Original Article
Association between angiotensin I-converting enzyme gene polymorphism and susceptibility to cancer: a meta analysis

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Abstract: Background: Angiotensin I-converting enzyme (ACE) gene plays an important role in the pathogenesis of cancers. The association between ACE insertion/deletion (I/D) polymorphism and the risk of various cancers has been studied. However, the results of these studies remain conflicting. Therefore, we performed a meta-analysis to evaluate the association between ACE I/D polymorphism and the risk of cancers. Methods: PubMed, Embase, ScienceDirect, Springer, CNKI, Wanfang, Weipu, CBM databases and Google Scholar were searched for case-control studies on ACE I/D polymorphism and the risk of cancers, published up to Dec 31, 2013. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association between ACE I/D polymorphism and cancer risk. Results: Thirty-five published studies with 5007 cases and 8173 controls were included. Overall, there were no significant association between ACE I/D polymorphism and the risk of cancers (II vs. ID+DD OR = 1.05, 95% CI = 0.89-1.23, I vs. D OR = 1.00, 95% CI = 0.89-1.13). However, when stratified by ethnicity, we found a significant association between this polymorphism and cancer risk in Caucasians (II vs. ID+DD: OR = 1.43, 95% CI = 1.02-2.00, I vs. D: OR = 1.23, 95% CI 1.01-1.49). Conclusion: ACE I/D polymorphism is associated with the cancer risk in Caucasians.

Keywords: ACE I/D, single nucleotide polymorphism, cancer risk, meta-analysis

Introduction
Angiotensin I-converting enzyme (ACE) is a zinc metallopeptidase which converts angiotensin I to angiotensin II. ACE is one of the key enzymes in human renin-angiotensin system (RAS) [1]. It plays an important role in the modulation of vascular homeostasis, inflammation and angiogenesis [2-4]. ACE is expressed in many tissues and systems including lung, vasculature, kidney, heart, and testes [5]. Emerging evidence has shown that the expression of ACE is up-regulated in several types of cancers [6-9]. Moreover, ACE inhibitors are currently considered being used as novel antineoplastic therapies [6, 10].

The ACE gene is located on human’s chromosome 17q23 that consists of 26 exons and 25 introns [11]. The ACE insertion/deletion (I/D) polymorphism of 287bp Alu repeat sequence in intron 16 (rs4646994) has been reported [11]. Although the I/D polymorphism is not located in the coding region of the ACE gene, subjects with ACE D allele exhibits a higher plasma ACE level and activity [12]. The I/D polymorphism account for 20% to 50% of the variance in ACE expression or activity in blood and tissues among individuals [13].

Up to now, a number of studies were conducted to evaluate the association between ACE I/D polymorphism and risk of different types of cancers in diverse populations. However, the results from the published studies remain conflicting rather than conclusive. Therefore, we performed a meta-analysis on all eligible case-control studies to clarify the association between ACE I/D polymorphism and cancer risk.
Methods

Literature search

We conducted the literature search by using the PubMed, Embase, ScienceDirect, Springer, CNKI, Wanfang, Weipu, CBM databases and Google Scholar for relevant articles published (update to Dec 31, 2013) with the following search terms: “ACE” or “angiotensin I converting” and “polymorphism” or “insertion/deletion” and “cancer” or “carcinoma” or “tumor”. In addition, the studies were identified by manual search of the reference lists of reviews and retrieved studies. The inclusion criteria were: (1) the study evaluated the association between ACE polymorphism and cancer risk in human; (2) a case-control study; (3) genotype distributions in both cases and controls were available for estimating an odds ratio with 95% confidence interval (CI) and P value, (4) genotype distributions of controls must be consistent with Hardy-Weinberg equilibrium (HWE). Main exclusion criteria of studies were as follows: (1) case reports, reviews, letters and editorial articles; (2) only case population; (3) duplicate of previous publication; and (4) the distribution of genotypes among controls are consistent with HWE.

Data extraction

Two investigators (Zhang and Cheng) extracted the data from all eligible studies independently. We checked all potentially relevant studies and reached a consensus on all items. From each study, the following information was extracted: first author’s name, year of publication, country of origin, ethnicity, definition of case, source of control selection and the genotype frequencies in cases and controls.
## Table 1. Distribution of ACE genotype and allele among cancer patients and controls

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<th>Author</th>
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<th>Country</th>
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<th>Control</th>
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Statistical analysis

For each case-control study, we first examined whether the genotype distributions in control group were consistent with Hardy-Weinberg equilibrium by Pearson’s X$^2$ test. Heterogeneity was evaluated by the X$^2$ based Q statistic and was considered statistical significant at $P$ value < 0.10. $P$ value was also used to measure the percentage of variability in studies that due to heterogeneity rather than chance. When the effects were assumed to be homogenous, fixed-effects model was used (the Mantel-Haenszel method); otherwise, it was more appropriate to use random-effects model (DerSimonian and Laird method) [14-16]. The strength of associations between ACE I/D polymorphism and cancer risk were measured by ORs with 95% CIs. The pooled ORs were evaluated for the homozygote comparison (II vs. DD),
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heterozygote comparison (ID vs. DD), dominant model (II+ID vs. DD) recessive model (I vs. ID+DD), and haploid model (I vs. D) comparison. The funnel plots as well as Begg’s tests and Egger’s test were used to investigate publication bias [17]. Sensitivity analysis was performed to assess the stability of the results by sequentially excluding each study [18]. All statistical analyses were performed by using the Revman 5.2 software (Cochrane Library Software, Oxford, UK) and STATA11.0 (STATA Corporation, College Station, TX, USA).

Results

Studies characteristics

Overall, 35 publications [13, 19-52] including 5007 cases and 8137 controls were available for this meta-analysis based on the inclusion and exclusion criteria (Figure 1). The main characteristics of these studies are summarized in Table 1. There were 22 studies of Asian populations, 13 studies of Caucasians population. Of the 35 studies, 7 articles were population-based and 28 articles were hospital-based. The diagnosis of most of the cases was based on pathology. Healthy subjects matched for age and sex were used as controls. Polymerase chain reaction (PCR) was performed for genotyping.

Meta-analysis

A summary of the meta-analysis results of the association between ACE I/D polymorphism and cancer risk is shown, there are no significant association was found between ACE I/D polymorphism and the risk of cancers (II vs. DD OR = 0.97, 95% CI 0.76-1.24, ID vs. DD OR = 0.98, 95% CI = 0.79-1.21, II+ID vs. DD OR = 0.99, 95% CI = 0.80-1.23, II vs. ID+DD OR = 1.05, 95% CI = 0.89-1.23, I vs. D OR = 1.00, 95% CI = 0.89-1.13). However, in the subgroup analyses by ethnicity, there was a significant association between this ACE I/D polymorphism and cancer risk in Caucasians (II vs. ID+DD: OR = 1.43, 95% CI = 1.02-2.00, I vs. D: OR = 1.23, 95% CI 1.01-1.49) (Figures 2, 4). In the subgroup analyses by cancer types, no significant association was found under different genetic models.

Test of heterogeneity

For the overall analysis, the Q-statistic was significant and I² showed stable variation under the comparisons (II vs. DD: P < 0.00001, I² = 74%; ID vs. DD P < 0.00001, I² = 76%; II+ID vs. DD P < 0.00001, I² = 79%; II vs. ID+DD P < 0.00001, I² = 67%; I vs. D P < 0.00001, I² = 78%). In the subgroup analyses of ethnicity, the I² showed inconsistent with the former, the I² of II vs. ID+DD are 46% and 77%. While there is no notable difference of I² in I vs. D, the former is 78%, the latter are 78% and 76% (Figures 2, 4).

Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was investigated by excluding each study at a time. The omission of any study made no significant difference. This is indicating that the results of our meta-analysis were statistically reliable.

Publication bias

Begg’s funnel plot and Egger’s test were performed to assess the publication bias of the literatures. Egger’s test did not show any evidence of publication bias (t = 0.16, P = 0.871 for II vs. ID+DD and t = -0.78, P = 0.440 for I vs. D, respectively) (Figures 3, 5).
Discussion

Human ACE is the key enzyme in the renin-angiotensin system, which works in the regulation of blood pressure, the number of red blood cell, cardiovascular homeostasis and serum electrolytes. In recent years there were more evidences indicating that ACE was associated with the pathogenesis of cancer, even it was the trigger events at least in some group of patients with cancer. It may influence tumor cell adhesion, proliferation, migration, angiogenesis and metastatic behaviors [53]. Some studies showed that the ACE inhibitor could lower the breast cancer risk [10]. But in some meta-analyses, show that there were no significant association between the ACE I/D polymorphisms and breast cancer risk. In different cancer studies, have the inconsistent and conflict result. On the other hand, there are some studies about the risk of ACE gene polymorphism with variety of cancers, for example, in prostate...
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In the pathogenesis of cancers, it has been reported that the ACE gene polymorphism is associated with clinical outcome parameters [54]. It is noteworthy that RAS inhibitors caused reductions in growth and angiogenesis in tumor cell lines [55, 56]. Also it have been demonstrated that the ACE, besides angiotensin II production, is the inactivation of bradykinin [57]. That is known to established role in tumor formation through its ability to stimulate growth and increase vascular permeability [57]. In these sex hormone-related neoplasias cancers, oestrogens increase hepatic synthesis of the renin substrate angiotensinogen, which is converted to angiotensin I, the substrate of ACE [58].

In short, the ACE gene plays an important role in the pathogenesis of cancers. Up to now, a number of original studies have been carried out to investigate whether ACE I/D polymorphism confer individual's susceptibility to cancer. However, the results from the published studies were conflicting. We conducted an updated meta-analysis including with 5007 cases and 8173 controls from 35 case-control studies to evaluate the association between ACE I/D polymorphism and the cancer risk.

There are no significant association between ACE I/D polymorphism and cancer risks under any genetic model in the total population. However, in the subgroup analyses by ethnicity, we found that the ACE I/D polymorphism were associated with increased cancers risk in Caucasians. There was an aggregated OR of 1.43 (95% CI = 1.02-2.00) for increased cancer susceptibility under recessive comparison. This indicates that the ACE I/D polymorphism may contribute to pathogenesis of cancers in Caucasians. Even though the D genotype has been reported that associated coronary heart disease and hypertension. No associations were found between this polymorphism and the cancers risk in Asians, which was consistent with previous reports [13, 28, 30, 31].

The heterogeneity was found in almost all comparisons in our meta-analysis. To get more full and accurate detail of the precious data, we used the random-effect models. The results are stable with the sensitivity analysis which did not change the results of the meta-analysis. Meanwhile, there are no publication bias for the risk of cancer in the ACE I/D polymorphism studies.

There were some limitations of our meta-analysis. First, the control subjects were not uniformly defined because of some study only including unitary gender and some reproductive system cancer such as prostatic cancer. Second, in several studies, the larger tumor sizes and lymph node metastases were significantly associated with the DD genotype. Third, all the included studies were from European, Asian and Latino populations, further studies are necessary to contain more findings for other ethnic populations. Fourth, cancer is a multifactorial disease. Due to lack of original data, we could not evaluate the potential interactions of gene-gene and gene-environment.

In conclusion, the I allele of ACE I/D genotype may confer the risk of cancer in Caucasians, but not in Asian. More studies would be of great value to explore the interaction between the ACE I/D polymorphism and cancer risk.

Acknowledgements

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References


ACE gene polymorphism and colorectal cancer in Romanian patients. Chirurgia (Bucur) 2009; 104: 553-556.


