# Association between p73 gene G4C14-to-A4T14 polymorphism and risk of lung cancer: A meta-analysis

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## Abstract

**Objective:** To explore the correlation between p73 G4C14-to-A4T14 polymorphism and lung cancer risk.

**Methods:** The meta analysis was conducted from October 2017 to March 2018, and comprised studies published till March 27, 2018, that addressed the relationship between the p73 G4C14-to-A4T14 polymorphism and risk of lung cancer, and were available on databases including PubMed, Web of Science, Embase, Cochrane Library and China National Knowledge Infrastructure. Pooled odds ratio with corresponding 95% confidence interval and subgroup analysis between ethnicities were carried out to assess the association between the two parameters using four different models. Stata 12 was used for data analysis.

**Results:** For overall population, there was no significant risk of lung cancer for the polymorphism under allele and dominant genetic models. However, reduced risks were found under homozygous (AT/AT vs GC/GC; p=0.02) and recessive (AT/AT vs GC/AT + GC/GC; p=0.02) comparison models. Subgroup analysis between ethnicities demonstrated reduced risk of lung cancer for the polymorphism under the four genetic comparison models for Asian population, but increased risk for the Caucasian group.

**Conclusions:** AT/AT variant carriers possessed reduced susceptibility of lung cancer in the general population. Ethnic differences for the p73 gene polymorphism played an important role in lung cancer susceptibility.


**Keywords:** Tumour protein 73, Polymorphism, Lung cancer, Association, Risk, Genetic susceptibility. (JPMA 70: 313; 2020)

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## Introduction

Lung cancer, primarily non-small cell lung cancer (NSCLC), is the main cause of cancer-related death in males worldwide, and the incidence has been significantly increased in the past two decades.[1] Studies have shown that lung cancer is a complex disease caused by the interaction of environmental factors and host genes in many steps of the carcinogenesis process.[2] It is estimated that smoking accounts for 87%[3] of all lung cancers, but only a small percentage of smokers, approximately 21%, develop lung cancer, indicating that there is an inter-individual variation in the genetic susceptibility to lung cancer in the general population. The genetic susceptibility may be related to gene variants mediated in carcinogen metabolism, deoxyribonucleic acid (DNA) damage repair, cell cycle control and apoptosis.[4] Therefore, the study of genetic variations associated with lung cancer may help to fully elucidate the pathogenesis of this malignancy, including its formation and progression, and to predict the risk of individuals developing the malignancy.

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The p73 gene, a member of p53 family, is located to the human chromosome 1p36.33. As a tumour-suppresser gene similar to p53, p73 mimics p53 functions and transcriptionally activates p53-responsive genes by induction of cell cycle arrest or cell apoptosis. It has been demonstrated that p73 gene commonly undergoes loss of heterozygosity (LOH) in various types of cancer, including approximately 62% in lung cancer patients.[5] Additionally, compared with adjacent normal tissues, higher p73 expression levels in lung tumour tissues are associated with p53 mutations, suggesting a role of p73 in compensating for the loss of p53 function.[6-8] These results suggested that the p73 gene play a vital role in the pathogenesis of lung cancer.[6-9]

To date, there are approximately 19 single nucleotide polymorphisms (SNPs) in p73 gene reported.[10-12] Among them, the two common SNPs at positions 4 (G-A) and 14 (C-T) in the non-coding region of exon 2 of p73 gene are in complete linkage disequilibrium with one another as one variant. It has been reported that the AT variant can hypothetically form a stem-loop structure and modulate the p73 function, perhaps by altering the efficiency of translation initiation.[10] Many studies investigated the relationship between the G4C14-to-A4T14 polymorphism and lung cancer susceptibility in various populations. However, the results of these studies are confusing rather than conclusive and all published studies to date have

suffered from limited statistical power due to small sample size.[8,13-21] The current meta analysis was planned to assess the correlation between lung cancer risk and p73 G4C14-to-A4T14 polymorphism.

## Materials and Methods

The meta analysis was conducted from October 2017 to March 2018, and comprised studies published till March 27, 2018, that addressed the relationship between p73 G4C14-to-A4T14 polymorphism and the risk of lung cancer. Combining terms, like 'p73', 'G4C14-to-A4T14', 'polymorphism' and 'lung cancer', were used on databases including PubMed, Web of Science, Embase, Cochrane Library and China National Knowledge Infrastructure (CNKI). The reference lists of retrieved articles and reviews were searched for relevant studies, and only studies with full text were included. If there were more than one instance of the same patient population included in several studies, only the complete and the most recent studies were chosen. The following criteria were applied for inclusion of the eligible studies: case-control designed studies; studies investigating the relationship between p73 G4C14-to-A4T14 polymorphism and lung cancer; sufficient genotype frequencies of G4C14-to-A4T14 polymorphism were available for estimating the odds ratio (OR). The reasons for exclusion were: review articles; case-only studies; and studies with overlapping data. As a whole, this meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[22]

Information, including publication year, first author, numbers of cases and controls, ethnicity of the study population, and country of origin, were carefully extracted from each eligible study independently by two authors according to the current study's inclusion criteria. A minimum number of patients benchmark was not set as a criterion for a study's inclusion in the meta-analysis. Disagreements were resolved by reaching a consensus among all the researchers.

As a whole, the strength of association between p73 G4C14-to-A4T14 polymorphism and lung cancer risk was estimated by odds ratio (OR) with 95% confidence interval (CI). Fixed and random effects models were applied to calculate the pooled ORs. With the ORs, forest plot was generated using Review Manager 5.0 software.[23] Four different genetic comparison models,[24] namely allele comparison model (AT vs GC), homozygous model (AT/AT vs GC/GC), dominant model (AT/AT + GC/AT vs GC/GC) and recessive model (AT/AT vs GC/GC + GC/AT), were used respectively for the evaluation of the association between the lung cancer risk and p73 G4C14-to-A4T14 polymorphism. Meanwhile, stratification analysis also was performed in Caucasian and Asian ethnicities. Heterogeneity between studies was estimated using chi-square-based Q statistic, and $p<0.10$ was considered statistically significant. I-square metric statistic was calculated to determine the proportion of variability resulting from between-study heterogeneity, and 75% <I2, ,<50% I2 and <25% I2 were interpreted respectively as extreme, moderate and large or low heterogeneity. Standard error of log (Logor) of each study was plotted against log to estimate the possible publication bias by Begg's funnel plot,[25] and asymmetry of the funnel plot suggested a possible publication bias. Additionally, the method of Egger's linear regression[26] was used to test the asymmetry of a funnel plot. The t-test suggested by Egger's test was applied to estimate the significance of intercept, and $p<0.05$ was considered a potential statistical publication bias. Furthermore, sensitivity analysis was conducted to evaluate whether the individual study influenced the pooled results. In this meta-analysis, the sensitivity and Egger's test were calculated using Stata 12.0 Software,[27] while the rest of the calculations were performed using the Review Manager 5.0 software.

## Results

A total of 9 eligible case-control studies addressing the relationship between p73 G4C14-to-A4T14 polymorphism and lung cancer risk[8,13,15-21] were identified. The publication year of these studies ranged from 2004 to 2017. In all studies, the patients were histologically confirmed and the control groups were free of lung cancer and matched for gender and age. These studies were conducted in various populations of the two different ethnicities (Table-1), with 7 on Asian population[8,13,16,18-21] and 2 on Caucasian population[15,17] for p73 G4C14-to-A4T14 polymorphism. Total 4217 cases and 5050 controls were found in these studies. In terms of genotype frequency, for the case group, 57% GC/GC-homozygous genotype individuals, 37% GC/AT-heterozygous and 6% AT/AT homozygous individuals illustrated the p73 G4C14-to-A4T14 polymorphism. For the control group, GC/GC-homozygous, GC/AT-heterozygous and AT/AT homozygous genotype frequencies were 57%, 36% and 7%, respectively. The allele frequencies in case and control groups were 24% and 25%, respectively. Additionally, for one study,[17] only the dominant model was applied in the analysis as the GC/AT and AT/AT genotype frequencies were unavailable (Table-1).

For all studies, no significant association between p73

**Table-1:** Distribution of p73 GC/GC-AT/AT genotypes.

| First author (year) | Ethnicity (Country) | | Frequency of GC/GC-ATAT genotype GC/GC | GC/AT | AT/AT | PHWE |
|---|---|---|---|---|---|---|
| Li (2004) | Caucasians (America) | Case | 593 | 394 | 67 | |
| | | Control | 721 | 67 | 53 | 0.436 |
| Hu (2005) | Asian(China) | Case | 255 | 149 | 21 | |
| | | Control | 295 | 248 | 45 | 0.471 |
| Choi (2006) | Asian(Korean) | Case | 320 | 221 | 41 | |
| | | Control | 338 | 212 | 32 | 0.87 |
| Schabath (2006) | Caucasians (America) | Case | 486 | NA | NA | |
| | | Control | 540 | NA | NA | NA |
| Zhang (2013) | Asian(China) | Case | 163 | 116 | 14 | |
| | | Control | 247 | 120 | 13 | 0.74 |
| Wang (2014) | Asian(China) | Case | 101 | 59 | 8 | |
| | | Control | 102 | 68 | 25 | 0.74 |
| Wang (2015) | Asian(China) | Case | 108 | 68 | 10 | |
| | | Control | 104 | 68 | 26 | NA |
| Li (2017) | Asian(China) | Case | 94 | 80 | 12 | |
| | | Control | 98 | 71 | 27 | NA |
| Wu (2017) | Asian(China) | Case | 294 | 149 | 17 | |
| | | Control | 490 | 361 | 71 | 0.691 |

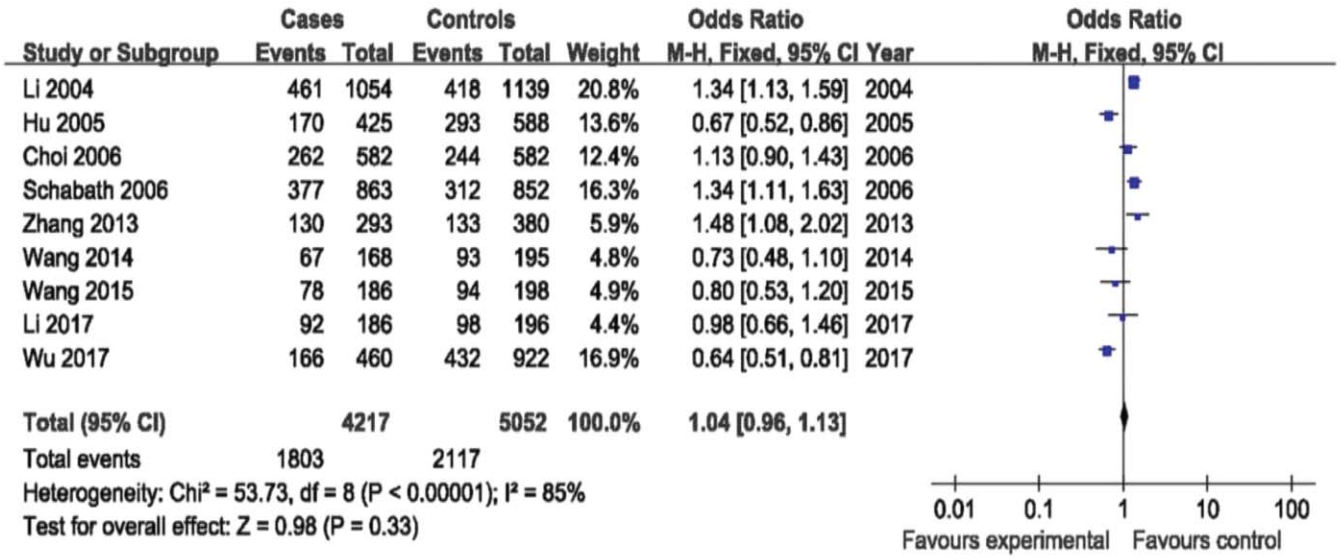
NA, not available; PHWE, the P value for Hardy-Weinberg equilibrium in the control group;

**Table-2**: Meta-analysis for association between p73 GC/GC-ATAT polymorphisms and lung cancer risk under different comparison models.

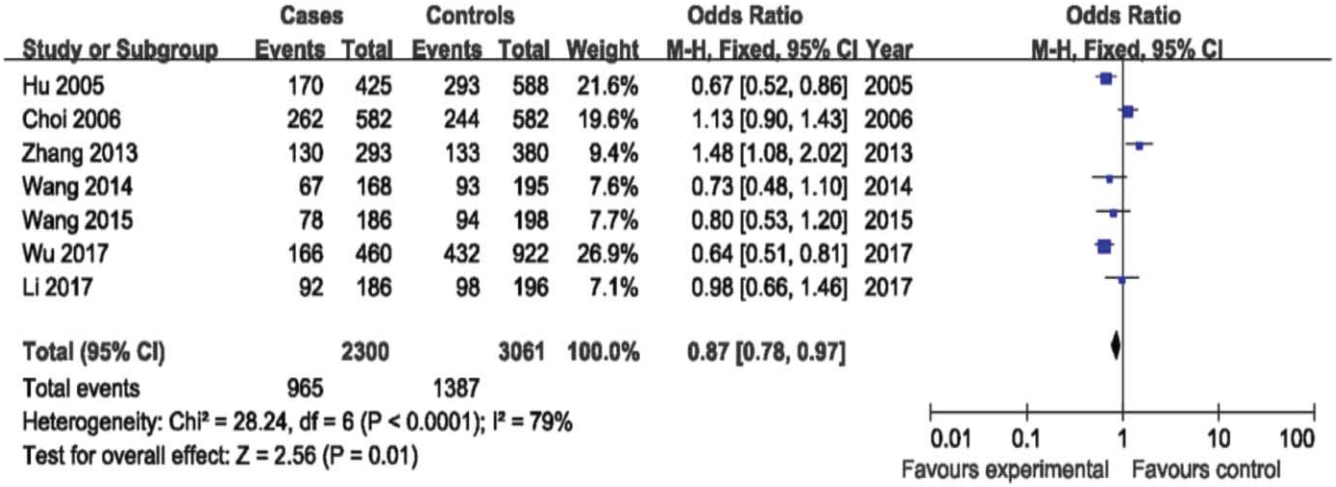
| | Ethnicity | OR Fixed effects (95% CI) | p | Random effects (95% CI) | p | $I^2$ % | P value Q text |
|---|---|---|---|---|---|---|---|
| GC/GC-ATAT | | | | | | | |
| Alleles (AT vs GC) | All | 0.95 ( 0.89 – 1.03 ) | 0.22 | 0.89 ( 0.71 – 1.21 ) | 0.32 | 88 | 0.00001 |
| | Asian | 0.85 ( 0.78 – 0.93 ) | 0.0003 | 0.84 ( 0.67 – 1.05 ) | 0.13 | 82 | 0.00001 |
| | Caucasian | 1.21 ( 1.11 – 1.48 ) | 0.0006 | 1.28 ( 1.11 – 1.48 ) | 0.0006 | – | – |
| AT/AT vs GC/GC | All | 0.80 ( 0.66 – 0.97 ) | 0.02 | 0.69 ( 0.42 – 1.13 ) | 0.14 | 81 | 0.00001 |
| | Asian | 0.63 ( 0.50 – 0.79 ) | 0.0001 | 0.61 ( 0.37 – 0.98 ) | 0.04 | 74 | 0.0008 |
| | Caucasian | 1.54 ( 1.05 – 2.24 ) | 0.03 | 1.54 ( 1.05 – 2.24 ) | 0.03 | – | – |
| AT/AT vs (AT/GC + GC/GC) | All | 0.80 ( 0.66 – 0.96 ) | 0.02 | 0.70 ( 0.45 – 1.07 ) | 0.1 | 77 | 0.0001 |
| | Asian | 0.65 ( 0.52 – 0.81 ) | 0.0002 | 0.62 ( 0.40 – 0.95 ) | 0.03 | 69 | 0.004 |
| | Caucasian | 1.39 ( 0.96 – 2.01 ) | 0.08 | 1.39 ( 0.96 – 2.01 ) | 0.08 | – | – |
| (AT/AT + AT/GC) vs GC/GC | All | 1.04 ( 0.96 – 1.13 ) | 0.33 | 0.98 ( 0.78 – 1.23 ) | 0.85 | 85 | 0.00001 |
| | Asian | 0.87 ( 0.78 – 0.97 ) | 0.01 | 0.88 ( 0.69 – 1.13 ) | 0.32 | 79 | 0.0001 |
| | Caucasian | 1.34 ( 0.18 – 1.53 ) | 0.00001 | 1.34 ( 1.18 – 153 ) | 0.00001 | 0 | 0.99 |

G4C14-to-A4T14 polymorphism and lung cancer risk was found under the allele comparison model (p=0.22), and under the dominant model (p=0.33) (Figure-1) as calculated with fixed effects method. However, decreased lung cancer risk were found under the homozygous (p=0.02) and the recessive (p=0.02) comparison models for all studies. Additionally, there was significant reduced risk of lung cancer in Asian ethnicity as estimated under allele (p=0.0003), homozygous (p=0.0001), recessive (p=0.0002) and dominant (p=0.01) comparison models. For Caucasian ethnicity, there was an increase of lung cancer risk for p73 G4C14-to-A4T14 polymorphism under allele (p=0.0006), homozygous (p=0.03), recessive (p=0.08) and dominant (p=0.000001) comparison models. Between-study heterogeneity was extreme under different comparison models for all ethnicities (Table-2). To eliminate the heterogeneity, the 9 studies were subjected to subgroup analysis. However, the heterogeneity only reduced a litter for subgroup of Asian ethnicity, which suggested that most of the studies could not be grouped helpfully according to ethnicity and region.

A




B




C

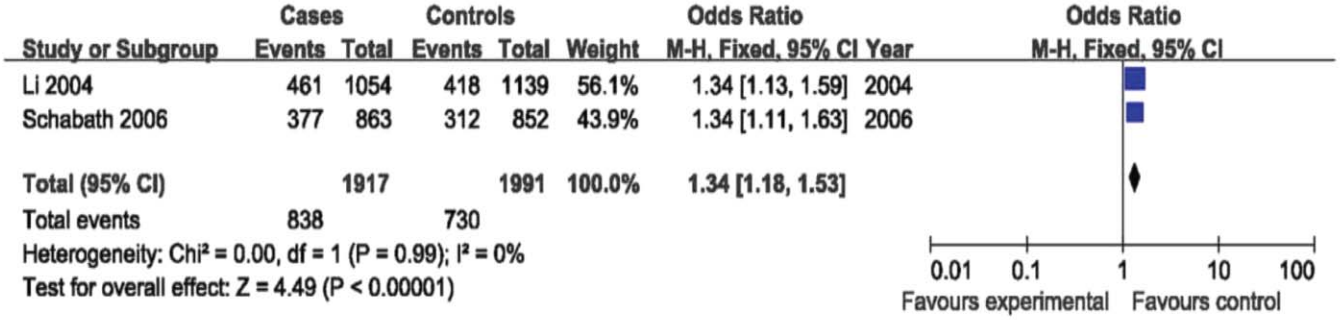



**Figure-1:** Forest plots of p73 G4C14-A4T14 polymorphism and risk of lung cancer under dominant comparison model (AT/AT + GC/AT vs GC/GC) for overall population (A), Asian population (B) and Caucasian population (C), respectively.

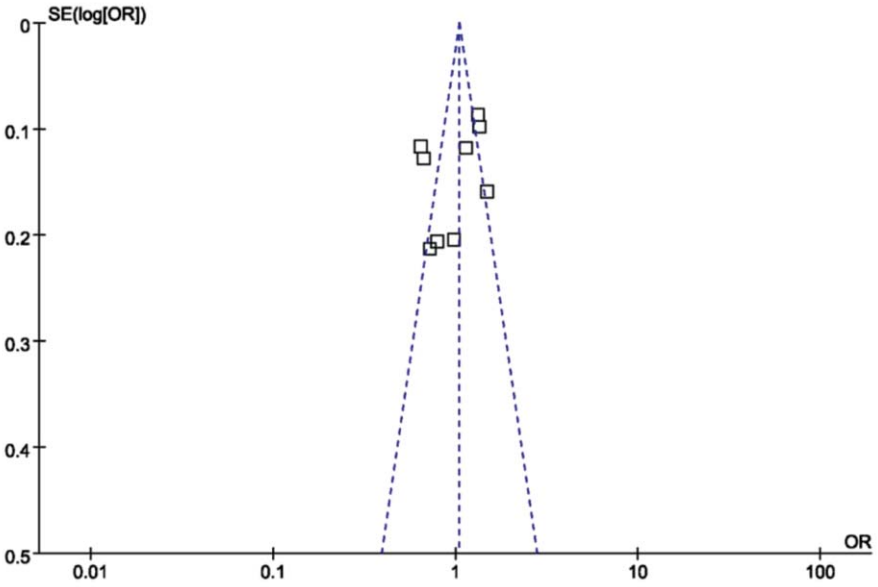



**Figure-2:** Funnel plots analysis for publication bias between p73 G4C14-A4T14 polymorphism and risk of lung cancer.

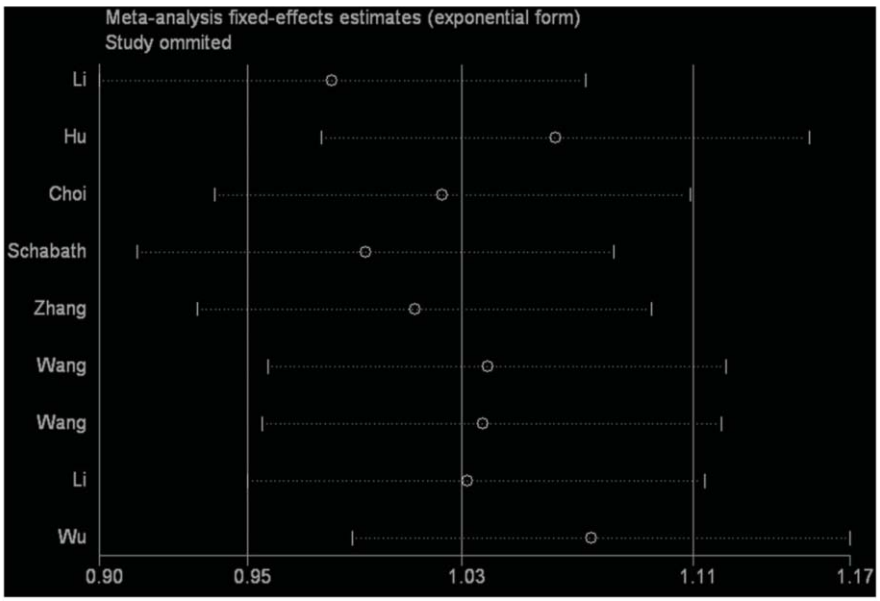



**Figure-3:** Sensitivity analysis of the correlation between p73 G4C14-A4T14 polymorphism and risk of lung cancer.

The sharp of funnel plot was symmetry for p73 G4C14-to-A4T14 polymorphism in overall population and subgroup comparison under different genetic models (Figure-2). Egger's test did not reveal significant asymmetry for p73 G4C14-to-A4T14 polymorphism under allele model (p=0.281). There was no obvious evidence showing potential publication bias.

Sensitivity analysis illustrated that there were no individual study influencing the pooled ORs (Figure-3), indicating the results of this meta-analysis were stable.

## Discussion

It has been well established that the individuals' susceptibility[28] to certain kinds of malignancy are different even when they are exposed to an identical environment. This difference can be explained by the host factors, including gene polymorphisms. Thus, it is reasonable to assess the possible correlation between genetic susceptibility and the risk of cancer. The p73 gene, the structural and functional homology of p53, shares 63% sequence similarity with p53 in DNA binding, transactivation and oligomerisation domains.[10,29] Ectopically overexpressed p73-induced cell cycle arrest and apoptosis in evident in a p53-like manner by transactivating overlapping sets of p53 responsive genes, such as p21 and Bax.[29] Existing data showed that p73 activity may, to some extent, compensate for the loss of p53 function observed in some premalignant lesions.[30,31] Two common SNPs G4C14-to-A4T14 are located just upstream of initial codon AUG in exon 2 of p73 gene,[10] and accumulating evidences demonstrated that p73 G4C14-to-A4T14 polymorphism affect the p73 function and play an important role in development of various cancer, including lung cancer.

In the past two decades, studies have investigated the relationship between p73 gene G4C14-to-A4T14 polymorphism and the risk of development of lung cancer.[8,13-21] However, the results of these studies were in-conclusive and even contradictory. Three studies reported significant correlation between lung cancer risk and the G4C14-to-A4T14 polymorphism, suggesting AT allele carriers (AT/AT or GC/AT) possess elevated lung cancer susceptibility compared to GC/GC homozygous variant by using dominant ( AT/AT + GC/AT vs GC/GC) genetic model.[15,17,21] In contrast, the other five reports arrived at the opposing conclusion, suggesting that p73 AT allele is associated with reduced lung cancer risk.[13,16,18-20] Additionally, Choi et al.[8] suggested no association between

the p73 G4C14-to-A4T14 polymorphism and lung cancer risk in a Korean population. To get a more comprehensive relationship between p73 G4C14-to-A4T14 polymorphism and the risk of lung cancer, the current meta-analysis was conducted with available publications investigating the effects of p73 G4C14-to-A4T14 polymorphism on the risk of lung cancer. Taken together, we didn't find a significant association between p73 G4C14-to-A4T14 polymorphism and lung cancer risk as calculated with allele (AT vs GC) and dominant genetic models for overall studies. However, reduced cancer risk was found by using homozygous (AT/AT vs GC/GC) and recessive (AT/AT vs (AT/GC + GC/GC)) comparison models in overall population for all studies, suggesting that AT/AT homozygous variant individuals hypothetically possess reduced lung cancer risk in general population. Furthermore, stratification analysis by ethnicities between Caucasian and Asian subgroups revealed confusing or even opposing results, as there was increased lung cancer risk in Caucasian subgroup for p73 G4C14-to-A4T14 polymorphism, as assessed by the four genetic comparison models, while, in contrast, there was reduced risk for the Asian subgroup. Although the relationship between the p73 gene function and the pathogenesis of lung cancer risk remains to be fully elucidated, it is difficult to give a satisfactory explanation for the discrepancy in results between ethnicities in this meta-analysis. The results would be due to the limited statistical power because of the small sample size. Another possibility is that this p73 GC/AT polymorphism is in linkage disequilibrium (LD) with other putative aetiological variants and the LD mode is different across different ethnic populations. In addition, inadequate study design, such as non-random sampling, different genotyping methods and the pitfalls of unknown confounders, should be considered. However, these hypotheses need to be tested in future by large-scale comprehensive analyses with more case-control studies. In this meta-analysis, careful publication search, strict inclusion criteria, precise data extraction, and strict statistical analysis were ensured to avoid potential heterogeneity. However, potential heterogeneities emerged in the comparisons for overall and Asian population by different genetic models. Heterogeneities may have resulted from the study design, ethnicity differences, selection of the control groups, lifestyle factors, and so on. No substantial publication bias was found by Begg's and Egger's tests.

The interpretation of the results in this meta-analysis should be considered with caution in view of the limitations. Firstly, only the publication with full text were included in the analysis, thus non-significant or negative results remain unpublished, although no significant publication bias was found. Secondly, the number of the included publications in this meta-analysis were inadequate for comprehensive analysis of the correlation between p73 gene G4C14-to-A4T14 polymorphism and the lung cancer risk. Therefore, more case-control studies are needed for subsequent analysis. Thirdly, unadjusted estimates were used for this meta-analysis, and a more accurate analysis needs to be performed using individual data, if available, which would enable the researchers to adjust other covariates, including family history, smoking status, types of the lung cancer, and environmental factors.

## Conclusion

There was no significant correlation between lung cancer risk and G4C14-to-A4T14 polymorphism under the dominant and allele models. However, reduced risks were found in overall population under homozygous and recessive models, revealing AT/AT variant carriers possessed reduced lung cancer susceptibility in the general population. There was a reduced association between p73 G4C14-to-A4T14 polymorphism and lung cancer risk in the Asian subgroup, while the association was increased in the Caucasian subgroup, indicating ethnic differences play a vital role on the correlation between p73 gene polymorphisms and the risk of lung cancer.

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