Angiotensin II type 1 receptor gene A1166C polymorphism and breast cancer susceptibility

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ABSTRACT. Numerous studies have evaluated the association between the angiotensin II type-1 receptor (AGTR1) gene A1166C polymorphism and breast cancer risk. However, the specific association is controversial. The aim of the present study was to derive a more precise estimation of the relationship. A comprehensive research was conducted of the PubMed and the Google Scholar databases through February 2015. Data were assessed using STATA version 12.0. Pooled odds ratios with 95%CIs were derived from the fixed-effect or random-effect models. A total of 911 patients with breast cancer and 1284 controls from 5 case-control studies were included in this meta-analysis. The meta-analysis results showed no significant association between the *AGTR1* gene A1166C polymorphism and breast cancer risk. Similarly, in the subgroup analysis regarding ethnicity, no associations were observed. Heterogeneity and publication bias were not observed in this meta-analysis. The A1166C polymorphism in the AGTR1 gene may not be a risk factor for breast cancer. Further, large, and well-designed studies are needed to confirm this conclusion.

Key words: Angiotensin II type-1 receptor; Breast cancer; Meta-analysis; Polymorphism

INTRODUCTION

Breast cancer is the most common cancer among women worldwide, accounting for 23% of new cancer cases and 14% of cancer deaths in 2008 (Jemal et al., 2011). The development of breast cancer is a complex and multi-factorial disease, including environmental factors, genetic factors, and gene-environment interactions (Zhu et al., 2010). It is well-known that reproductive factors (age at first birth and breastfeeding) contributes to an increased risk of breast cancer. In addition, other risk factors such as age, personal, or family history of breast disease may contribute to an increased risk of breast cancer (Shah et al., 2014). However, not all exposed individuals develop lung and breast cancers, suggesting that genetic factors play a role in these conditions. A previous meta-analysis demonstrated that the cadherin-1 gene may be involved in the pathogenesis of breast cancer (Gu et al., 2014).

The renin-angiotensin system (RAS) has been shown to be involved in many cardiovascular diseases, including hypertension, coronary heart disease, cardiomyopathy, and congestive heart failure (Sekuri et al., 2005). In addition, local RAS in tissues may be related to the occurrence and development of tumors (Suganuma et al., 2005). Angiotensin II, the major biologically active component of the RAS, exerts its effects via 2 distinct subtypes of angiotensin II receptors: angiotensin II type-1 receptor (AGT1R) and angiotensin II type-2 receptor (Zhu et al., 2003). The AGT1R protein is a member of the 7-transmembrane G-protein-coupled receptor family; its expression is upregulated in most tumors (Rosenthal and Gavras, 2009). A previous study showed that an AGT1R blocker can inhibit the growth of breast cancer cells (Chae et al., 2011).

This gene polymorphism was found to be linked to RAS activity, and women carrying a low-activity genotype of the angiotensin-converting enzyme gene have been found to have a 50% reduction in breast cancer risk (Koh et al., 2003). The human AGTR1 gene consists of 5 exons and spans over 55 kb of the genomic sequence on chromosome 3q21-25 (Guo et al., 1994). The A1166C variant (NCBI Ref. SNP ID: rs5186) is located in the 3' untranslated region, in which there is an A to C transversion (Zhao et al., 1999). A previous meta-analysis showed that the AGTR1 gene A1166C polymorphism is associated with the risk of hypertension (Wang et al., 2010).

To date, numerous studies have been performed to examine the relationship between the AGTR1 gene A1166C polymorphism and the risk of breast cancer. However, the results are controversial because of limited available data or disagreements among studies. In the present study, we evaluated this association by meta-analysis based on corrected data and recently published studies to determine the genetic contribution of the A1166C polymorphism to the risk of developing breast cancer.

MATERIAL AND METHODS

Eligibility of relevant studies

Two reviewers searched the Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar databases (http://scholar.google.co.uk/) to retrieve studies linking the AGTR1 gene A1166C polymorphism and breast cancer risk available through February 2015 without language restrictions and using the following key words: "angiotensin II type-1 receptor/AGT1R", "A1166C", "breast cancer", "polymorphism", "single-nucleotide polymorphism", and "genetic polymorphism". Additional eligible studies were identified by manually searching the reference lists of reviews and original articles. Studies reported by the same authors were checked for possible overlapping participant groups.

Inclusion and exclusion criteria

The selection criteria to identify an eligible study were as follows: a) case-control studies that addressed breast cancer cases and healthy controls; b) studies examining the association between the AGTR1 gene A1166C polymorphism and susceptibility to breast cancer; c) studies that included sufficient genotype data for extraction; and d) healthy controls were in Hardy-Weinberg equilibrium (HWE). The following studies were excluded: a) not case-control studies evaluating the association between the AGTR1 gene A1166C polymorphism and breast cancer risk; b) case reports, letters, reviews, meta-analyses, and editorial articles; c) reports in which the number of null and wild-type genotypes could not be ascertained; and d) healthy controls were not in HWE.

Data extraction

The 2 authors independently reviewed and extracted the required data. Disagreements were resolved through discussion among the authors until a consensus was reached. The following information was recorded for each study: first author, year of publication, area, number of patients and controls, distributions of genotype and alleles, and evidence of HWE (Table 1).

Table 1. Characteristics of the studies included in the meta-analysis.

| Study included	Area	Race	Cases/Controls	Genotypes for cases			Genotypes for controls			HWE test
				AA	AC	CC	AA	AC	CC	
Alves Corrêa (2009)	Brazil	Caucasian	101/307	65	31	5	157	135	15	0.04
Mendizábal-Ruiz (2011)	Mexico	Caucasian	64/224	44	17	3	121	83	20	0.30
Namazi (2010)	Iran	Caucasian	70/70	40	30	0	38	28	4	0.69
Ding (2014)	China	Asian	606/633	504	93	9	576	54	3	0.16
El Sharkawy (2014)	Egypt	Caucasian	70/50	37	31	2	38	12	0	0.33

Statistical analysis

The odds ratio (OR) corresponding to the 95%CI was used to assess the association between the AGTR1 gene A1166C polymorphism and the risk of breast cancer under homozygote comparison (AA *vs* CC), heterozygote comparison (AA *vs* CA), dominant model (CC+CA *vs* AA), and recessive models (AA + CA *vs* CC). The heterogeneity among these studies was evaluated using the I^2 test. I^2 ranges from 0 to 100% and represents the proportion of inter-study variability that can be attributed to heterogeneity rather than to chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. $I^2 > 50\%$ indicated heterogeneity across studies, and the random-effect model was used for meta-analysis; otherwise, the fixed-effect model was used. HWE in the controls was tested by the chi-square test for goodness of fit, and $P < 0.05$ indicated significant disequilibrium. To assess the reliability of the outcomes in the meta-analysis, sensitivity analysis was performed to exclude studies whose allele frequencies in controls exhibited significant deviation from HWE (Li et al., 2014). Publication bias was investigated by the Begg test (Begg and Mazumdar, 1994). All statistical analyses were performed by using STATA version 12.0 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of retrieved studies

A total of 49 potentially relevant publications were systematically identified by searching relevant databases. Based on the preliminary search criteria, 44 studies were excluded as they did not satisfy the inclusion criteria. A total of 5 studies with 911 cases and 1284 controls were included in the meta-analysis (Alves Corrêa et al., 2009; Namazi et al., 2010; Mendizábal-Ruiz et al., 2011; Ding et al., 2014; El Sharkawy et al., 2014). The study characteristics are summarized in Figure 1 and Table 1. All studies were published in English and the sample sizes ranged from 120-1239 participants. The controls were all healthy individuals and were age- and gender-matched with patients. Four studies included patients of European descent and 1 study included patients of Asian descent. The genotype distributions in the controls of all studies were in accordance with HWE, except that of Alves Corrêa et al. (2009).
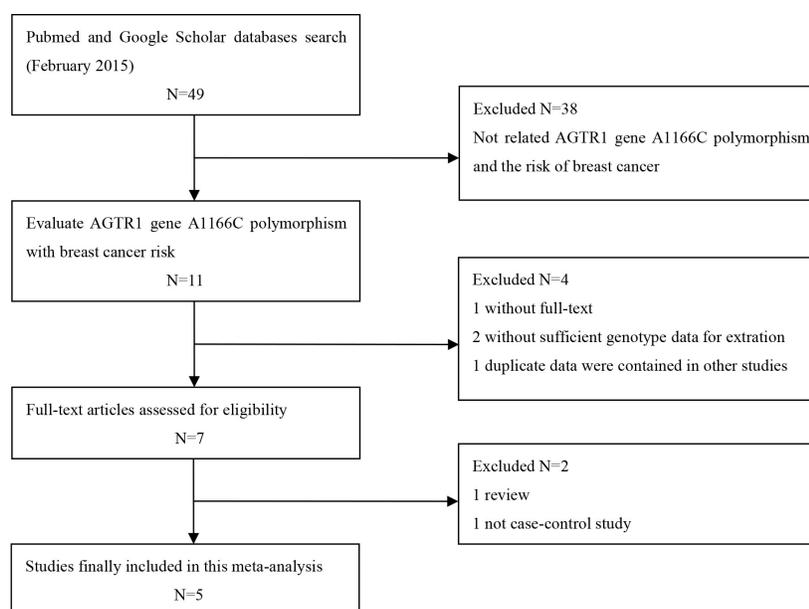
Figure 1. Flow diagram of study search and selection process.

Meta-analysis results

The results of the associations between the AGTR1 gene A1166C polymorphism and breast cancer risk, the heterogeneity test, and the test of publication bias are shown in Figure 2 and Table 2. The combined results based on all studies showed that variant genotypes were not associated with an increased breast cancer risk in different genetic models (AA *vs* CC: OR = 1.05, 95%CI = 0.36-3.10; AA *vs* AC: OR = 0.92, 95%CI = 0.48-1.74; dominant model: OR =1.08, 95%CI = 0.56-2.11; recessive model: OR = 1.02, 95%CI = 0.57-1.80). In subgroup analysis based on ethnicity, no significant association was found between the AGTR1 gene A1166C polymorphism

and breast cancer risk in Caucasians (AA *vs* CC: OR = 1.68, 95%CI = 0.83-3.39; AA *vs* AC: OR = 1.10, 95%CI = 0.57-2.10; dominant model: OR = 0.89, 95%CI = 0.47-1.70; recessive model: OR = 1.47, 95%CI = 0.73-2.97).
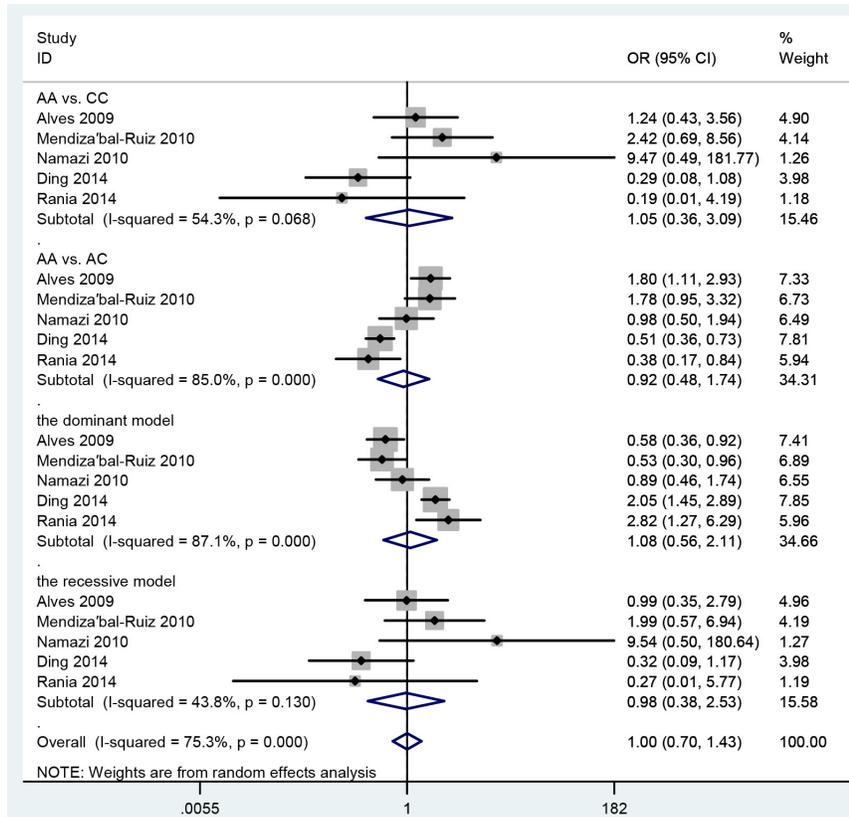

Study ID	OR (95% CI)	% Weight
AA vs. CC		
Alves 2009	1.24 (0.43, 3.56)	4.90
Mendiza'bal-Ruiz 2010	2.42 (0.69, 8.56)	4.14
Namazi 2010	9.47 (0.49, 181.77)	1.26
Ding 2014	0.29 (0.08, 1.08)	3.98
Rania 2014	0.19 (0.01, 4.19)	1.18
Subtotal (I-squared = 54.3%, p = 0.068)	1.05 (0.36, 3.09)	15.46
AA vs. AC		
Alves 2009	1.80 (1.11, 2.93)	7.33
Mendiza'bal-Ruiz 2010	1.78 (0.95, 3.32)	6.73
Namazi 2010	0.98 (0.50, 1.94)	6.49
Ding 2014	0.51 (0.36, 0.73)	7.81
Rania 2014	0.38 (0.17, 0.84)	5.94
Subtotal (I-squared = 85.0%, p = 0.000)	0.92 (0.48, 1.74)	34.31
the dominant model		
Alves 2009	0.58 (0.36, 0.92)	7.41
Mendiza'bal-Ruiz 2010	0.53 (0.30, 0.96)	6.89
Namazi 2010	0.89 (0.46, 1.74)	6.55
Ding 2014	2.05 (1.45, 2.89)	7.85
Rania 2014	2.82 (1.27, 6.29)	5.96
Subtotal (I-squared = 87.1%, p = 0.000)	1.08 (0.56, 2.11)	34.66
the recessive model		
Alves 2009	0.99 (0.35, 2.79)	4.96
Mendiza'bal-Ruiz 2010	1.99 (0.57, 6.94)	4.19
Namazi 2010	9.54 (0.50, 180.64)	1.27
Ding 2014	0.32 (0.09, 1.17)	3.98
Rania 2014	0.27 (0.01, 5.77)	1.19
Subtotal (I-squared = 43.8%, p = 0.130)	0.98 (0.38, 2.53)	15.58
Overall (I-squared = 75.3%, p = 0.000)	1.00 (0.70, 1.43)	100.00

NOTE: Weights are from random effects analysis

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Figure 2. Forest plot of breast cancer associated with AGTR1 gene A1166C polymorphism.

Table 2. Summary ORs and 95%CI of AGTR1 gene A1166C polymorphism and breast cancer risk.

| Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I²	P	OR	95%CI	z	P
Overall	AA *vs* CC	911	1284	Random	54.3%	0.07	1.05	0.36-3.10	0.24	0.81
	AA *vs* AC			Random	85.0%	0.00	0.92	0.48-1.74	0.24	0.81
	Dominant model			Random	87.1%	0.00	1.08	0.56-2.11	0.24	0.81
	Recessive model			Fixed	43.8%	0.13	1.02	0.57-1.80	0.24	0.81
Caucasian	AA *vs* CC	305	651	Fixed	22.0%	0.28	1.68	0.83-3.39	0.34	1.00
	AA *vs* AC			Random	75.8%	0.01	1.10	0.57-2.10	0.34	1.00
	Dominant model			Random	77.3%	0.00	0.89	0.47-1.70	0.34	1.00
	Recessive model			Fixed	14.9%	0.32	1.47	0.73-2.97	0.34	1.00
Consistent with HWE	AA *vs* CC	810	977	Random	65.2%	0.04	1.01	0.20-5.08	0.34	0.73
	AA *vs* AC			Random	79.7%	0.00	0.76	0.39-1.47	0.34	0.73
	Dominant model			Random	84.6%	0.00	1.28	0.62-2.66	0.34	0.73
	Recessive model			Random	57.9%	0.07	1.01	0.24-4.34	0.34	0.73

OR = odds ratio; CI = confidence interval.

Sensitivity analysis

Sensitivity analysis was performed following the removal of study by Alves Corrêa et al. (2009) because of the genotype distribution in the control groups deviating from HWE, while the estimated pool OR remained unchanged (Table 2). Therefore, sensitivity analysis confirmed that the data analyzed in this meta-analysis was statistically robust.

Publication bias

A funnel plot was used to assess publication bias. There was no evidence of publication bias based on the funnel plot (Figure 3 and Table 2), indicating that publication bias was low in the present meta-analysis (all P > 0.05).
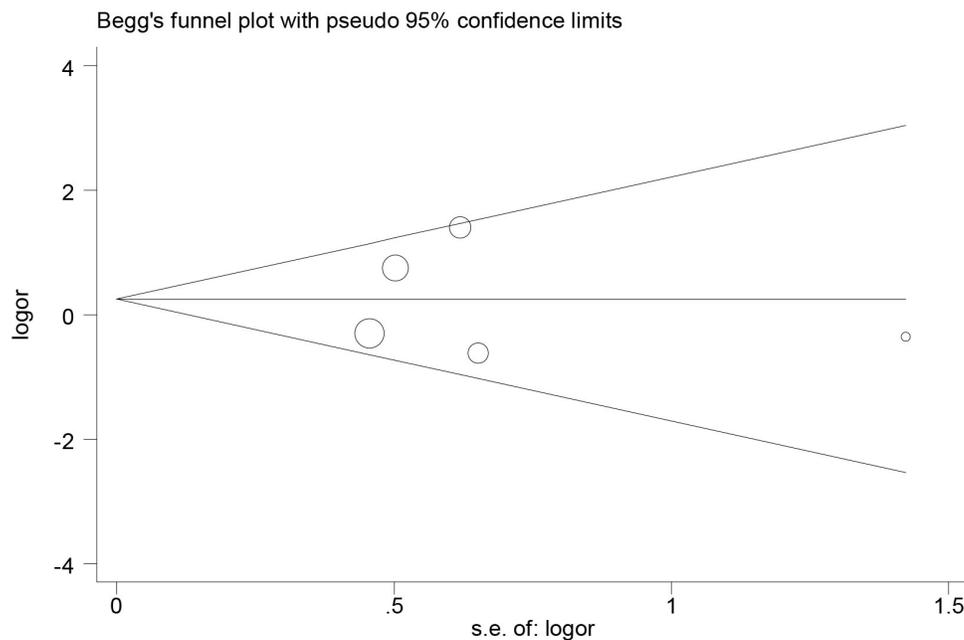
Figure 3. Begg's funnel plot test of publication bias for the association of AGTR1 gene A1166C polymorphism and breast cancer.

DISCUSSION

There is increasing evidence that RAS influences tissue angiogenesis, cellular proliferation, apoptosis, and inflammation (Ager et al., 2008). A meta-analysis study showed that AGT1R was markedly overexpressed in 10-20% of breast cancer cases and was highly overexpressed in several breast cancer cases by more than 100-fold (Rhodes et al., 2009). In addition, previous studies indicated that AGT1R blockers inhibited tumor growth and angiogenesis (Herr et al., 2008). Genetic polymorphisms altering the level of protein expressed are predicted to have a substantial influence on disease activity (Tahara et al., 2009). Alves Corrêa et al. (2009) were the first to

analyze the relationship between the A1166C polymorphism and breast cancer, and that there is no association between A1166C polymorphism and risk of breast cancer in Brazilian women. In recent years, several studies have been conducted to evaluate the association between the AGTR1 gene A1166C polymorphism and breast cancer risk. However, individually published studies have shown inconclusive results. In the present study, we carried out quantitative meta-analysis that increased the statistical power to derive a more precise estimation of this association.

In the present meta-analysis, the correlation between the AGTR1 gene A1166C polymorphism and susceptibility to breast cancer was evaluated. Five independent case-control studies were included, with a total of 911 patients and 1284 healthy control subjects. The meta-analysis results showed no association between the A1166C polymorphism and the susceptibility to breast cancer. Because the result may be affected by ethnicity, we performed race-related subgroup analysis, and the results showed significant associations between the A1166C polymorphism and breast cancer risk in Caucasians. One study examining an Asian population could not be included in our subgroup meta-analysis, and further studies in Asians and African should be performed. There was no evidence of publication bias in this meta-analysis. As the eligible study number was limited in the meta-analysis, caution should be exercised when considering this conclusion.

The AGTR1 gene A1166C polymorphism may be affected by gene-gene interactions. Namazi et al. (2013) found that the A1166C polymorphism in the AGTR1 gene was not significantly associated with the risk of breast cancer alone, but the A1166C polymorphism increased the risk of breast cancer when combined with the angiotensin-1 converting enzyme gene I/D polymorphism among Iranian women. In contrast, Ding et al. (2014) did not find a synergistic role of the AGTR1 gene A1166C polymorphism and angiotensin-1 converting enzyme gene I/D polymorphism among Chinese women. Because of the difference in genetic backgrounds and the environment in which the subjects lived, further studies examining gene-gene and gene-environment interactions should be evaluated in future analyses.

There were some limitations to this study. First, when searching publications, we only included articles in English, which may have eliminated relevant publications or unpublished studies in other languages. Second, the pooled estimates were not based on adjustment by confounding factors, such as gender, age, and smoking history. Third, the effects of gene-gene and gene-environment interactions were not addressed in this meta-analysis.

In conclusion, this meta-analysis suggests that the A1166C polymorphism in the AGTR1 gene may be not associated with breast cancer risk. However, further studies are necessary to investigate these associations.

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