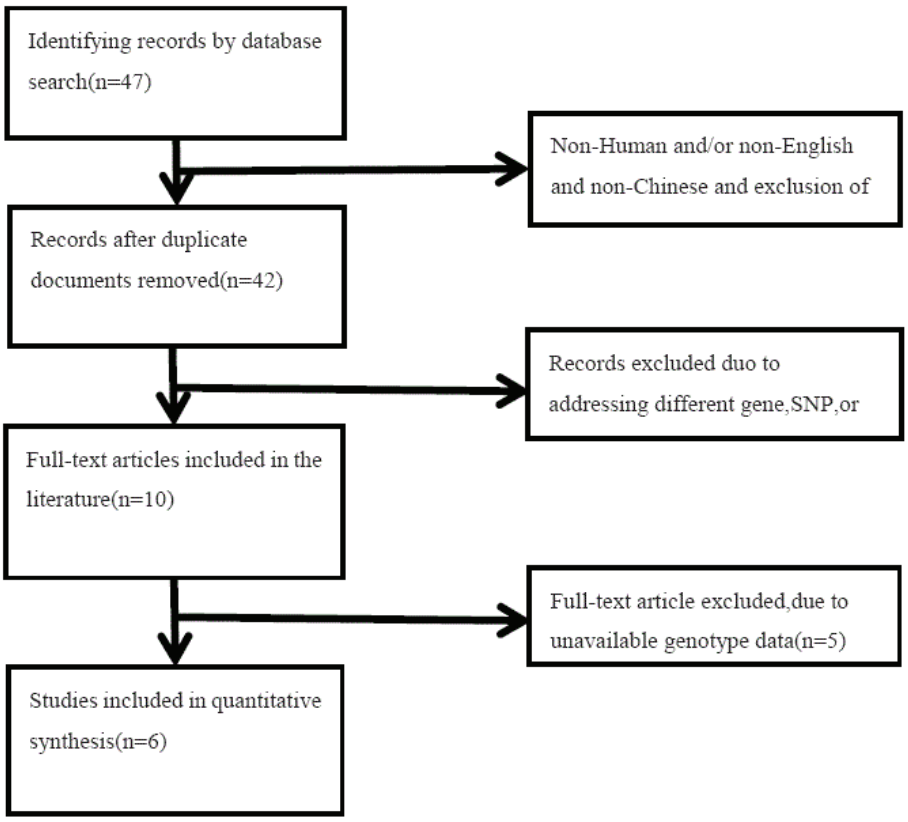


Figure 1: Flow chart of literature search and research selection.

Authors	Publication year	Country	Ethnicity	Genotype(case/control)			HWE
				GC/GC	GC/AT	AT/AT	YES
Akio [11]	2003	Japanese	Asian	109/130	68/95	12/10	0.215
Wang [12]	2014	China	Asian	87/102	57/68	8/25	0.24
Jun [17]	2007	Korea	Asian	266/338	184/212	35/32	0.87
Wang [18]	2015	China	Asian	108/104	68/68	10/26	YES
Wu [19]	2017	China	Asian	294/490	149/361	17/71	0.691
Wen [20]	2017	China	Asian	94/98	80/71	12/27	NO

Table 1: Characteristics of incorporated studies.

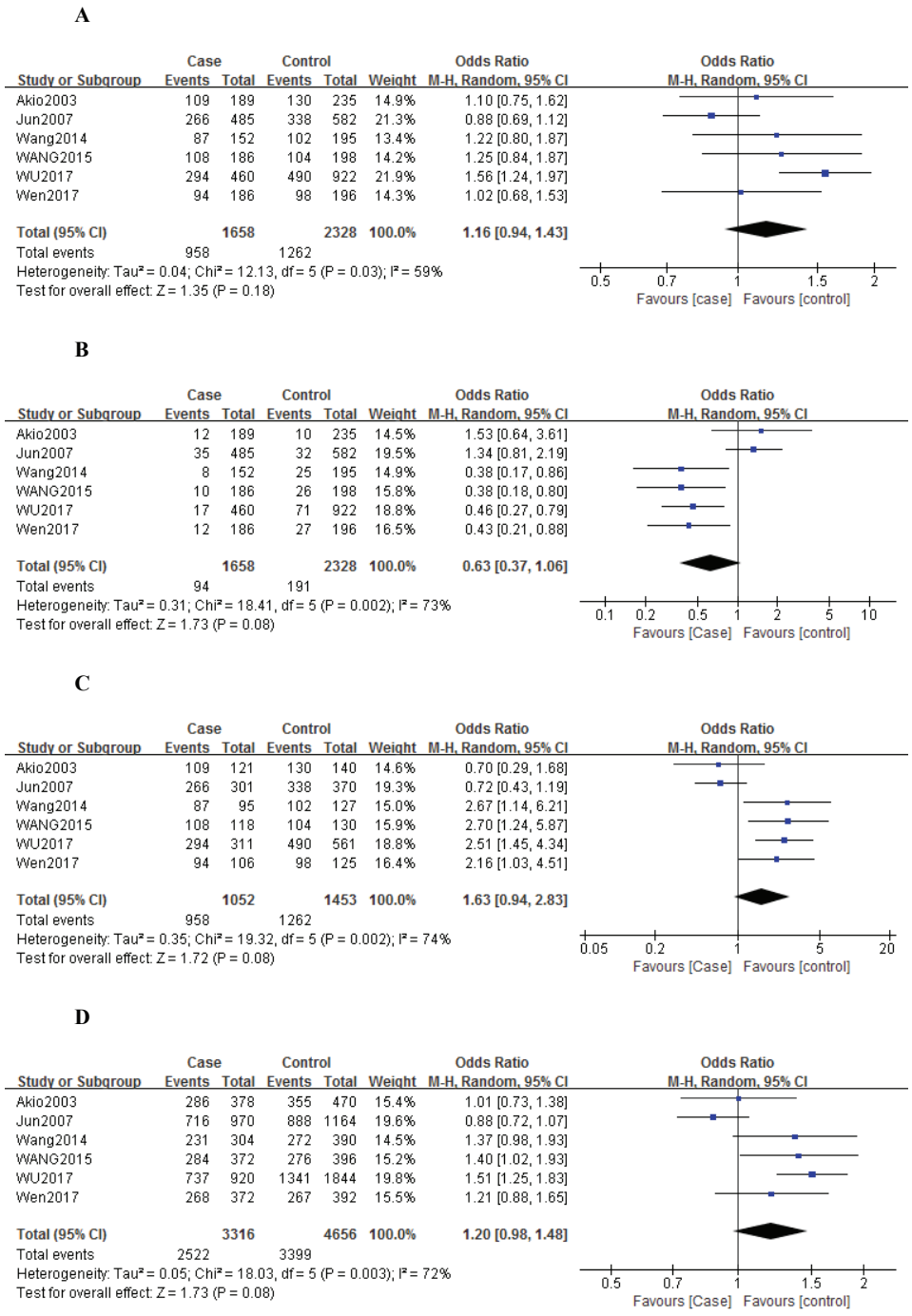
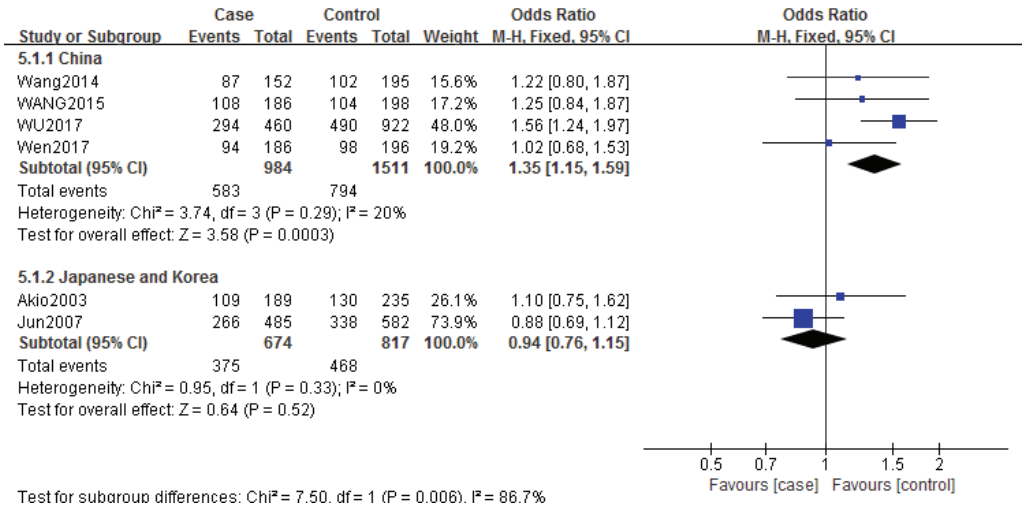
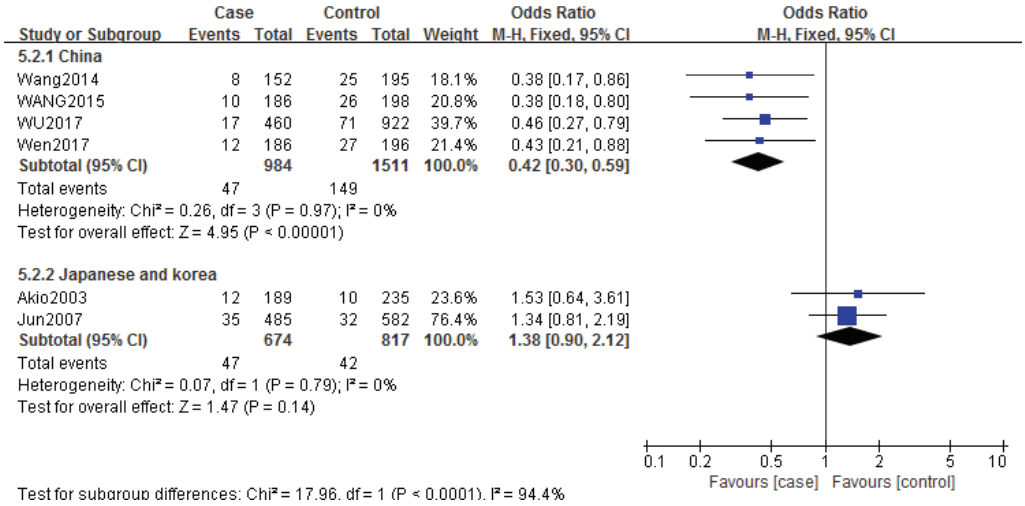


Figure 2: Meta-analysis of genetic polymorphism and non-small lung cancer. (A) Recessive model; (B) Dominant model; (C) Co-dominat model; (D) Allelic model.

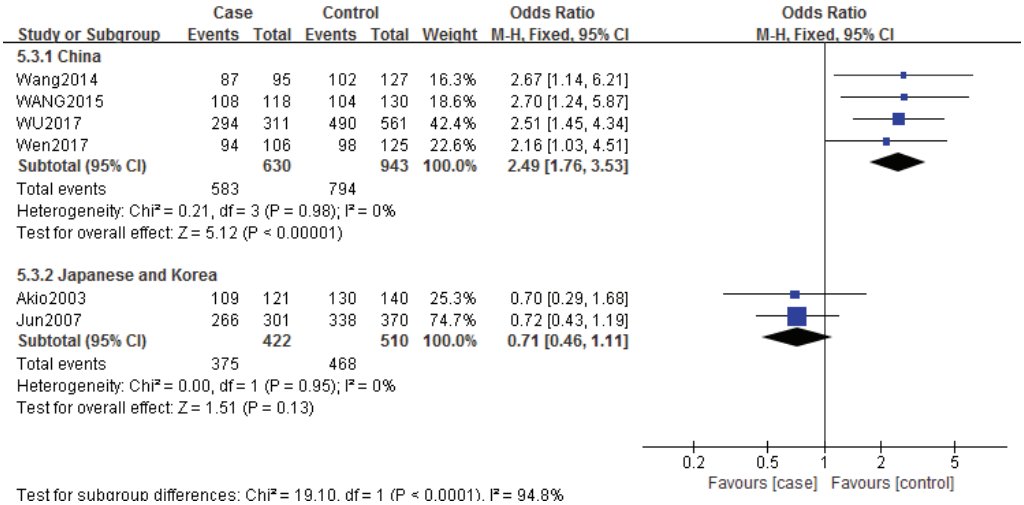
A


Case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
5.1.1 China
Wang2014 87 152 102 195 15.6% 1.22 [0.80, 1.87]
WANG2015 108 186 104 198 17.2% 1.25 [0.84, 1.87]
WU2017 294 460 490 922 48.0% 1.56 [1.24, 1.97]
Wen2017 94 186 98 196 19.2% 1.02 [0.68, 1.53]
Subtotal (95% CI) 984 1511 100.0% 1.35 [1.15, 1.59]
Total events 583 794
Heterogeneity: Chi² = 3.74, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 3.58 (P = 0.0003)
5.1.2 Japanese and Korea
Akio2003 109 189 130 235 26.1% 1.10 [0.75, 1.62]
Jun2007 266 485 338 582 73.9% 0.88 [0.69, 1.12]
Subtotal (95% CI) 674 817 100.0% 0.94 [0.76, 1.15]
Total events 375 468
Heterogeneity: Chi² = 0.95, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Chi² = 7.50, df = 1 (P = 0.006), I² = 86.7%
0.5 0.7 1 1.5 2
Favours [case] Favours [control]

B


Case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
5.2.1 China
Wang2014 8 152 25 195 18.1% 0.38 [0.17, 0.86]
WANG2015 10 186 26 198 20.8% 0.38 [0.18, 0.80]
WU2017 17 460 71 922 39.7% 0.46 [0.27, 0.79]
Wen2017 12 186 27 196 21.4% 0.43 [0.21, 0.88]
Subtotal (95% CI) 984 1511 100.0% 0.42 [0.30, 0.59]
Total events 47 149
Heterogeneity: Chi² = 0.26, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 4.95 (P < 0.00001)
5.2.2 Japanese and korea
Akio2003 12 189 10 235 23.6% 1.53 [0.64, 3.61]
Jun2007 35 485 32 582 76.4% 1.34 [0.81, 2.19]
Subtotal (95% CI) 674 817 100.0% 1.38 [0.90, 2.12]
Total events 47 42
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Chi² = 17.96, df = 1 (P < 0.0001), I² = 94.4%
0.1 0.2 0.5 1 2 5 10
Favours [case] Favours [control]

C


Case
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
5.3.1 China
Wang2014 87 95 102 127 16.3% 2.67 [1.14, 6.21]
WANG2015 108 118 104 130 18.6% 2.70 [1.24, 5.87]
WU2017 294 311 490 561 42.4% 2.51 [1.45, 4.34]
Wen2017 94 106 98 125 22.6% 2.16 [1.03, 4.51]
Subtotal (95% CI) 630 943 100.0% 2.49 [1.76, 3.53]
Total events 583 794
Heterogeneity: Chi² = 0.21, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 5.12 (P < 0.00001)
5.3.2 Japanese and Korea
Akio2003 109 121 130 140 25.3% 0.70 [0.29, 1.68]
Jun2007 266 301 338 370 74.7% 0.72 [0.43, 1.19]
Subtotal (95% CI) 422 510 100.0% 0.71 [0.46, 1.11]
Total events 375 468
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Chi² = 19.10, df = 1 (P < 0.0001), I² = 94.8%
0.2 0.5 1 2 5
Favours [case] Favours [control]

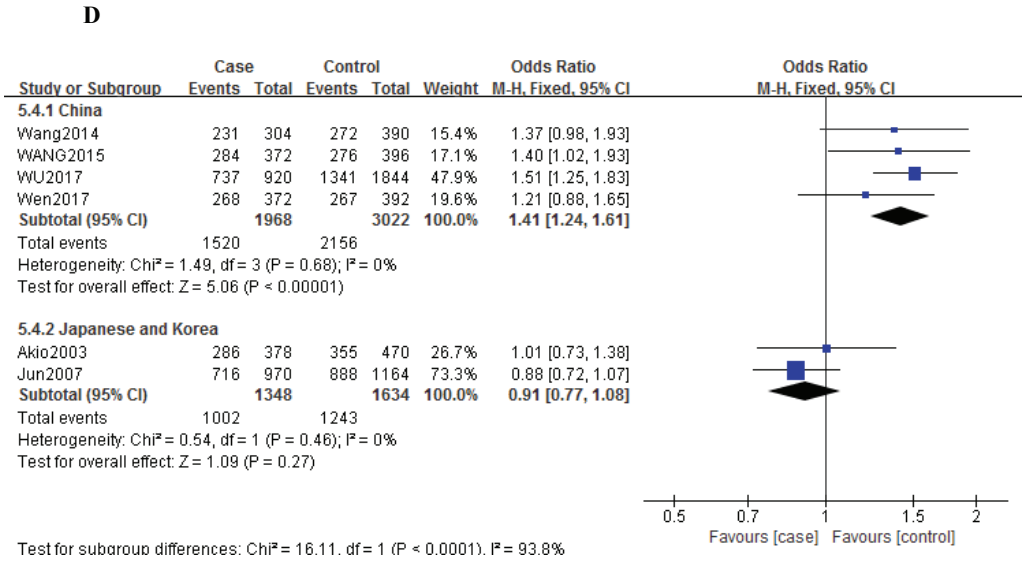


Figure 3: Subgroup analysis by country. (A) Recessive model; (B) Dominant model; (C) Co-dominat model; (D) Allelic model.

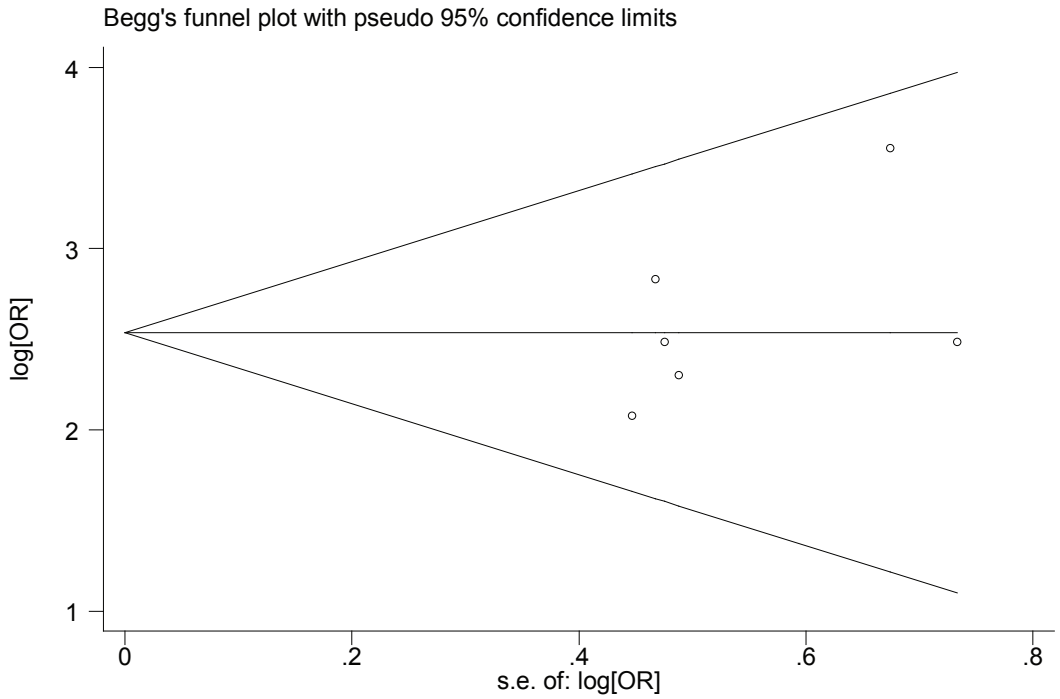


Figure 4: Begg's funnel plot for Publication bias test for all included studies (GC/AT+AT/AT *vs.* GC/GC).

Publication bias analysis

As depicted in Figure 4 (the dominant model), the funnel plot showed no evidence for obvious asymmetry. We used the Egger's test to further quantitatively estimate the publication bias, the result indicated no existence of significant publication bias (P=0.273). This indicated that in the present study there is no publication bias, and the result is credible.

Discussion

In this study, we performed a meta-analysis to clarify the relation between p73 polymorphism and non-small cell lung cancer. We found significant association of p73 polymorphism with non-small cell lung cancer in a recessive, dominant, co-dominant and allelic model in Chinese population but not in Japanese and Korean. The *p73* gene was identified at chromosome 1p36.33 in 1977 [21], a site which had

been proved to commonly undergo loss of heterozygosity (LOH) in various kinds of cancer [21-23]. In addition, LOH had been reported to occur in 62% of lung cancer patients at the *p73* gene [24], indicating that in the development of lung cancer *p73* gene probably play an important role [25,26]. Two completely linked single-nucleotide polymorphisms (SNPs) at position 4(G→A) and (C→T) (designated as G4C14-to-A4T14, rs numbers 2273953 and 1801173) in intron 1 of the *p73* gene have been certified to be related to the lung cancer risk [27,5]. Only three genotypes are possible: GC/GC, GC/AT and AT/AT, because these SNPs are in complete linage equilibrium. The association between polymorphism in previous studies and the development of various types of cancer risk have been reported. Studies have found that carriers with AT allele genotype have significantly increased risk of lung cancer than GC/GC genotype in the north of China [28] and non-Hispanic whites [29]. Another study found no significant relationship between the G4C14-to-A4T14 polymorphism and the risk of lung cancer in Korea [30] and Japan [31]. Otherwise, another study found that crowd with AT allele genotype has reduced risk of lung cancer in Chinese [32]. Liu's meta-analysis suggested that p73 G4C14-to-A4T14 polymorphism may play a important role in development of lung cancer in Caucasians [33]. However, all the above articles did not classify lung cancer by pathology. Above all, association between p73 polymorphism and NSCLC was not clear. The present study has shown that significant association of p73 polymorphism with non-small cell lung cancer in a recessive, dominant, co-dominant and allelic model in Chinese population but not in Japanese and Korean. However, further research and screening of etiological relations between the functional polymorphism loci of *p73* gene and the susceptibility of NSCLC is still needed. Some limitation of this meta-analysis should be addressed. Firstly, the total number of cases and controls was somewhat small to detect the potential exist of marginal effect. Therefore, more studies with larger sample size and providing more detail information are needed. Secondly, there was significant between-study heterogeneity from studies of p73 polymorphism, and the genotype distribution also showed deviation from HWE in some studies. Finally, potential publication bias may exist in this meta-analysis, as studies with negative results are more likely not to be published.

Conclusion

In conclusion, based on the combined data, this meta-analysis demonstrated that there was no clear association between p73 G4C14-to-A4T14 polymorphism and overall non-small lung cancer risk, but we observed increased risk of lung cancer in Chinese population.

Funding

This work was supported by Science and Technology Office of Henan province. The project name: Preparation and Screening and the Role in EMT of N-Cadherin, CD146. The project number: 154100510021.

Acknowledgements

The authors acknowledge Professor Yuanlin Song for his assistance in performing chart review.

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