

Associations Between I/ D polymorphism in the ACE gene and lung cancer: an updated systematic review and a meta-analysis

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Abstract

Background

This study has evaluated the association between the I/D polymorphism in the *ACE* gene and lung cancer risk by constructing a meta-analysis.

Methods

The heterogeneity in the study was tested by the Q-test and I^2 , and then the random ratio or fixed effect was utilized to merge the odds ratios (OR) and 95% confidence interval (CI), to estimate the strength of the association between *ACE* polymorphisms and susceptibility to lung cancer. We have performed Sensitivity analysis. Using funnel plot and Begger's regression test investigated the publication bias. All data Statistical analyses were performed using Stata 12.0 and Revman 5.3.

Results

A total of 4307 participants (2181 patients; 2126 controls) were included in twelve case-control studies selected. No significant association was found between the *ACE* I/D polymorphism and lung cancer risks (II vs ID + DD: OR = 1.22, 95% CI = 0.89–1.68; II + ID vs DD: OR = 1.21, 95% CI = 0.90–1.63; I vs D: OR = 1.15, 95% CI = 0.95–1.39). In the subgroup analysis by ethnicity, no significant association between this polymorphism and lung cancer risks was also found among Asia and Caucasian populations for the comparison of II vs ID + DD, II + ID vs DD and I vs D genetic models.

Conclusion

Our study indicated that the *ACE* I/ D polymorphism was not associated with the risk of lung cancer.

Background

Lung cancer had become the largest malignant tumor in terms of harm to human health and life [1, 2]. The incidence and mortality of lung cancer were also increasing year by year, and its proportion in tumor mortality was also expanding[2]. Five-year survival rate of lung cancer was only about 15% [3].

The human angiotensin-converting enzyme (*ACE*) gene located on chromosome 17q23 and had a gene length of 21 kp, which was consisted of 26 exons and 25 introns [4]. The biological significance of the *ACE* gene was that the 16th intron had an insertion/deletion sequence, producing three genotypes, insertion homozygous (II), deletion homozygous (DD), and Insertion/deletion of heterozygous type (ID). The level of *ACE* activity in serum was related to the I/D polymorphism of *ACE* gene [5]. The II genotype exhibits low activity, the DD gene exhibits high activity, and the heterozygous ID genotype has activity between the two [6].

In recent years, there have been many studies on the role of *ACE I/D* polymorphism in the risk of lung cancer, but there were some contradictions among the results of these studies. Some study showed an obviously trend of the *ACE 'II'* genotype with increased risk of lung cancer [7, 8], while the other study also showed the *DD* genotype of *ACE* may contribute to a higher risk of lung cancer [9-12], but additional one study showed *ACE 'ID'* genotypes might increase the risk of lung cancer [13], and yet others displayed no association between *ACE I/D* polymorphism and lung cancer [14-18]. To more accurately assess the potential relationship between the *ACE I/D* polymorphism and the risk of lung cancer, we performed a meta-analysis using all eligibility published literature.

Methods

Search strategies

We conducted a comprehensive search of the literature in the Web of Science, Pubmed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI) electronic database, covering relevant studies published until June 31, 2019. The keywords for the search were as follows: (“angiotensin-converting enzyme” OR “*ACE*”) AND (“polymorphism” OR “variant” OR “mutation”) AND (“Lung cancer” OR “lung neoplasm”). The literature on relevant data was searched in English and Chinese respectively. In addition, the retrieved articles and references were performed manual searches. Referring to the Preferred Reporting Project (PRISMA) Guide for Systematic Evaluation and Meta-Analysis [19], an information flow diagram related to the final eligibility data was constructed by screening all retrieved literatures.

Inclusion and Exclusion Criteria

Screening for the studies of the relationship between *ACE I/D* polymorphism and the risk of Lung cancer according to the following inclusion criteria: (1) the design of study was case-control; (2) The full text can be found; (3) the genotype information of the *ACE I/D* polymorphism were available; (4) the relationship of the *ACE I/D* polymorphism and the risk of Lung cancer was evaluated; The major exclusion criteria were: (1) not a case-control study; (2) repeating early publications (studies used in different publications for the same sample data, including only the most complete samples after careful review); (3) Unpublished articles, conference papers, meta-analysis and systematic reviews; (4) family-based pedigree research. This meta-analysis strictly followed the requirements of the preferred reporting project for the systematic review and meta-analysis guidelines. [19].

Data Extraction

The analysis data of the selected studies were independently extracted by two researchers using standard data-collection forms. Studies related information extracted from each literature were as follows: First author, Year of publication, Country of origin, Mean age and Gender in cases and controls, Numbers of cases and controls, Hardy-Weinberg equilibrium, Genotyping method, Source of controls, and available genotype frequency information for *ACE I/D*. If the same sample data appeared in multiple publications, only the publication with the largest sample size was included in the study. The differences

between the two investigators were resolved through discussion. If the discussion could not resolve the objection between the two, the objection would be judged by the third investigator. All data were obtained from the full text of the published research and the author was not contacted for further information.

Study Quality Assessment

Two evaluators evaluated the quality of the included studies according to the Newcastle-Ottawa Scale (NOS) [20], which is applicable to the quality assessment of observational studies. The difference between the two evaluators was reported and resolved by the third evaluator. The scores of research quality mainly include the following three aspects: (1) Selection of the case groups and control groups (4 stars); (2) Quality of confounding factors correction in case and control population (2 stars); and (3) determination of the exposure of interest in the studies (3 stars). For each item numbered in the selection and exposure categories, one study can be rated as up to one star, and comparability can be assigned up to two stars. Higher scores indicate an increase in the quality of the research method. Studies with scores equal to or higher than 6 are considered high quality studies.

Data Analysis

The heterogeneity in the study was tested by the Q-test and I^2 , and then the random ratio or fixed effect was utilized to merge the odds ratios (OR) and 95% confidence interval (CI). The significance of the pooled OR was analyzed by Z-test ($P < 0.05$ Judged statistically significant). To estimate the strength of the association between *ACE* polymorphisms and susceptibility to lung cancer, we have performed Sensitivity analysis. Using funnel plot and Begger's regression test investigated the publication bias. All data Statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, United States) and Revman 5.3.

Results

Literature Search and Study Characteristics

The flow chart of the literature search was shown in Figure 1. 279 potentially relevant articles were selected in the preliminary online search. After verifying and deleting 104 duplicate articles, 175 articles entered the final review. Through the review of the title and abstract, 15 articles were included for full-text review. Finally, 12 articles were included in the final study. These studies were published between 2005 and 2018, and 12 articles included 2181 lung cancer patients and 2126 controls. Except for one study, the distribution of genotypes in controls in other studies followed HWE. In addition, the NOS scores for all studies ranged from 6 to 8 points, so that the selected articles were considered to be good in methodological quality. The relevant feature information of the included articles was in tables 1 and table 2.

Meta-analysis results

The heterogeneity of the three genetic models was determined by Q test and I squared statistics. As shown in Figure 2, there was serious heterogeneity in the three models (II vs ID + DD: $P < 0.001$, $I^2 = 77.9\%$; II + ID vs DD: $P = 0.002$, $I^2 = 61.7\%$; I vs D: $P < 0.001$, $I^2 = 73.0\%$), thus the random-effect model was employed in analysis of the three models. Our results revealed that there were no significant associations between *ACE* I/D polymorphism and Lung cancer under the model of II vs ID + DD (OR = 1.22, 95% CI = 0.89–1.68, $P = 0.22$), II + ID vs DD (OR = 1.21, 95% CI = 0.90–1.63, $P = 0.21$) and I vs D (OR = 1.15, 95% CI = 0.95–1.39, $P = 0.15$). In subgroup analysis by Ethnicity, no significant association was found in three models in both Caucasian and Asian populations (Table 3). Sensitivity analysis was used to assess the impact of each individual study on the pooled OR by sequentially removing each eligible study. Our results suggest that none of the studies affected the overall outcome of the pooled OR (Figure 3). Begg's funnel plot was used to assess publication bias, and the results showed that publication bias was not reflected in the three genetic models. (II vs ID + DD: $P = 0.41$; II + ID vs DD: $P = 0.34$; I vs D: $P = 0.89$) (Figure 4).

Discussion

Recent studies have reported that *ACE* may be involved in the development of tumors [21-23]. *ACE* was a key enzyme in the renin-angiotensin system, which converted angiotensin I to angiotensin II and inactivates bradykinin. The mechanism of action may be due to the fact that angiotensin II can stimulate the synthesis of DNA and protein in vascular smooth muscle cells, and promote the synthesis and secretion of vascular endothelial growth factor [24]. On the other hand, it may be because bradykinin can increase the permeability of the cell membrane to electrolytes and peptides. *ACE* can inactivate bradykinin [25], but low expression of *ACE* in tumor tissues can promote invasive growth of malignant tumors. There are more and more published studies investigating the association between this polymorphism and lung cancer risk; however, there are inconsistencies and conflicts in the results. To further assess the association between *ACE* I/D polymorphism and lung cancer risk, we used a meta-analysis to analyze 12 case-control studies, including 2181 cases and 2126 controls.

The results of this meta-analysis showed no significant association was found in the three genetic models of comparison. Although previous studies have revealed that *ACE* may produce a certain effect in the etiology of lung cancer, our results suggest that these effects may not be caused by *ACE* gene mutations. The exact pathogenesis of AEC in the etiology of lung cancer remains unclear. Our results may suggest that *ACE* I/D polymorphism did not affect cancer risk. Moreover, considering that this polymorphism may affect serum *ACE* levels, and *ACE* levels may affect the risk of lung cancer, the risk of lung cancer is not directly caused by *ACE* gene mutation. Therefore, future research is necessary to determine the association between *ACE* polymorphism, *ACE* levels and cancer risk.

Previously, a meta-analysis was applied for eight published studies [7, 9, 10, 12, 14, 16-18] by Cheng et al [26], it included 1612 cases and 1442 controls, the results shown that the *ACE* gene I/D polymorphism was not associated with lung cancer. Wang et al [27] also conducted a meta-analysis of six published studies with 807 cases and 816 controls [7, 9, 12, 14, 17], the results also showed *ACE* I/D polymorphism

may not be associated with lung cancer risk. In our study, a total of 12 studies were enrolled, including 2181 cases and 2126 controls. So the statistical power of the current analysis was better than the previous two meta-analyses. Compared with other studies, this study is more comprehensive about the relationship between ACE I/D polymorphism and lung cancer risk. Despite the differences between the studies included in the analysis, the results of our study suggest that the ACE I/D polymorphism may not lead to cancer risk, which is consistent with Cheng's study and Wang 's study.

However, there are certain limitations in our research. First, databases that include only published research in both Chinese and English are selected for analysis, and other language or unpublished potential research may be missed. Second, due to the lack of raw data, we were unable to assess potential interactions of gene-genes and genes-environments. Third, the meta-analysis includes data from Europeans and Asians, so the results of this item apply only to these two ethnic groups. Fourth, among the three models, heterogeneity may greatly influence the conclusion of the meta-analysis.

Conclusion

In summary, our study showed that the *ACE I/D* polymorphism did not increase or decrease the risk of susceptibility to lung cancer. Further well-designed studies should be conducted to identify our findings in different populations and age groups, such as different races in Asia, Europe and other populations, or children and adults. Future research will also need to explore the *ACE I/D* gene-gene or the possible role of gene-environment interactions in susceptibility to lung cancer.

Abbreviations

OR: odds ratios; CI: confidence interval; ACE: angiotensin-converting enzyme; CNKI: China National Knowledge Infrastructure; NOS: Newcastle-Ottawa Scale;

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: yes

Availability of data and material: yes

Competing interests: The authors declare that they have no competing interests

Funding: Not applicable.

Authors' contributions:

JC and RL: Conceptualization, data curation, formal analysis, methodology, writing and review and editing

MS and MZ: Software, supervision, validation, visualization.

All authors have read and approved the manuscript

Informed consent: NA

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Figures

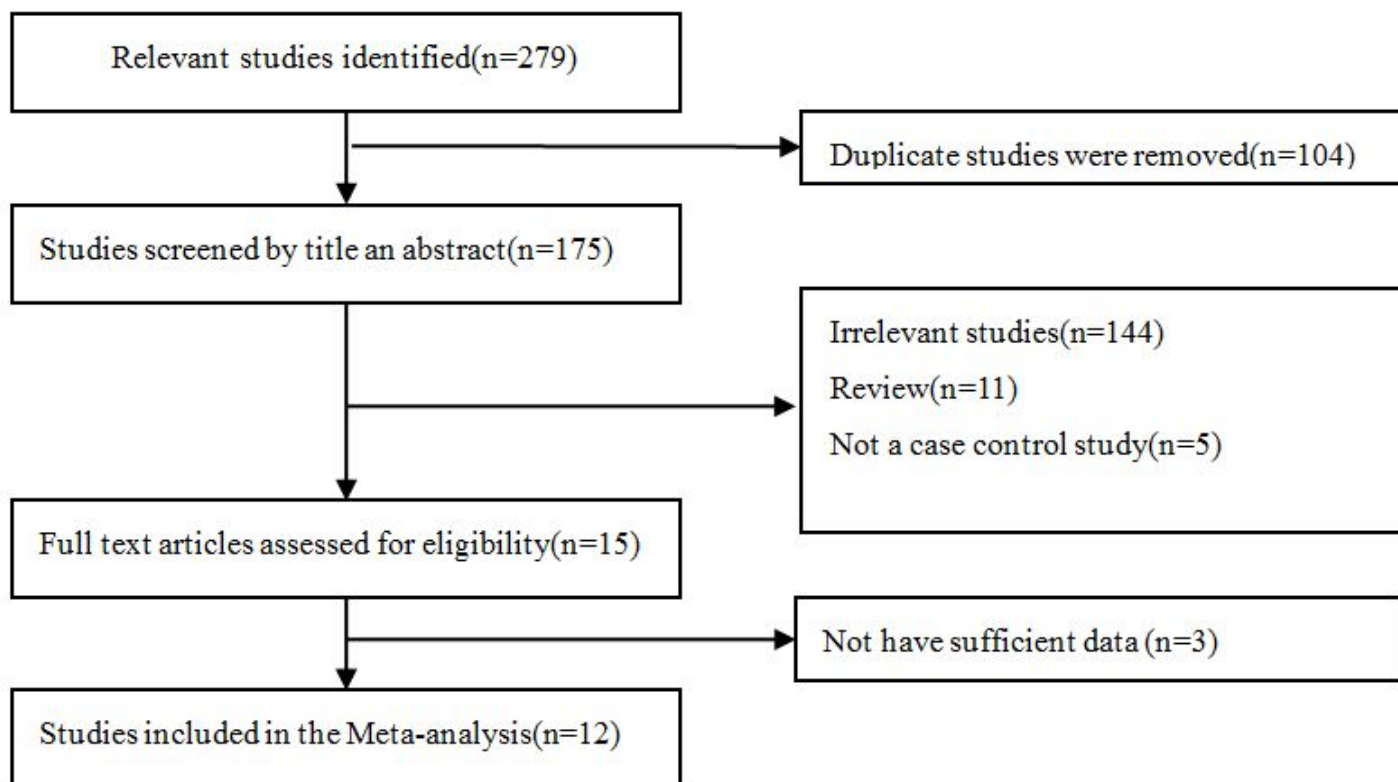


Figure 1

The flow sheet of identification of eligible studies

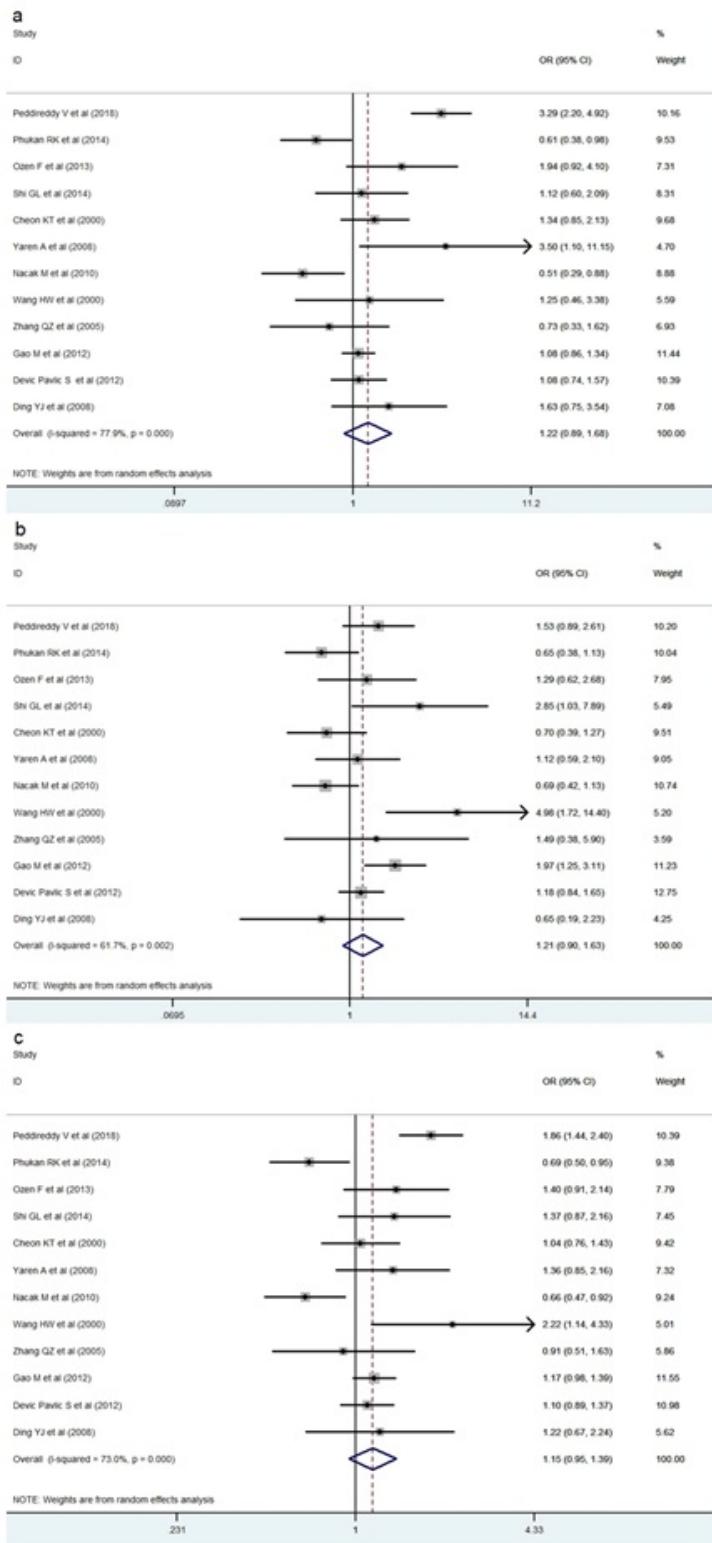
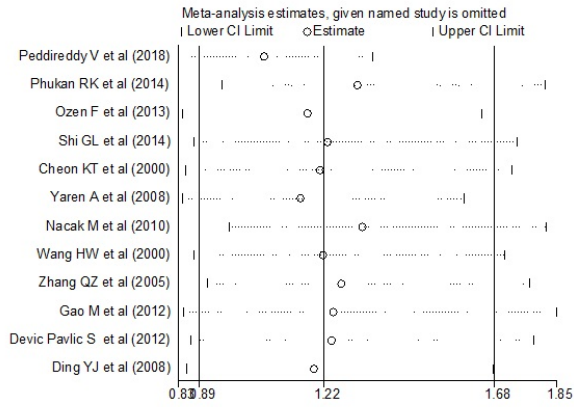


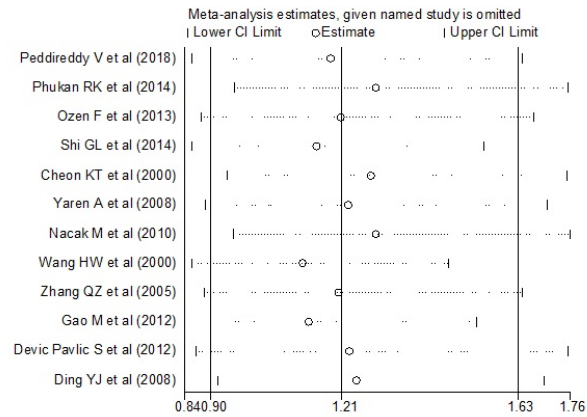
Figure 2

Forest plots of the ACE I/D polymorphism under different genetic models. a is the model of II vs ID+DD; b is the model of II+ID vs DD; c is the model of I vs D.

a



b



c

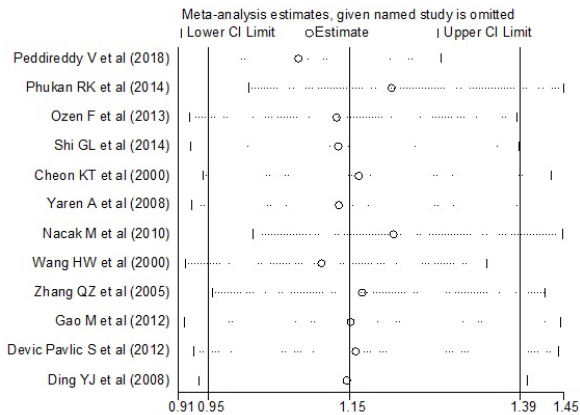
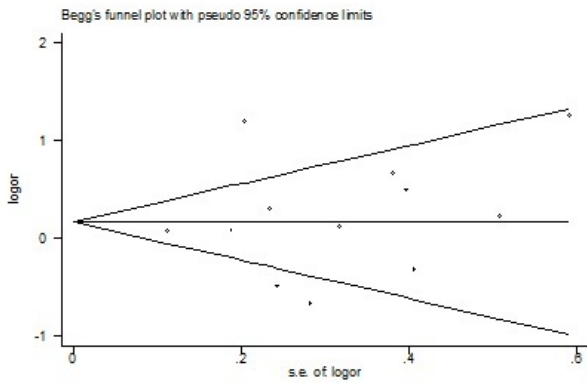


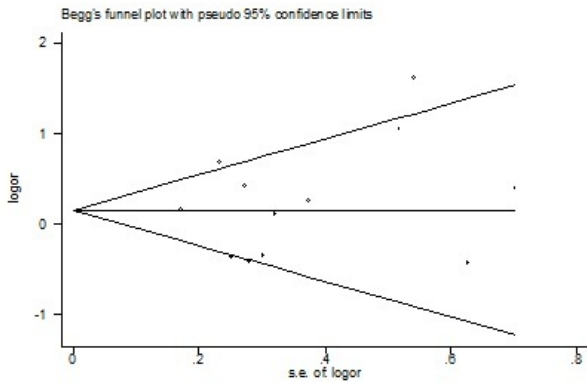
Figure 3

Sensitivity analysis examining the association between the ACE I/D polymorphism and risk of Lung Cancer under these model (II vs ID+DD, II+ID vs DD, I vs D).

a



b



c

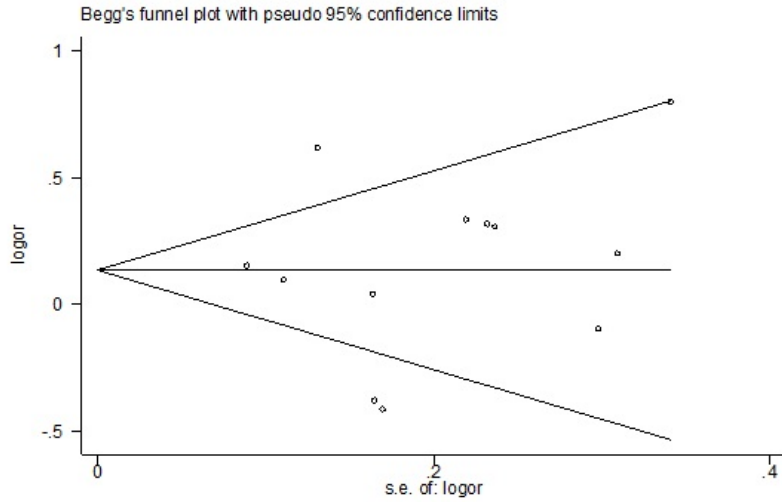


Figure 4

Begg's funnel plot for publication bias analysis. a is the model of II vs ID+DD; b is the model of II+ID vs DD; c is the model of I vs D.

Supplementary Files

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