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# Association between *ACE* A240T polymorphism and cancer risk: a meta-analysis

**Yingjun Xiao[1,2], Zheqing Dong[2], Ji Zhu[2], Jinbiao You[2] and Jun Fan[1]**

## Abstract

**Objectives:** The relationship between the A240T polymorphism in the angiotensin-converting enzyme (*ACE*) gene and cancer risk remains controversial. Therefore, we conducted a meta-analysis of relevant studies from the published literature.

**Methods:** We comprehensively searched available databases to identify eligible studies on the relationship of *ACE* A240T polymorphism with cancer risk. We calculated pooled odds ratios (OR) with 95% confidence intervals (CI) and then evaluated heterogeneity and publication bias.

**Results:** Eight case-control studies were identified from five articles. Results showed that the *ACE* A240T polymorphism was related to cancer risk (AT vs AA: OR 2.14, 95% CI: 1.51–3.04; TT vs AA: OR 1.07, 95% CI: 0.90–1.27; recessive model: OR 0.48, 95% CI: 0.31–0.77; dominant model: OR 2.13, 95% CI: 1.54–2.97). The same conclusion was made for subgroup analysis by race or cancer type. In the subgroup analysis by quality score assessment, the *ACE* A240T polymorphism contributed to cancer risk in high-quality studies but not in low-quality studies.

**Conclusion:** The A240T polymorphism in the *ACE* gene might be related to the risk of cancer. Nevertheless, large-scale studies should be performed to obtain convincing evidence on the roles of *ACE* A240T polymorphism on cancer risk.

## Keywords

Cancer, *ACE* gene, angiotensin-converting enzyme, genetic variant, meta-analysis, risk

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[1]State Key Laboratory for Diagnosis and Treatment of Infectious Disease, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Zhejiang, China
[2]Clinical Laboratory, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

**Corresponding author:**
Jun Fan, State Key Laboratory for Diagnosis and Treatment of Infectious Disease, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China.
Email: fanjun@zju.edu.cn

## Introduction

Cancer is one of the most frequent causes of death in economically developing and developed countries. According to the updated global estimation in 2018, approximately 42 million people across the world suffered from any type of cancer.[1] Although great efforts have been made to clarify the mechanisms of carcinogenesis, much remains unknown. Many risk factors that promote carcinogenesis have been identified, such as family history of cancer, dietary habits, alcohol use, obesity, smoking, and occupational exposures.[2] However, most individuals exposed to these environmental factors never develop cancer, whereas many cancer cases develop among individuals without these known risk factors, suggesting that genetic susceptibility is a more significant indication of an individual's risk of cancer.

The renin angiotensin system (RAS), which mostly participates in systemically modulating cardiovascular homeostasis, has been reported to be expressed in a number of tumor types.[3] Angiotensin-converting enzyme (ACE) is one of the most important members of the RAS family, with frequent reports on the overexpression of ACE in the neoplastic stages.[4] The *ACE* gene is located on chromosome 17 (17q23) in humans, spanning 21 kb and comprising 26 exons and 25 introns.[5] Two *ACE* polymorphisms are reported to be related to circulating ACE concentration, the A240T polymorphism in the 5′-flanking region and the 287-bp Alu insertion/deletion (I/D) polymorphism in intron 16.[6] A previous meta-analysis showed a possible relationship of the *ACE* I/D polymorphism with susceptibility to cancer.[7]

In this study, we explored the correlation of the *ACE* A240T polymorphism with cancer risk. Generally, outcomes based on meta-analyses are likely to be more convincing than those of a single study. Therefore, this meta-analysis was conducted to determine the potential correlation of the *ACE* A240T polymorphism with cancer risk.

## Material and methods

### Literature and search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[8] A search of the PubMed and Embase databases was conducted using the following search terms: "renin angiotensin system, RAS or ACE", "polymorphism or variant", and "cancer, neoplasm or tumor". A manual search was conducted for additional studies based on the references of the original studies. When overlapping or the same data were found, the most recent, large-scale articles were chosen.

### Inclusion criteria and data extraction

Studies included in the present meta-analysis had to meet the inclusion criteria as follows: (1) case-control studies for assessment of the correlation of the *ACE* A240T polymorphism with cancer risk; (2) odds ratios (OR) and 95% confidence intervals (CI) could be calculated from adequate genotype information; and (3) studies had to include a clear description of case and control sources. The following exclusion criteria were used: (1) not case-control studies assessing the relationship of the *ACE* A240T polymorphism with cancer risk; (2) editorials, letters, meta-analyses, case reports, or reviews; (c) studies that lacked complete raw data or useful information; or (4) duplicate publications.

### Data extraction

Relevant publications were independently reviewed by two investigators (J. Y. and J. F.)

for information extraction in accordance with a standard data form. Discrepancies were discussed until agreement was reached. The following information was extracted from every study: region, genotype frequencies in cases and controls, numbers of cases and controls, year of publication, first author, and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

### Quality score assessment

Two investigators (Y. X. and Z. D.) independently assessed the quality of included studies in line with relevant criteria (Table 1), covering sources of cases, sources of controls, specimens of cases determining genotypes, HWE in controls, and total sample size.[9]

**Table 1.** Scale for quality assessment of studies included in the meta-analysis.

| Criteria | Score |
|---|---|
| Source of cases | |
| Selected from population or cancer registry | 3 |
| Selected from hospital | 2 |
| Selected from pathology archives, but without description | 1 |
| Not described | 0 |
| Source of controls | |
| Population-based | 3 |
| Blood donors or volunteers | 2 |
| Hospital-based (cancer-free patients) 1 | 1 |
| Not described 0 | 0 |
| Specimens of cases determining genotypes | |
| White blood cells or normal tissues | 3 |
| Tumor tissues or exfoliated cells of tissue | 0 |
| Hardy-Weinberg equilibrium in controls | |
| Hardy-Weinberg equilibrium | 3 |
| Hardy-Weinberg disequilibrium | 0 |
| Total sample size | |
| $\geq$1000 | 3 |
| $\geq$500 but $<$1000 | 2 |
| $\geq$200 but $<$500 | 1 |
| $>$0 but $<$200 | 0 |

Discrepancy was resolved following discussion. For this assessment, the range of the total score was from 0 (worst) to 15 (best). Articles with scores $\geq$10 were considered high quality; otherwise, studies were considered low quality.

### Statistical analysis

STATA version 11.0 (Stata Corp., College Station, TX, USA) was used for statistical analysis. The relationship between *ACE* A240T polymorphism and cancer risk was evaluated using ORs and corresponding 95% CI. Heterogeneity was determined using $I^2$ values. In the case of insignificant heterogeneity of pooled ORs between studies, a fixed-effects model was conducted using the Mantel–Haenszel method; otherwise, a random-effects model with DerSimonian and Laird methods was used. A sensitivity test was conducted by excluding a single study every time from the pooled analysis, to determine the impact of each study on the overall ORs. Moreover, we conducted subgroup analyses to investigate the effects of tumor type, race, and quality score assessment. Finally, publication bias was evaluated qualitatively by preparing funnel plots and quantitatively by Egger's test. A $P$-value $< 0.05$ in Begg's test suggested significant publication bias.

## Results

### Eligible studies

The study selection process is shown in Figure 1. The literature search of PubMed and EMBASE yielded 84 relevant papers; five articles, including eight case-control studies were included in this meta-analysis.[3,10–13] The publication years ranged from 2003 to 2016. Detailed information of the included five papers is given in Table 2. Of these, three studies were in Caucasians, four were in Asians, and one study focused on

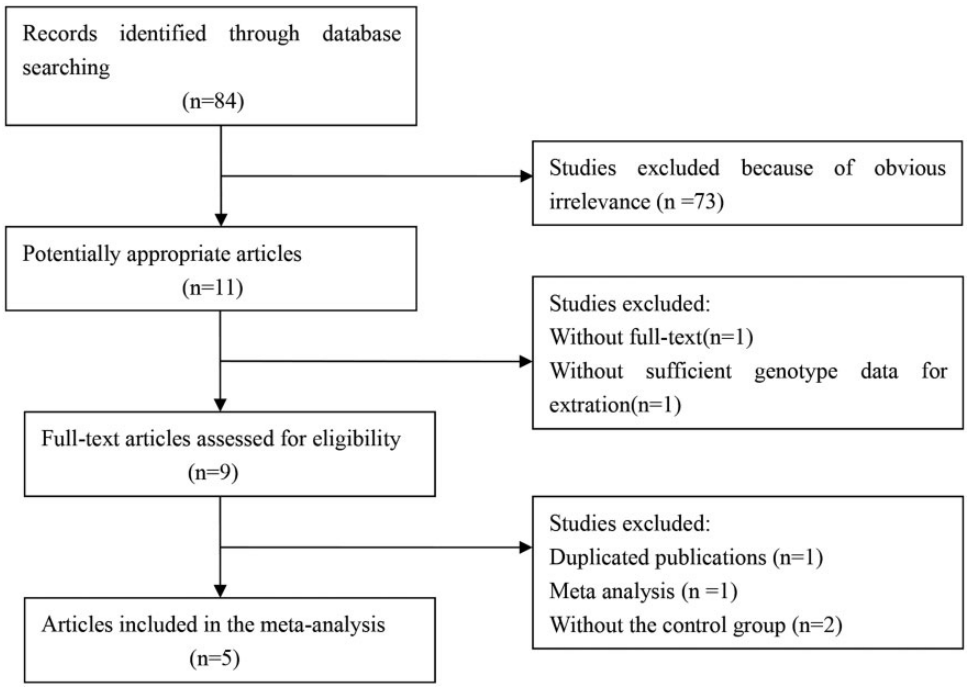


**Figure 1.** Flow diagram of included and excluded studies.

**Table 2.** Characteristics of the included studies of *ACE* A240T polymorphism.

| Study included | Year | Area | Race | Cancer type | Genotypes for cases | | | Genotypes for controls | | | HWE test | Quality scores |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TT | AT | AA | TT | AT | AA | | |
| Koh | 2003 | Singapore | Asian | BC | 29 | 79 | 76 | 63 | 318 | 271 | 0.03 | 8 |
| Haiman a | 2003 | USA | African | BC | 42 | 116 | 90 | 78 | 276 | 280 | 0.44 | 11 |
| Haiman b | 2003 | USA | Asian | BC | 43 | 159 | 125 | 56 | 180 | 155 | 0.75 | 11 |
| Haiman c | 2003 | USA | Caucasian | BC | 17 | 109 | 124 | 78 | 267 | 312 | 0.08 | 11 |
| Haiman d | 2003 | USA | Caucasian | BC | 48 | 128 | 129 | 70 | 195 | 161 | 0.40 | 11 |
| Mendizábal-Ruiz | 2010 | Mexico | Asian | BC | 3 | 31 | 28 | 3 | 18 | 29 | 0.93 | 9 |
| Ding | 2015 | China | Asian | BC | 76 | 294 | 236 | 75 | 303 | 255 | 0.30 | 12 |
| Pringle | 2016 | Australia | Caucasian | EC | 28 | 90 | 65 | 23 | 70 | 60 | 0.73 | 10 |

HWE, Hardy–Weinberg equilibrium; BC, breast cancer; EC, endometrial cancer.

Africans. All included studies were written in English. The genetic distributions of controls were consistent with HWE in all studies except for Koh et al.[3] The studies included seven breast cancer studies and one endometrial cancer study concerning the *ACE* A240T polymorphism. In terms of quality scores, all studies except Koh et al. and Mendizábal-Ruiz et al.[3,11] were classified as high quality with a quality score $\geq$10.

### Overall and subgroup analyses

The major outcomes, ORs and 95% CIs, of the *ACE* A240T polymorphism with cancer risk in this meta-analysis are shown in Table 3. The *ACE* A240T polymorphism was correlated with cancer risk when all eligible studies were pooled into the meta-analysis (TT vs. AA: OR 1.07, 95% CI: 0.90–1.27, $P = 0.06$; AT vs. AA: OR 2.14, 95% CI: 1.51–3.04, $P = 0.00$; dominant model: OR 2.13, 95% CI: 1.54–2.97, $P = 0.00$; recessive model: OR 0.48, 95% CI: 0.31–0.77, $P = 0.00$). In subgroup analyses stratified by ethnicity, cancer type, and study quality, statistically significant associations were observed. However, we found that the *ACE* A240T polymorphism did not contribute to cancer risk in low-quality studies (Figure 2).

### Sensitivity analysis

To confirm the influence of every study on the overall OR, sensitivity analysis was performed by omitting a single study each time. As shown in Figure 3, no individual study exerted any impact on the pooled OR qualitatively, suggesting that the pooled outcomes were robust.

### Publication bias

Egger's funnel plots were prepared for evaluation of publication bias of enrolled studies on the *ACE* A240T polymorphism. As shown in Figure 4, the shape of the plots showed no obvious asymmetry, suggesting no evidence of publication bias in the collected studies on *ACE* A240T.

## Discussion

Cancer is a common cause of mortality worldwide; the disease originates from complicated interrelationships between environmental and genetic factors. RAS is a promising signaling pathway that is involved in tumor metastasis, angiogenesis, and homeostasis.[14] Until now, a number of studies have been conducted to evaluate the relationship of *ACE* A240T polymorphism with risk of different types of cancers; however, results have been controversial. The identification of novel genetic and molecular predictors is essential for successful early diagnosis and prevention of tumors. Therefore, we conducted this meta-analysis to determine the relationship of this polymorphism with cancer risk, aiming at more comprehensive and accurate outcomes.

**Table 3.** Summary ORs and 95%CI of *ACE* A240T polymorphism with cancer risk.

| | | TT vs AA | AT vs AA | Dominant model | Recessive model |
|---|---|---|---|---|---|
| Variables | N | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Total | 8 | 1.07 (0.90–1.27) | 2.14 (1.51–3.04) | 2.13 (1.54–2.97) | 0.48 (0.31–0.77) |
| Race | | | | | |
| Asian | 4 | 1.15 (0.90–1.47) | 2.79 (1.39–5.63) | 2.79 (1.48–5.26) | 0.42 (0.19–0.92) |
| Caucasian | 3 | 0.79 (0.58–1.06) | 1.90 (1.27–2.84) | 1.84 (1.21–2.79) | 0.42 (0.33–0.54) |
| African | 1 | – | – | – | – |
| Cancer type | | | | | |
| BC | 7 | 1.07 (0.80–1.42) | 2.02 (1.40–2.93) | 2.02 (1.43–2.86) | 0.50 (0.30–0.84) |
| EC | 1 | – | – | – | – |
| Quality | | | | | |
| High | 6 | 1.00 (0.76–1.33) | 2.12 (1.56–2.87) | 2.09 (1.53–2.85) | 0.47 (0.32–0.71) |
| Low | 2 | 2.58 (0.97–2.56) | 1.44 (1.02–2.02) | 4.03 (0.33–50.03) | 0.37 (0.02–6.52) |

OR, odds ratio; CI, confidence interval; BC, breast cancer; EC, endometrial cancer.

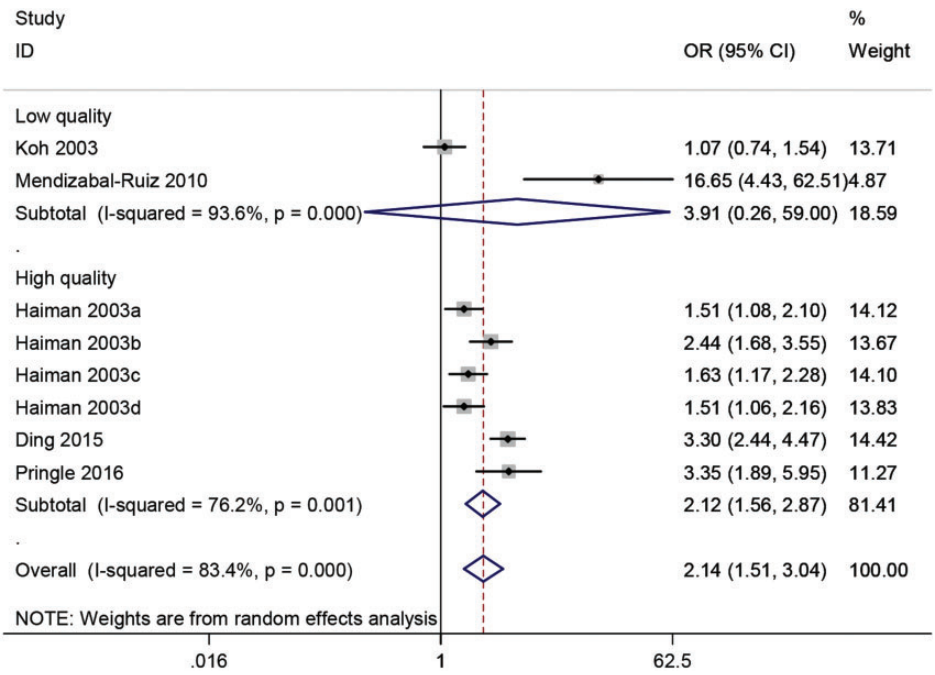


**Figure 2.** Stratification analyses by quality score assessment between *ACE* A240T polymorphism and cancer susceptibility for genotype AT versus AA. The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. OR, odds ratio; CI, confidence interval.

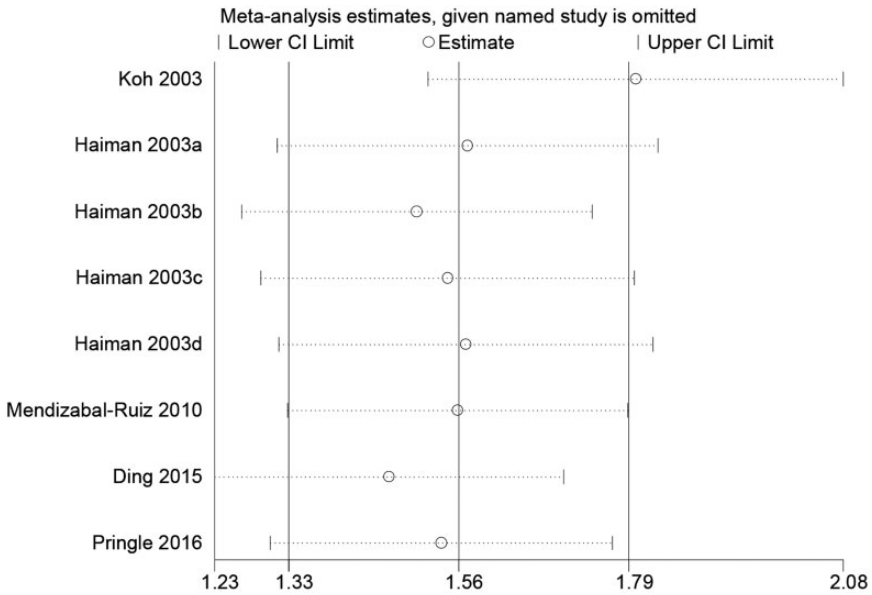


**Figure 3.** Sensitivity analyses between *ACE* A240T polymorphism and cancer risk.

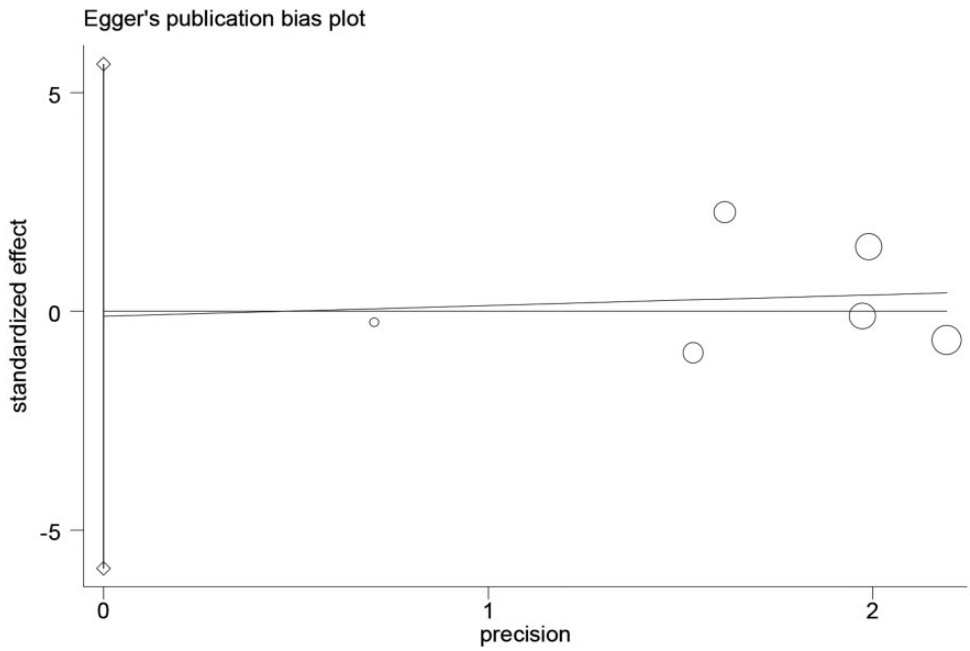


**Figure 4.** Funnel plot for publication bias test. Each point represents an individual study for the indicated association. LogOR, natural logarithm of OR. Perpendicular line, mean effect size.

The *ACE* A240T polymorphism was related to tumor risk when all eligible studies were pooled in the meta-analysis. Stratified analysis by races revealed a significant correlation in both Asians and Caucasians. Only one study focused on Africans; therefore, more studies are needed to draw further conclusions. The analysis stratified by cancer type showed similar results. Stratified analysis by quality score assessment showed that this polymorphism was positively correlated with cancer risk in high-quality studies, but not in low-quality studies, suggesting that the result of our meta-analysis is credible. The mechanism underlying the association remains unclear. Serum ACE levels are shown to be increased in subjects carrying the 240 T allele.[6] The primary effector molecule of this system is angiotensin II (ANG II) and is formed after two cleavage steps via renin and ACE. ANG II mediates its physiological effects through two G protein-coupled receptors, angiotensin II type 1 receptor (AGTR1) and angiotensin II type 2 receptor (AGTR2).[15] Although ACE is found in a wide variety of human normal tissues, increased expression of ACE is often found in the corresponding neoplastic tissues, suggesting that its overexpression is involved in carcinogenesis.[16] In conclusion, the A240T polymorphism in the *ACE* gene might be related to an increased risk of cancer.

This meta-analysis had some limitations. First, we failed to investigate gene-gene and gene-environment interplays, data that were absent from the original studies. Second, data from only eight studies were included and analyzed, limiting the statistical power of the meta-analysis. Thus, large-scale studies are needed to obtain robust outcomes in the future. Third, we included only studies published in English, which may have introduced a publication bias. Finally, heterogeneity was

observed in some models. Thus, age and sex should be matched in all cases and controls; this could not be addressed due to insufficient clinical data.

Our meta-analysis suggests that the *ACE* A240T polymorphism is likely to be related to cancer risk. Further large-scale genetic correlation studies are needed to produce convincing outcomes regarding the influence of *ACE* as well as other genes within the RAS system on cancer risk.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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## ORCID iD

Jun Fan https://orcid.org/0000-0003-4419-0312

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