Original Article

jraas

Journal of the Renin-Angiotensin-Aldosterone System
2015, Vol. 16(4) 851–857

DOI: 10.1177/1470320315588234
jra.sagepub.com
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Association of angiotensin II type 1 receptor (A1166C) polymorphism with breast cancer risk: An update meta-analysis

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Abstract

Objective: Previous studies on the relationship between angiotensin II type 1 receptor (*AT1R*) gene (A1166C) polymorphism and breast cancer did not reach the same conclusion. In the present study, we aimed to further evaluate the relationship between the *AT1R* gene A1166C polymorphism and breast cancer risk.

Methods: We selected five case-control studies related to *AT1R* gene A1166C polymorphism and breast cancer by searching PubMed, EMBase, Chinese Biomedical Literature Database, Chinese CNKI, Web of Science, and the Wanfang database. We utilized Q-test and I^2 test to detect the heterogeneity between each study. A random-effects model ($I^2 > 50\%$; $p < 0.10$) or a fixed-effects model ($I^2 < 50\%$; $p > 0.10$) was utilized to merge the odds ratio (OR) and 95% confidence interval (CI) during the meta- analyses.

Results: The present study included 972 patients with breast cancer and 1336 cancer-free control subjects. By meta-analysis, we found A1166C polymorphism was associated with decreased risk for breast cancer in Caucasian population in an additive model (C vs. T: OR = 0.77, 95% CI: 0.62–0.96, $p = 0.02$). However, we did not find associations in other genetic models (AC+CC vs. AA: OR = 0.78, 95% CI: 0.50–1.22, $p = 0.28$; CC vs. AA+AC: OR = 1.64, 95% CI: 0.94–2.85, $p = 0.08$).

Conclusion: We concluded that *AT1R* gene A1166C polymorphism was associated with reduced risk for breast cancer.

Keywords

Breast cancer, angiotensin II type 1 receptor, gene polymorphism, meta-analysis

Date received: 16 December 2014; accepted: 24 March 2015

Introduction

Breast cancer is one of the most common malignant tumors in women.[1] However, the pathogenesis of breast cancer remains unclear.[2–4] Previous studies have suggested that the renin–angiotensin system (RAS) is involved in the mechanism of breast cancer.[5–7] Also, recently published data indicated that angiotensin II, the main biologically active peptide of RAS, contributed to breast cancer development and progression.[8,9] The peptide hormone angiotensin II is a potent vasoconstrictor that exerts its actions through the angiotensin II type 1 receptor (*AT1R*). Angiotensin II receptors are of two types: type 1 (AT1) receptor and type 2 (AT2) receptor.[10] Receptor binding studies provide important information regarding the distribution of AT1 and AT2 receptors and the sites of action and physiological roles of angiotensin.[11,12] Polymorphism in the *AT1R* A1166C gene (SNP ID: rs5186) has been widely studied and found to be associated with breast cancer.[13–15]

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The *AT1R* gene is composed of five exons located on chromosome 3q, where the first four exons encode the 5′-untranslated region (5′- UTR). A polymorphism in the 3′-UTR of the *AT1R* gene leads to the transfer of adenine (A) to cytosine (C) base at the 1166 position.[16,17] The *AT1R* gene plays an important role in the pathogenesis of breast cancer and the cardiovascular system.[18,19] Several studies have suggested that *AT1R* A1166C gene polymorphism is associated with breast cancer risk and prognosis,[13,15,20–22] while other studies have shown no significant association with breast risk.[23,24] In 2010, Xi et al. performed a meta-analysis and found that *AT1R* A1166C polymorphisms might be implicated in the pathogenesis of breast cancer.[25] However, Xi et al.'s conclusion was limited by the small sample size (only two publications included).

Therefore, we performed an update meta-analysis to further clarify the relationship between *AT1R* A1166C polymorphism and breast cancer risk.

Materials and methods

Literature identification

To identify all the articles that reported the association of *AT1R* A1166C polymorphisms with breast cancer risk, we conducted a computerized literature search of PubMed, EMBase, Chinese Biomedical Literature Database, Chinese CNKI, Web of Science, and the Wanfang database using the terms "breast cancer (Mesh)," "angiotensin II type 1 receptor" or "AT1R," "polymorphism" or "SNP," "genotype," or "variation" without any restriction on language or publication year. By means of online retrieval and literature review, references obtained using the above-mentioned databases were reviewed again to ensure that no relevant studies were missed.

All the included studies had to meet the following inclusion criteria: (1) independently published case-control or cohort studies on the relation between *AT1R* polymorphism and breast cancer; (2) similar themes and methods; (3) the genotype data available. We excluded the literature in which the relevant data are not available or there is heterogeneity of gene polymorphism in the control population.

Quality assessment and data extraction

Two reviewers (Fangguo Chen and Guiling Chen) independently evaluated the studies and extracted the data using a standard approach according to the above-mentioned inclusion criteria. Discrepancies were resolved through discussion. The Cochrane Handbook 5.2 quality evaluation criteria were utilized to assess the methodological quality of included studies. Literature that had been reported repeatedly or poor-quality literature were excluded from the included studies.

For each study, we extracted the first author's last name, year of publication, ethnicity of participants, numbers of cases and controls, and frequency of AA, AC, and CC genotypes. The Hardy–Weinberg equilibrium was assessed using the χ^2 test.

Statistical analysis

We performed the meta-analyses utilizing RevMan 5.2 software. Both Q-test and I^2 test were directly utilized to examine the heterogeneity between each study. The association between A1166C polymorphisms of the *AT1R* gene and the risk of breast cancer was estimated by calculating pooled odds ratio (OR) and 95% confidence interval (CI). The significance of the pooled OR was determined by Z test ($p < 0.05$ was considered statistically significant). A random- or fixed-effects model was used to calculate pooled effect estimates in the presence ($p < 0.10$) or absence ($p > 0.10$) of heterogeneity, respectively. Subgroup analyses were performed according to ethnicity. 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 to the overall ORs. Publication bias was assessed by RevMan 5.2 statistical software to make the funnel plot. A $P < 0.05$ was considered as a significant difference.

Results

Study identification

As shown in Figure 1, 48 literature studies were preliminarily detected; 42 of these were excluded as being obviously irrelevant from reading their titles and abstracts. Thus, six articles met the inclusion criteria. However, the study by Koh et al. was excluded because it examined the associations of three *AT1R* polymorphisms (namely A168G, C535T, and T825A) rather than A1166C polymorphism.[26] Therefore, five studies with a total of 972 patients with breast cancer and 1336 cancer-free control subjects were included in this research.[15,20–23] Four of these studies were performed in a Caucasian population,[15,20,22,23] while only one study was conducted in a Chinese population.[21] The characteristics of the studies included are shown in Table 1.

Association of A1166C polymorphism and breast cancer risk

The results of meta-analysis of the association between breast cancer and *AT1R* gene polymorphism in five case-control studies are shown in Figures 2 and 3. The heterogeneity test of the various studies revealed heterogeneous results ((AC+CC) vs. AA: $I^2 = 85\%$, $p < 0.0001$; C allele

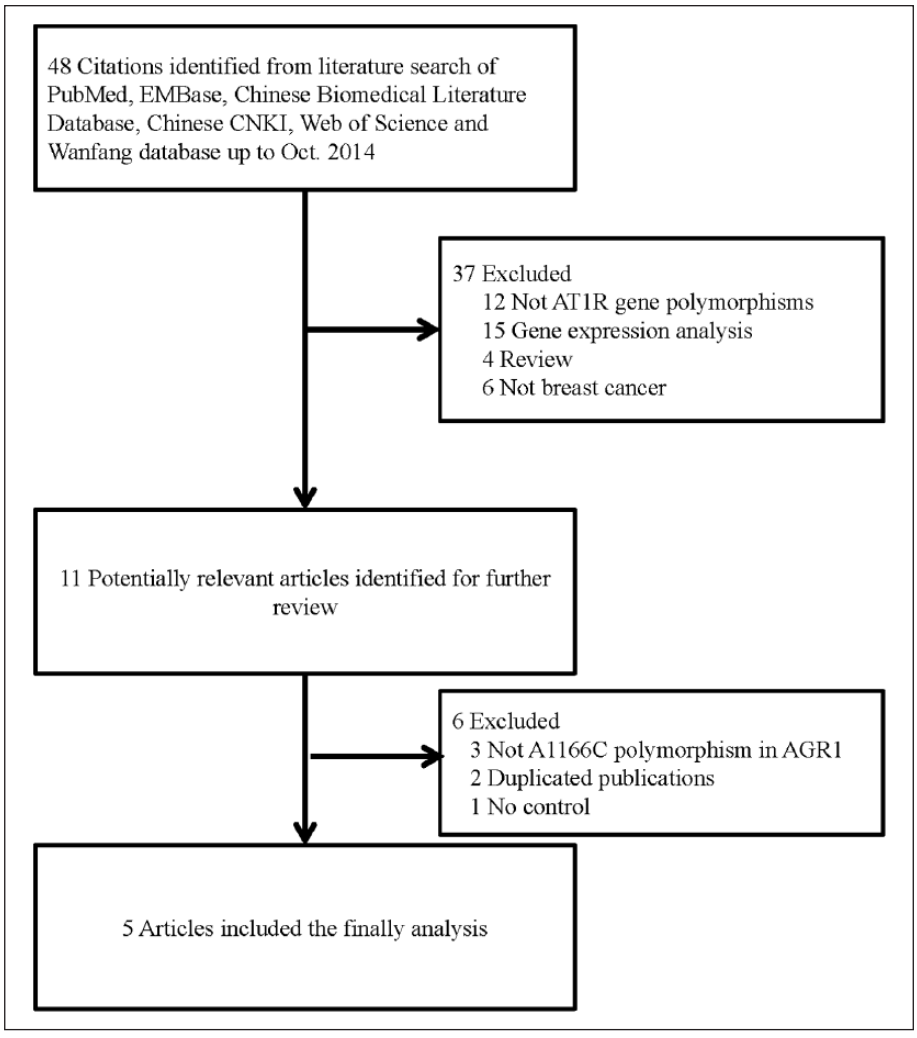

Figure 1. Flow chart of literature identification.

Table 1. The characteristics of the included studies.

Author	Year	Country	Ethnicity	Genotyping methods	Groups	N.	H-WE	A1166C genotypes			Alleles	
								AA	AC	CC	A	C
Alves Corrêa et al.[15]	2009	Brazil	Caucasian	PCR-RFLP	case	101	Yes	65	31	5	161	41
					control	307		157	135	15	449	165
Ding et al.[21]	2014	China	Asian	PCR-RFLP	case	606	Yes	504	93	9	1101	111
					control	633		576	54	3	1206	60
Fishchuk et al.[22]	2013	Ukraine	Caucasian	PCR-RFLP	case	131	Yes	72	47	12	191	71
					control	102		64	24	14	152	52
Mendizábal-Ruiz et al.[20]	2010	Mexico	Caucasian	PCR-RFLP	case	64	Yes	44	17	3	105	23
					control	224		121	83	20	325	123
Namazi et al.[23]	2010	Iran	Caucasian	PCR-RFLP	case	70	Yes	40	30	0	110	30
					control	70		38	28	4	104	36

vs. A allele: $I^2 = 85\%$, $p < 0.0001$); therefore, we used the random-effects model in the analysis. However, we did not find heterogeneity between each study in a dominant model (AA+AC vs. CC: $I^2 = 44\%$, $p = 0.13$); thus we used the fixed-model to merge the OR value. In all studies, including Caucasian and Asian populations, we did not

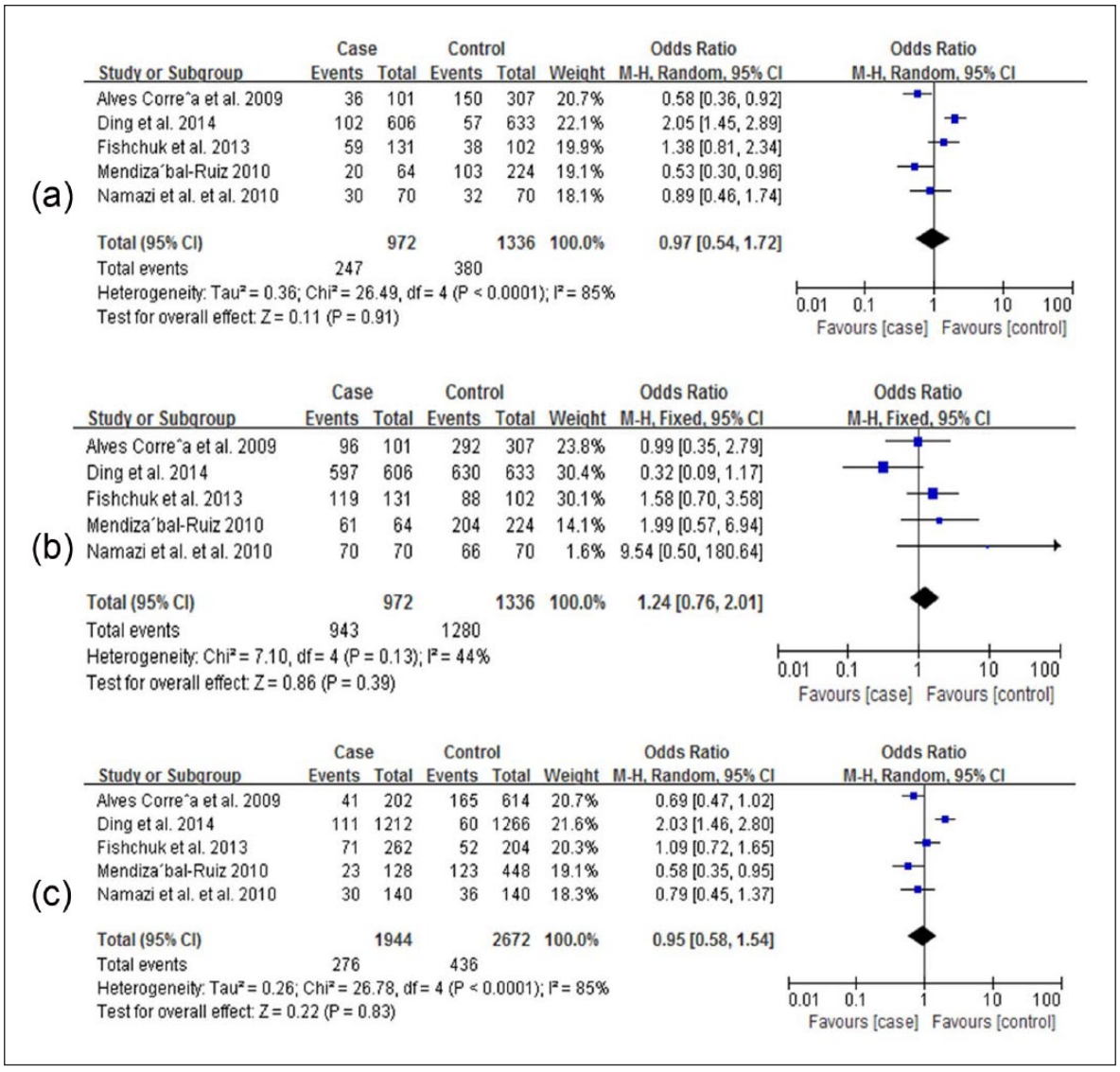

Figure 2. Forest plot of breast cancer risk associated with *AT1R* polymorphism in total population. The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI: (a) (AC+CC) vs. AA; (b) CC vs. (AA+AC); (c) C allele vs. A allele.

find an association between A1166C polymorphism and breast cancer in any genetic model ((AC+CC) vs. AA: OR = 0.97, 95% CI: 0.54–1.72, $p = 0.91$; (AA+AC) vs. CC: OR = 1.24, 95% CI: 0.76–2.01; C allele vs. A allele: OR = 0.95, 95% CI: 0.58–1.54, $P = 0.83$; Figure 2). Subgroup analysis according to ethnicity suggested that A1166C polymorphism was associated with decreased risk for breast cancer in Caucasian populations in an additive model (C vs. T: OR = 0.77, 95% CI: 0.62–0.96, $p = 0.02$). However, we did not find association in other genetic models (AC+CC vs. AA: OR = 0.78, 95% CI: 0.50–1.22; CC vs. AA+AC: OR = 1.64, 95% CI: 0.94–2.85) in Caucasian populations (Figure 3).

Publication bias analysis

The result of Egger's test did not show statistical evidence for bias (data not shown). This indicates that there is no publication bias, and the result of the study is credible.

Sensitivity analysis

We deleted one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall ORs. The pooled ORs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall ORs.

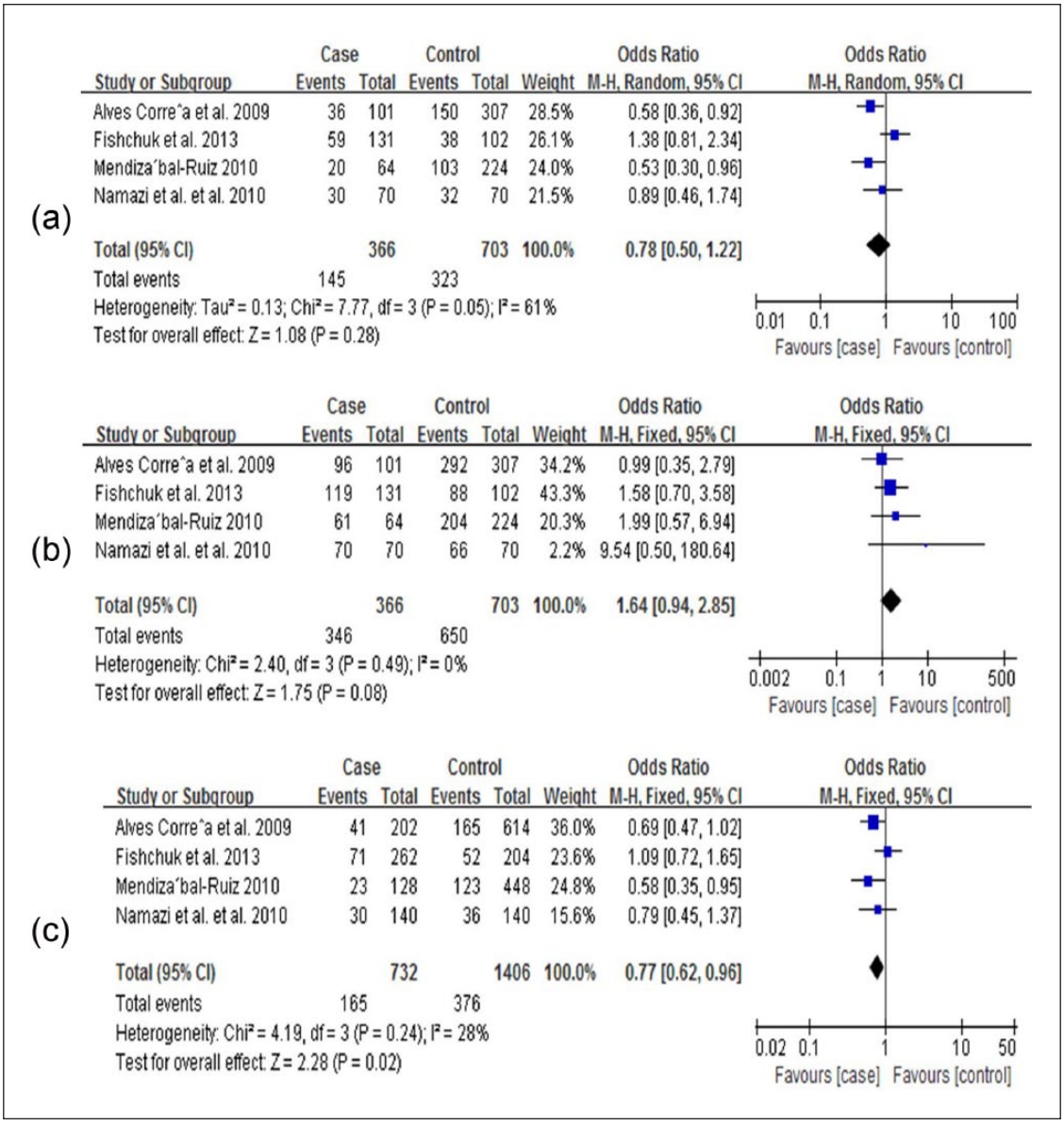

Figure 3. Forest plot of breast cancer risk associated with *AT1R* polymorphism in Caucasian population. The squares and horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI: (a) (AC+CC) vs. AA; (b) CC vs. (AA+AC); (c) C allele vs. A allele.

Discussion

In the present study, we performed a meta-analysis to evaluate the association of *AT1R* gene A1166C polymorphism with breast cancer. We found C allele carriers have a lower risk for breast cancer in Caucasian populations. This study is an update meta-analysis in which the results were different from the previous one.[25] Previous studies suggested that the RAS plays an important role in the regulation of cell proliferation, angiogenesis, and inflammation,[27,28] which indicated that RAS genes might be implicated in the carcinogenesis.

AT1R not only has an important role in the regulation of blood pressure and cardiovascular homeostasis,[29,30] but also influences tumor cell proliferation, migration, angiogenesis, and inflammation.[31,32] Recently, a SNPs A1166C polymorphism was reported to be associated with the risk for breast cancer.[15,21,22] However, the results were inconsistent between each study.

One published meta-analysis including only two case-control studies showed a significant association between *AT1R* polymorphism and breast cancer risk.[25] However, there are several studies that had not been included in their meta-analysis.

In the present study, we included five case-control studies to perform a meta-analysis. The results suggested that the *AT1R* 1166C allele is a protective factor for breast cancer in Caucasian populations. However, we did not find that the 1166CC genotype was associated with reduced risk for breast cancer. Since only one study was conducted in an Asian population,[21] we did not include this study in the subgroup analysis. This fact may be a limitation of our study.

In conclusion, the present study suggests that the 1166C allele of the *AT1R* gene is associated with reduced risk for breast cancer in Caucasian populations. However, there is still a need for further research and screening of etiological relations between the functional polymorphism loci of the *AT1R* gene and the susceptibility of breast cancer.

Conflict of interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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