Association of angiotensin II type 1 receptor gene A1166C polymorphism with cancer risk: An updated meta-analysis

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Abstract

Objective: The association between angiotensin II type 1 receptor (AGTR1) gene A1166C polymorphism and cancer risk has been investigated in many studies. However, the results have been inconclusive. A meta-analysis was performed to obtain a more precise estimation of the relationship.

Methods: The PubMed and China National Knowledge Infrastructure databases were searched for published literature. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strengths of association.

Results: Ten studies, including 1553 patients and 1904 controls, were included in the meta-analysis. Overall, there were no significant associations between the AGTR1 gene A1166C polymorphism and cancer risk in the general population (CC vs AA: OR = 1.09, 95% CI = 0.50–2.37; AC vs AA: OR = 1.54, 95% CI = 0.81–2.91; dominant model: OR = 1.46, 95% CI = 0.77–2.79; recessive model: OR = 1.12, 95% CI = 0.84–1.49). In a subgroup analysis by nationality and cancer type, the results also showed no association between this polymorphism and cancer risk.

Conclusions: This meta-analysis demonstrated that the AGTR1 gene A1166C polymorphism does not appear to be related to the risk of cancer.

Keywords
Angiotensin, polymorphism, meta-analysis, cancer

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Introduction

Cancer has a major impact on public health and the economy. Worldwide, there were 14 million new cancer cases in 2012 and the number is projected to rise to almost 22 million by 2030. Despite the efforts exerted by many researchers to elucidate the mechanisms of carcinogenesis, the process remains unclear to date. A variety of risk factors have been identified to contribute to cancer, including alcohol consumption, cigarette smoking, obesity, occupational exposures, family history of cancer and diet. However, most individuals exposed to these environmental factors never develop cancer, while many cancer cases develop among individuals without those known risk factors, suggesting that genetic susceptibility is a more significant indication of an individual’s risk of cancer.

The renin–angiotensin system (RAS) influences sodium balance, extracellular fluid volume and systemic vascular resistance. In addition, the local RAS in tissues may be related to the occurrence and development of tumors. Angiotensin II, the major biologically active component of the RAS, exerts its effects via two distinct subtypes of angiotensin II receptors: the angiotensin II type 1 receptor (AGTR1) and angiotensin II type 2 receptor. The AGTR1 protein is a member of the 7-transmembrane G protein-coupled receptor family, and its expression is upregulated in most tumors.

The AGTR1 gene is composed of five exons located on chromosome 3q, where the first four exons encode the 5′-untranslated region. The A1166C polymorphism (single
nucleotide polymorphisms identifier: rs5186) is located in the 3'-untranslated region of AGTR1 and leads to the transversion of an adenine (A) to a cytosine (C) base at the 1166 position. Previous meta-analyses suggested that the A1166C polymorphism in AGTR1 may be associated with susceptibility to hypertension and myocardial infarction.

So far, several studies have explored the association between the A1166C polymorphisms of the AGTR1 gene and cancer risk. However, the conclusions have been inconsistent. Individual studies might have been underpowered to detect overall effects. Some studies were limited by their sample size and subsequently were underpowered to detect effects that may exist. To evaluate the possible association between the AGTR1 gene A1166C polymorphism and cancer risk, we performed a meta-analysis by pooling all eligible studies to calculate the estimate of overall cancer risk, and to evaluate influence of cancer types and ethnicity.

Materials and methods

Selection of studies

All case-control studies assessing the association between the AGTR1 gene A1166C polymorphism and cancer risk published from May 2000 through May 2018 were identified by searching the PubMed and China National Knowledge Infrastructure databases. There was no language limitation. The following search terms were used: ‘cancer’, ‘angiotensin II type 1 receptor/AGTR1’, ‘A1166C’ and ‘gene polymorphism’ for relevant citations. If more than one article was published using the same case series, only the study with the largest sample size was selected.

Inclusion and exclusion criteria

The studies included in the meta-analysis had to meet all the following inclusion criteria: (a) case-control studies addressing cancer cases and healthy controls; (b) studies examining the association between the AGTR1 gene A1166C polymorphism and susceptibility to cancer; and (c) studies including sufficient genotype data for extraction. The following studies were excluded: (a) not case-control studies evaluating the association between the AGTR1 gene A1166C polymorphism and cancer risk; (b) case reports, letters, reviews, meta-analyses or editorial articles; and (c) investigation not providing detailed data of ATIR A1166C genotype distributions.

Data extraction

To improve the reliability of the data, information was extracted from all eligible publications by two investigators independently according to the following characteristics: (a) name of the first author, (b) year of publication, (c) country, (d) ethnicity, (e) sample sizes of cases and controls, (f) genotype distribution in cases and controls, and (g) P-value for Hardy–Weinberg equilibrium (HWE) test in controls. Different ethnicity descents were categorized as Asian and Caucasian. Cancer types were classified as breast cancer (BC) and other cancers.

Statistical analysis

The association between the AGTR1 gene A1166C polymorphism and the risk of cancer was estimated by calculating pooled odds ratios (ORs) and 95% confidence intervals (CIs) using homozygote comparison (CC vs AA), heterozygote comparison (AC vs AA), a dominant model (CC + AC vs AA) and a recessive models (CC vs AC + AA). The heterogeneity among these studies was checked by the F test; when F > 50% indicated heterogeneity across studies, the random effects model was used for meta-analysis or else the fixed effects model was used. Subgroup analyses were performed by ethnicity and cancer types. Sensitivity analysis was performed to evaluate the stability of the results by removing one single study from the overall pooled analysis each time to check the influence of the removed data set on the overall ORs. Publication bias was assessed by Begg’s test (P < 0.05 was considered statistically significant). Data analysis was performed using STATA version 12.0 (Stata Corp LP, College Station, Texas, USA).

Results

Characteristics of the included studies

For cancer susceptibility related to the AGTR1 gene A1166C polymorphism, articles were retrieved via relevant databases. The literature selection process is shown in Figure 1. Finally, a total of 10 case-control publications met our inclusion criteria, including 1553 cases and 1904 controls. The genotype distributions of all articles were consistent with HWE except for Alves et al. and Fischuk et al. Each study in one publication was considered as a data set separately for pooling analysis. There were three studies of Asian descendants and seven studies of Caucasian descendants. There were seven studies on BC, one study on prostate cancer, one studies on aldosterone-producing adenoma, and one study concerning endometrial cancer. The general characteristics, and the allele and genotype distributions of the included articles, are shown in Table 1.

Quantitative synthesis

The main results regarding the meta-analysis and heterogeneity are listed in Table 2. Overall, no significant association between the AGTR1 gene A1166C polymorphism and cancer was observed under all genetic models (Figure 2:
CC vs AA: OR = 1.09, 95% CI = 0.50–2.37; AC vs AA: OR = 1.54, 95% CI = 0.81–2.91; dominant model: OR = 1.46, 95% CI = 0.77–2.79; and recessive model: OR = 1.12, 95% CI = 0.84–1.49).

In the subgroup analysis based on ethnicity, results of subgroup analysis confirmed that there were not significant associations between the AGTR1 gene A1166C polymorphism and cancer risk in both Asian and
Caucasian populations. In the subgroup analysis by cancer type, no significant association was observed in both the BC and other cancer groups. In the subgroup analysis based on HWE, we detected no significant association between the AGTR1 gene A1166C polymorphism and cancer risk, especially regarding BC. No material alteration was detected, suggesting that our results are statistically robust.

**Sensitivity analysis**

A sensitivity analysis was conducted to evaluate the stability of the results by deleting one study at a time. The results of the sensitivity analysis showed that no individual study significantly affected the pooled ORs (Figure 3).

**Publication bias**

A funnel plot and Begg’s test were used to assess publication bias. There was no evidence of publication bias in our study (Figure 4). The results imply that the publication bias was low in the present meta-analysis.

**Discussion**

Cancer is currently one of the leading causes of death worldwide. It is proving to be a serious socioeconomic burden on the healthcare systems of different countries and deteriorates the quality of life of patients. Despite advances in treatment, the prognosis still remains incompletely understood. Cancer is a multifactorial disease and various studies suggest that environmental factors interplay with various polymorphisms in carcinogenesis. There is increasing evidence that the RAS influences tissue angiogenesis, cellular proliferation, apoptosis and inflammation. In addition, previous studies have indicated that AGTIR blockers inhibit tumor growth and angiogenesis.

Previous studies have found that AGTR1 A1166C may be located in the binding site for microRNA-155 (miR-155) and that the A allele enhances miR-155 binding affinity compared to the C allele, resulting in decreased AGTR1 protein expression. The expression of AGTR1 protein is upregulated in most tumors. Theoretically, the A allele may be a protective factor in cancer development. To date, several meta-analyses have investigated the relationship between AGTR1 gene A1166C polymorphism and cancer risk, but the results have been inconclusive. Some studies found that the CC homozygote might be a protective factor of BC development. Liu et al. found that the CC homozygote was associated with a significantly decreased risk of cancer, especially in a Caucasian population. However, after removing non-HWE studies or small sample size studies, Liu et al. found that the significant association between AGTR1 gene A1166C polymorphism and cancer risk became null, suggesting that HWE violation and small sample sizes were significant sources of heterogeneity in the meta-analysis.

In the present study, we included 10 case-control studies to perform a meta-analysis. The results suggested that the AGTR1 gene A1166C polymorphism was not associated with susceptibility to cancer. However, considering other possible confounding factors that would influence the results of the analysis, we further conducted several subgroup analyses. In the stratified analysis by ethnicity and cancer type, the results showed no significant association with cancer. In addition, when stratifying via limiting studies that were consistent with HWE, the meta-analysis data yielded the same conclusions, suggesting that the meta-analysis was realistic. Furthermore, sensitivity and publication bias analyses were used to confirm the robustness of our results. However, large and well-designed studies are warranted to validate our findings. Moreover, more gene–gene and gene–environment interactions should also be considered in future analyses, which should lead to

### Table 2. Summary of different comparative results.

| Variables   | N | CC vs AA OR (95% CI) | AC vs AA OR (95% CI) | Dominant model OR (95% CI) | Recessive model OR (95% CI) |
|-------------|---|---------------------|---------------------|---------------------------|-----------------------------|
| Ethnicity   |   |                     |                     |                           |                             |
| Asians      | 3 | 3.57 (0.37–34.54) R | 2.87 (0.53–15.59) R | 2.97 (0.53–16.66) R       | 1.39 (0.60–3.23) R          |
| Caucasians  | 7 | 0.78 (0.33–1.84) R  | 1.14 (0.71–1.82) R  | 1.07 (0.66–1.71) R        | 0.98 (0.81–1.18) F          |
| Cancer type |   |                     |                     |                           |                             |
| BC          | 7 | 1.29 (0.47–3.56) R  | 1.78 (0.75–4.21) R  | 1.73 (0.72–4.12) R        | 1.14 (0.79–1.64) R          |
| The others  | 3 | 0.73 (0.14–3.64) R  | 1.61 (1.04–2.49) R  | 1.06 (0.49–2.27) F        | 1.13 (0.80–1.58) F          |
| HWE         |   |                     |                     |                           |                             |
| Yes         | 8 | 1.23 (0.42–3.64) R  | 1.73 (0.81–3.71) R  | 1.66 (0.76–3.64) R        | 1.23 (0.89–1.72) R          |
| No          | 2 | 0.78 (0.40–1.50) R  | 0.87 (0.61–1.26) R  | 0.84 (0.60–1.19) R        | 0.76 (0.55–1.07) R          |

BC: breast cancer; CI: confidence interval; F: fixed effects model; HWE: Hardy–Weinberg equilibrium; OR: odds ratio; R: random effects model.
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better, more comprehensive understanding of the association between this polymorphism and cancer risk.

Some limitations of our meta-analysis should be mentioned. First, lack of the original information of the included publications limited further evaluation of gene–gene and gene–environment relationships. Second, all included studies were retrospective studies, which may result in subject selection bias, therefore affecting the reliability of the final results. Third, this meta-analysis only included published literature, and there may have been some relevant unpublished studies, possibly introducing publication bias.

In summary, our study suggests that the AGTR1 gene A1166C polymorphism might not be associated with cancer risk. Large-scale case-control studies are warranted to investigate the possible gene–gene and gene–environment interrelationships in terms of cancer risk.

Figure 2. Forrest plot of odds ratios for association between the AGTR1 gene A1166C polymorphism and cancer.

CI: confidence interval; ID: identifier; OR: odds ratio.
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References
1. Jia J, Ren J, Yan D, et al. Association between the XRCC6 polymorphisms and cancer risks: A systematic review and meta-analysis. *Medicine (Baltimore)* 2015; 94: e283.
2. Marron M, Boffetta P, Zhang ZF, et al. Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. *Int J Epidemiol* 2010; 39: 182–196.
3. Wang JG and Staessen JA. Genetic polymorphism in the renin-angiotensin system: Relevance for susceptibility to cardiovascular disease. *Eur J Pharmacol* 2000; 410: 289–302.
4. Suganuma T, Ino K, Shibata K, et al. Functional expression of the angiotensin II type 1 receptor in human ovarian carcinoma cells and its blockade therapy resulting in suppression of tumor invasion, angiogenesis, and peritoneal dissemination. *Clin Cancer Res* 2005; 11: 2686–2694.
5. Zhu YC, Zhu YZ, Lu N, et al. Role of angiotensin AT1 and AT2 receptors in cardiac hypertrophy and cardiac remodeling. *Clin Exp Pharmacol Physiol* 2003; 30: 911–918.
6. Rosenthal T and Gavras I. Angiotensin inhibition and malignancies: A review. *J Hum Hypertens* 2009; 23: 623–635.
7. Poirier O, Georges JL, Ricardo S, et al. New polymorphisms of the angiotensin II type 1 receptor gene and their associations with myocardial infarction and blood pressure: The ECTIM study. *J Hypertens* 1998; 16: 1443–1447.
8. Wang JL, Li Xue, Hao PP, et al. Angiotensin II type 1 receptor gene A1166C polymorphism and essential hypertension in Chinese: A meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2010; 11: 127–135.
9. Feng X, Zheng BS, Shi JJ, et al. A systematic review and meta-analysis of the association between angiotensin II type
1. Hu and Chen

1 receptor A1166C gene polymorphism and myocardial infarction susceptibility. *J Renin Angiotensin Aldosterone Syst* 2014; 15: 307–315.

10. Alves Corrêa SA, Ribeiro de Noronha SM, Nogueira-de-Souza NC, et al. Association between the angiotensin-converting enzyme (insertion/deletion) and angiotensin II type 1 receptor (A1166C) polymorphisms and breast cancer among Brazilian women. *J Renin Angiotensin Aldosterone Syst* 2009; 10: 51–58.

11. Sierra Díaz E, Sánchez Corona J, Rosales Gómez RC, et al. Angiotensin-converting enzyme insertion/deletion and angiotensin type 1 receptor A1166C polymorphisms as genetic risk factors in benign prostatic hyperplasia and prostate cancer. *J Renin Angiotensin Aldosterone Syst* 2009; 10: 241–246.

12. Mendizábal-Ruiz AP, Morales J, Castro Martinez X, et al. RAS polymorphisms in cancerous and benign breast tissue. *J Renin Angiotensin Aldosterone Syst* 2011; 12: 85–92.

13. Namazi S, Monabati A, Ardeshir-Rouhani-Fard S, et al. Association of angiotensin I converting enzyme (insertion/deletion) and angiotensin II type 1 receptor (A1166C) polymorphisms with breast cancer prognostic factors in Iranian population. *Mol Carcinog* 2010; 49: 1022–1030.

14. Ouyang J, Wu Z, Xing J, et al. Association of polymorphisms in angiotensin II receptor genes with aldosterone-producing adenoma. *J Huaizhong Univ Sci Technolog Med Sci* 2011; 31: 301–305.

15. Fishchuk LE and Gorovenko NG. Genetic polymorphisms of the renin-angiotensin system in breast cancer patients. *Exp Oncol* 2013; 35: 101–104.

16. Ding P, Yang Y, Ding S, et al. Synergistic association of six well-characterized polymorphisms in three genes of the renin-angiotensin system with breast cancer among Han Chinese women. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 1232–1239.

17. El Sharkawy RM, Zaki AM, El Fattah Kamel A, et al. Association between the polymorphisms of angiotensin converting enzyme (peptidyl-dipeptidase A) INDEL mutation (I/D) and angiotensin II type I receptor (A1166C) and breast cancer among post menopausal Egyptian females. *Alex J Med* 214; 50: 267–274.

18. Pringle KG, Delforce SJ, Wang Y, et al. Renin-angiotensin system gene polymorphisms and endometrial cancer. *Endocr Connect* 2016; 5: 128–135.

19. Singh A, Srivastava N, Amit S, et al. Association of AGTR1 (A1166C) and ACE (I/D) polymorphisms with breast cancer risk in North Indian population. *Transl Oncol* 2018; 11: 233–242.

20. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9–29.

21. Herr D, Rodewald M, Fraser HM, et al. Potential role of renin-angiotensin-system for tumor angiogenesis in receptor negative breast cancer. *Gynecol Oncol* 2008; 109: 418–425.

22. Ceolotto G, Papparella I, Bortoluzzi A, et al. Interplay between miR-155, AT1R A1166C polymorphism, and AT1R expression in young untreated hypertensives. *Am J Hypertens* 2011; 24: 241–246.

23. Xi B, Zeng T, Liu L, et al. Association between polymorphisms of the renin-angiotensin system genes and breast cancer risk: A meta-analysis. *Breast Cancer Res Treat* 2011; 130: 561–568.

24. Chen F, Chen G, Dou Y, et al. Association of angiotensin II type 1 receptor (A1166C) polymorphism with breast cancer risk: An update meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 851–857.

25. Liu ZW, Weng MW, Dai F, et al. The relationship between angiotensin II type 1 receptor gene A1166C polymorphism and cancer risk: A meta-analysis. *Int J Clin Exp Med* 2016; 9: 9134–9142.