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Association between polymorphisms of the renin–angiotensin system genes and breast cancer risk: a meta-analysis

Bo Xi · Tao Zeng · Liu Liu · Yajun Liang · Weina Liu · Yuehua Hu · Jun Li

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Abstract The renin–angiotensin system (RAS) has been considered to be implicated in the development of breast cancer. However, the results are inconsistent. In this study, we conducted a meta-analysis to assess the association between four polymorphisms, including angiotensin I-converting enzyme (*ACE*) I/D and A240T, angiotensin II type 1 receptor (*AGTR1*) A1166C and angiotensinogen (*AGT*) M235T polymorphisms, and breast cancer risk. Published literature from PubMed, ISI web of science, and Embase databases were retrieved. All studies evaluating the association between *ACE* I/D, *ACE* A240T, *AGTR1* A1166C, or *AGT* M235T polymorphism and breast cancer risk were included. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using fixed- or random-effects model. Ten studies (1,650 cases and 9,283 controls) on *ACE* I/D polymorphism, six studies (1,316 cases and 2,632 controls) on *ACE* A240T polymorphism, three studies (235 cases and 601 controls) on *AGTR1* A1166C polymorphism, and two studies (273 cases and 3,547 controls) on *AGT* M235T polymorphism were included. Overall, the meta-analysis showed no significant association between I/D or A240T polymorphism and breast cancer risk in either genetic model. Further subgroup analysis by ethnicity also revealed non-significant association in Caucasian or Asian populations except for Africans (the statistically significant association for *ACE* I/D or A240T polymorphism in Africans derived from only one study). A marginally significant association was observed for *AGTR1* A1166C polymorphism in Caucasians (CC vs. AA: OR = 0.31, 95% CI 0.10–0.99). In addition, there was a significant association between *AGT* M235T polymorphism and breast cancer risk in Caucasians (OR = 1.45, 95% CI 1.12–1.88). The present meta-analysis suggested that *ACE* I/D and A240T polymorphisms might not be a good predictor of breast cancer risk, while *AGTR1* A1166C and *AGT* M235T polymorphisms might be implicated in the pathogenesis of breast cancer. Given the limited sample size, the findings warrant further investigation.

Keywords Renin–angiotensin system · ACE gene · AGT gene · AGTR1 gene · Polymorphism · Breast cancer

B. Xi · W. Liu · J. Li (✉)
Institute of Maternal and Child Health Care, School of Public Health, Shandong University, Jinan 250012, China
e-mail: lijunfy@sdu.edu.cn

T. Zeng
Institute of Toxicology, School of Public Health, Shandong University, Jinan 250012, China

L. Liu
Department of General Surgery, The Second Affiliated Hospital of Nan Chang University, Nanchang 330006, China

Y. Liang · Y. Hu
Graduate School, Peking Union Medical College, Beijing 100730, China

Introduction

Breast cancer is the most common cancer among women worldwide, which accounts for 16% of all female cancers [1]. Breast cancer has led to serious mortality, and is one of the main causes of global health burden. Although environmental factors, such as reproductive (e.g., age at first

birth and breastfeeding), behavioral (e.g., hormone-replacement therapy and alcohol consumption), and anthropometric risk factors (e.g., body mass index), could contribute to the increased risk of breast cancer, and genetic factors are also implicated in the pathogenesis of the disease [2, 3]. Up to now, a great number of genetic variants have been identified to be potentially associated with breast cancer risk [4, 5].

The renin–angiotensin system (RAS) is a hormonal signaling mechanism, which is implicated in the regulation of blood pressure and cardiovascular homeostasis. Angiotensin II (Ang II), the main component of the RAS, is converted from angiotensin I (Ang I) via angiotensin I-converting enzyme (*ACE*). Ang II exerts its physiological effects by binding to two pharmacologically distinct receptors, namely, Ang II type 1 receptor (*AGTR1*) and Ang II type 2 receptor(AGTR2) [6]. Moreover, *AGTR1* is the predominantly subtype to stimulate actions of Ang II on angiogenesis, cell growth, and cell proliferation in tissues, suggesting that the RAS might be involved in carcinogenesis [7].

The *ACE* gene, located on chromosome 17q23, contains many polymorphisms. The 287-bp Alu insertion/deletion (I/D) polymorphism in intron 16 and the A240T polymorphism in the 5′-flanking region (two polymorphisms are in tight linkage disequilibrium), are the most studied polymorphisms and have been related to ACE levels [8]. Experimental studies showed that Ang II exerted pro-mitotic, pro-proliferative and angiogenic effects [9], and *ACE* inhibitor could lower the risk of breast cancer in women, although the results have been inconsistent [10]. The angiotensinogen (*AGT*) gene (located on 1q42-43) includes one polymorphism M235T which results from a T/C transition in exon 2. *AGT* has two opposite properties, which could either benefit women through inhibiting cell proliferation or increase breast cancer risk by raising Ang II level which promotes angiogenic activity [11, 12]. The A1166C polymorphism with A/C transversion at position 1166 in the 3′untranslated region of *AGTR1* gene (located on 3q23) has been extensively studied in various diseases, especially for blood pressure [13].

So far, several studies have explored the association between the polymorphisms of RAS genes and breast cancer risk; however, the conclusions are inconsistent [14–25]. Taking *ACE* I/D polymorphism, for an example, several studies reported that D allele was positively [15, 20, 21, 23] or reversely [16] associated with breast cancer risk, while others showed no significant association [24]. The discrepancies may be due to many reasons, such as insufficient statistical power, recruitment procedures of the study population, and differences in the genetic and environmental backgrounds. Meta-analysis is a useful method to overcome the disadvantages of individual studies by increasing the statistical power. In this study, we performed a meta-analysis to assess the association between polymorphisms of RAS genes and breast cancer risk.

Materials and methods

Literature and search strategy

We searched the literature databases including PubMed (1950–2010), ISI web of science (1975–2010), and Embase (1966–2010).

The search strategy to identify all possible studies involved using combinations of the following key words: ("renin–angiotensin system" or "RAS" or "angiotensin-converting enzyme" or "ACE" or "Angiotensin II type 1 receptor" or "AGTR1" or "angiotensinogen" or "AGT") and ("polymorphism" or "variant") and ("breast cancer"). The reference lists of reviews and retrieved articles were hand-searched. Supplementary data were searched for missing data points. All searches were limited to studies published in English. If more than one article were published using the same case series, only the study with largest sample size was selected. The literature search was updated on December 10, 2010.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluating the association between *ACE* I/D, *ACE* A240T, *AGTR1* A1166C or *AGT* M235T polymorphism and the risk of breast cancer; (2) case–control or cohort design; and (3) sufficient data for calculation of odds ratio (OR) with confidence interval (CI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity; (5) source of control subjects; (6) numbers of cases and controls; and (7) numbers of genotypes for four polymorphisms in cases and controls. Two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements, and reached a consistent decision.

Statistical analysis

The association between four polymorphisms of RAS genes and the risk of breast cancer was estimated by calculating pooled OR and 95% CI. The significance of the pooled OR was determined by Z test ($P < 0.05$ was considered statistically significant). The Q test was performed to evaluate whether the variation was due to heterogeneity or by chance. A random- (DerSimonian–Laird method [26]) or fixed-(Mantel–Haenszel method [27]) effects model was used to calculate pooled effect estimates in the presence

($P \leq 0.10$) or absence ($P > 0.10$) of heterogeneity, respectively. Subgroup analyses were performed by ethnicity. Sensitivity analysis was performed to evaluate the stability of the results by removing the studies not in Hardy–Weinberg equilibrium. Publication bias was assessed by Egger's test [28] ($P < 0.05$ was considered statistically significant). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of studies

The literature search identified a total of 77 potential relevant articles (Fig. 1). Of these, 65 were excluded because of obvious irrelevance by reading their titles and abstracts. Thus, 12 articles met the inclusion criteria. However, the study by Koh et al. [14] was excluded because of examining the associations of three *AGR1* polymorphisms (namely A168G, C535T, and T825A) rather than A1166C polymorphism. The three pairs of articles [15, 17–21] contained the overlapping data, and then the article by Yuan et al. [17] was excluded because of lacking data for calculation of OR with 95% CI; the other two articles by González-Zuloeta Ladd et al. [18] and Yaren et al. [19] were excluded as reporting relatively small sample size. In addition, since the article by Haiman et al. [16] included four case–control studies with different ethnic/racial groups, they were regarded as separate studies in the following meta-analysis. Thus, ten studies [15, 16, 20–24] on *ACE* I/D polymorphism, six studies [15, 16, 23] on *ACE* A240T polymorphism, three studies [22–24] on *AGTR1* A1166C polymorphism, and two studies [23, 25] on *AGT* M235T polymorphism were included in the final meta-analyses. Of these studies, seven were on Caucasians [16, 20–24], two were on Asians [15, 16], and one was on Africans [16] for I/D polymorphism; three were on Caucasians [16, 23], two were on Asians [15, 16], and one was on Africans [16] for A240T polymorphism; all three studies [22–24] were on Caucasians for *AGTR1* A1166C polymorphism; all two studies [23, 25] were on Caucasians for *AGT* M235T polymorphism. Genotype distributions in the controls of all studies were in HWE except for two studies [20, 22] for I/D polymorphism, one study [15] for A240T polymorphism and one study [22] for AGTR1 A1166C polymorphism. The characteristics of the included studies are listed in Table 1.

Quantitative data synthesis

For *ACE* I/D polymorphism, eleven studies consisted of 1,650 cases and 9,283 controls were identified. Overall, the results showed no significant association between I/D polymorphism and breast cancer risk (for DD vs. II: OR = 1.22, 95% CI 0.81–1.84; for ID vs. II: OR = 0.85, 95% CI 0.69–1.05; for dominant model: OR = 0.97, 95% CI 0.76–1.22; for recessive model: OR = 1.32, 95% CI 0.86–2.04) (Table 2). In the subgroup analysis by ethnicity, no significant association was observed in all genetic models except for the association in Africans (the statistically significant association for *ACE* I/D polymorphism in Africans derived from only one study) (Table 2). Sensitivity analysis was performed after excluding the two studies by Yaren et al. [20] and Alves Corrêa et al. [22] deviated from HWE, and the results were not materially altered for I/D polymorphism in either genetic model (Table 2).

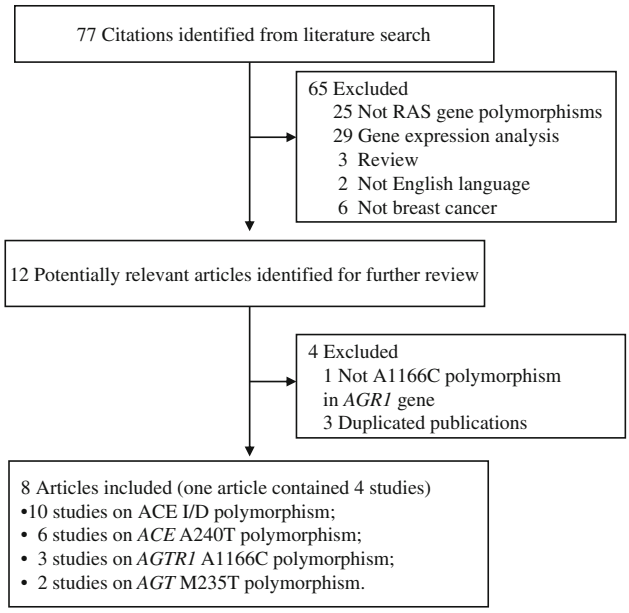

Fig. 1 Flow chart of meta-analysis

For *ACE* A240T polymorphism, six studies comprised 1,316 cases and 2,632 controls were identified. Overall, the results showed no significant association between A240T polymorphism and breast cancer risk (for co-dominant model: TT vs. AA: OR = 1.06, 95% CI 0.73–1.55, AT vs. AA: OR = 1.03, 95% CI 0.89–1.20; for dominant model: OR = 1.04, 95% CI 0.90–1.19; for recessive model: OR = 1.05, 95% CI 0.73–1.52) (Table 3). In the subgroup analysis by ethnicity, no significant association was observed in all genetic models except for the association in Africans (the statistically significant association for *ACE* A240T polymorphism in Africans derived from only one study) (Table 3). Sensitivity analysis excluding the study by Koh et al. [15] not in HWE further confirmed the null association (Table 3).

For *AGTR1* A1166C polymorphism, three studies comprised 235 cases and 601 controls were identified. Significant association between A1166C polymorphism and breast cancer risk was observed for AC versus AA and

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Daily alcohol consumption (Yes, %)		Family history of cancer (Yes, %)		Sources		Genotype distribution						P^{a}_{HWE}
								Cases	Controls	Cases			Controls			
				Cases	Controls	Cases	Controls			11	12	22	11	12	22	
ACE I/D polymorphism																
Koh et al. [15]	2003	Singapore	Asian	2.12	1.19	2.12	1.19	PB	PB	59	46	19	205	220	39	0.060
Haiman et al. [16][b]	2003	USA	African	3.60	1.49	8.27	1.78	PB	PB	62	118	77	100	310	221	0.614
Haiman et al. [16][b]	2003	USA	Asian	1.40	0.70	5.03	2.56	PB	PB	119	128	37	154	160	43	0.884
Haiman et al. [16][b]	2003	USA	Caucasian	1.84	0.85	6.25	1.42	PB	PB	73	127	49	189	301	162	0.055
Haiman et al. [16][b]	2003	USA	Caucasian	6.20	3.90	4.22	1.95	PB	PB	79	129	84	91	187	124	0.204
Yaren et al. [20]	2007	Turkey	Caucasian	NA	NA	NA	NA	HB	HB	2	24	31	7	12	33	0.005
Van der Knaap et al. [21]	2008	Netherlands	Caucasian	NA	NA	NA	NA	PB	PB	32	67	54	1,332	3,006	1,677	0.828
Alves Corrêa et al. [22]	2009	Brazil	Caucasian	NA	NA	NA	NA	HB	HB	20	20	61	53	113	141	0.001
Mendizábal-Ruiz et al. [23]	2010	Mexico	Caucasian	NA	NA	NA	NA	HB	PB	4	6	53	74	151	63	0.395
Namazi et al. [24]	2010	Iran	Caucasian	NA	NA	NA	NA	HB	PB	8	42	20	7	34	29	0.514
ACE A240T polymorphism																
Koh et al. [15]	2003	Singapore	Asian	2.12	1.19	2.12	1.19	PB	PB	54	49	21	201	230	43	0.046
Haiman et al. [16][b]	2003	USA	African	3.60	1.49	8.27	1.78	PB	PB	90	116	42	280	276	78	0.435
Haiman et al. [16][b]	2003	USA	Asian	1.40	0.70	5.03	2.56	PB	PB	125	159	43	155	180	56	0.748
Haiman et al. [16][b]	2003	USA	Caucasian	1.84	0.85	6.25	1.42	PB	PB	124	109	17	312	267	78	0.076
Haiman et al. [16][b]	2003	USA	Caucasian	6.20	3.90	4.22	1.95	PB	PB	129	128	48	161	195	70	0.400
Mendizábal-Ruiz et al. [23]	2010	Mexico	Caucasian	NA	NA	NA	NA	HB	PB	28	31	3	29	18	3	0.926
AGTR1 A1166C polymorphism																
Alves Corrêa et al. [22]	2009	Brazil	Caucasian	NA	NA	NA	NA	HB	HB	65	31	5	157	135	15	0.037
Mendizábal-Ruiz et al. [23]	2010	Mexico	Caucasian	NA	NA	NA	NA	HB	PB	44	17	3	121	83	20	0.296
Namazi et al. [24]	2010	Iran	Caucasian	NA	NA	NA	NA	HB	PB	40	30	0	38	28	4	0.694
AGT M235T polymorphism																
González-Zuloeta Ladd et al. [25][c]	2007	Netherlands	Caucasian	NA	NA	NA	NA	PB	PB	NA	NA	NA	NA	NA	NA	NA
Mendizábal-Ruiz et al. [23]	2010	Mexico	Caucasian	NA	NA	NA	NA	HB	PB	21	17	12	75	118	31	0.151

11, 12, and 22 represent homozygote for non-risk alleles, heterozygote, and homozygote for risk alleles, respectively

PB population-based; *HB* hospital-based; *NA* not available

[a] *P* for Hardy–Weinberg equilibrium test in controls

[b] They were different case–control studies in one publication

[c] This study did not provide the exact frequencies of genotypes in both cases and controls, and it just presented odds ratio with 95% confidence interval for MM versus TT + MT, which was 1.4 (1.1–1.9)

dominant model. However, after excluding the study by Alves Corrêa et al. [22] not in HWE, the association disappeared for AC versus AA and dominant model; while a marginally significant association was observed for CC versus AA (OR = 0.31, 95% CI 0.10–0.99) (Table 4).

For *AGT* M235T polymorphism, two studies comprised 273 cases and 3,547 controls were identified. As the study by González-Zuloeta Ladd [25] did not present the exact frequencies of genotypes in both cases and controls, and it just presented OR with 95% CI for MM versus MT + TT, which was 1.4 (1.1–1.9), thus, we calculated the summary OR with 95% CI under recessive model. There was significant association between M235T polymorphism and breast cancer risk (OR = 1.45, 95% CI 1.12–1.88).

Publication bias

Egger's test was performed to assess potential publication bias for *ACE* I/D polymorphism. No publication bias was detected among the included studies ($P = 0.07$ in homozygous

Table 2 Summary ORs and 95% CIs of the association between ACE I/D polymorphism and breast cancer risk

Genetic models	Ethnicity	No. of studies	OR	95% CI	Statistical model	I^2 (%)	P^a
Co-dominant model							
DD vs. II	Caucasian	7	1.40	0.80–2.48	Random	81.9	0.000
	Caucasian[b]	5	1.37	0.67–2.82	Random	87.2	0.000
	Asian	2	1.30	0.88–1.93	Fixed	5.9	0.303
	African	1	0.56	0.37–0.85	–	–	–
	All	10	1.22	0.81–1.84	Random	79.5	0.000
ID vs. II	Caucasian	7	0.91	0.66–1.23	Random	43.8	0.099
	Caucasian[b]	5	0.94	0.76–1.16	Fixed	0.0	0.787
	Asian	2	0.91	0.70–1.18	Fixed	38.6	0.202
	African	1	0.61	0.42–0.90	–	–	–
	All	10	0.85	0.69–1.05	Random	43.0	0.071
Dominant model	Caucasian	7	1.11	0.79–1.55	Random	59.8	0.021
	Caucasian[b]	5	1.10	0.75–1.60	Random	65.1	0.022
	Asian	2	0.98	0.76–1.25	Fixed	0.0	0.469
	African	1	0.59	0.41–0.85	–	–	–
	All	10	0.97	0.76–1.22	Random	59.4	0.008
Recessive model	Caucasian	7	1.40	0.76–2.61	Random	92.0	0.000
	Caucasian[b]	5	1.53	0.68–3.44	Random	94.3	0.000
	Asian	2	1.35	0.94–1.96	Fixed	57.6	0.125
	African	1	0.79	0.58–1.09	–	–	–
	All	10	1.32	0.86–2.04	Random	89.2	0.000

[a] P value for heterogeneity based on Q test

[b] Results after the two studies by Yaren et al. [20] and Alves Corrêa et al. [22] deviated from Hardy–Weinberg equilibrium were excluded

co-dominant genetic model; $P = 0.66$ in heterozygous co-dominant genetic model; $P = 0.09$ in dominant genetic model; and $P = 0.22$ in recessive genetic model). We did not assess the publication bias for *ACE* A240T, *AGTR1* A1166C, or *AGT* M235T polymorphism based on the knowledge of Cochrane Handbook for Systematic Reviews of Interventions (www.cochranehandbook.org) which states that the test for publication bias yields unreliable results when less than 10 studies are included in a meta-analysis.

Discussion

To the best of our knowledge, this study represents the first meta-analysis of the association between polymorphisms of RAS genes (*ACE* I/D, *ACE* A240T, *AGTR1* A1166C, and *AGT* M235T polymorphisms) and breast cancer risk. The findings suggested that *ACE* I/D and A240T polymorphisms were not likely to be implicated in the development of breast cancer among Caucasians and Asians, except for Africans; while *AGTR1* A1166C and *AGT* M235T polymorphisms might play a role in breast cancer risk among Caucasians. However, the conclusions should be made with caution because of the limited sample size, especially for the statistically significant association for *ACE* I/D and A240T polymorphisms in Africans.

Many studies supported that the RAS had an important role in the regulation of cell proliferation, angiogenesis, and inflammation [29], suggesting that RAS genes might be implicated in the carcinogenesis [7]. Up to now, *ACE* I/D is the exclusively studied polymorphism which might be related to breast cancer risk, while with conflicting results. Koh et al. [15] first reported that women with I allele had decreased risk of breast cancer in Chinese (ID + II vs. DD: OR = 0.54, 95% CI 0.29–0.99). Since then, several other studies were published. The study by Yaren et al. [20] showed that compared with II genotype, ID genotype was more commonly observed in breast cancer patients in Turk population($P = 0.03$). A prospective study conducted in Netherlands also demonstrated that DD genotype carriers had an increased risk of breast cancer compared with those with II/ID genotypes (hazard ratio = 1.47, 95% CI 1.05–2.04) [21]. More recently, the study by Mendizábal-Ruiz et al. [23] reported D allele was strongly associated with breast cancer risk (ID + DD vs. II: OR = 5.10, 95% CI 1.79–14.52). Contrary to these findings, in a multiethnic cohort study which included African Americans, Japanese, Latinas, and whites, women

Table 3 Summary ORs and 95% CIs of the association between ACE A240T polymorphism and breast cancer risk

Genetic models	Ethnicity	No. of studies	OR	95% CI	Statistical model	I^2 (%)	P^a
Co-dominant model							
TT vs. AA	Caucasian	3	0.73	0.52–1.02	Fixed	0.0	0.434
	Asian	2	1.28	0.68–2.40	Random	64.2	0.095
	Asian[b]	1	0.95	0.60–1.51	–	–	–
	African	1	1.68	1.07–2.61	–	–	–
	All	6	1.06	0.73–1.55	Random	63.2	0.018
AT vs. AA	Caucasian	3	0.97	0.78–1.20	Fixed	43.6	0.170
	Asian	2	0.98	0.76–1.26	Fixed	28.5	0.237
	Asian[b]	1	1.10	0.80–1.51	–	–	–
	African	1	1.31	0.95–1.80	–	–	–
	All	6	1.03	0.89–1.20	Fixed	33.6	0.184
Dominant model	Caucasian	3	0.92	0.75–1.12	Fixed	31.3	0.233
	Asian	2	1.02	0.80–1.30	Fixed	0.0	0.677
	Asian[b]	1	1.06	0.79–1.43	–	–	–
	African	1	1.39	1.03–1.88	–	–	–
	All	6	1.04	0.90–1.19	Fixed	38.5	0.149
Recessive model	Caucasian	3	0.77	0.56–1.05	Fixed	24.6	0.265
	Asian	2	1.33	0.60–2.96	Random	80.4	0.024
	Asian[b]	1	0.91	0.59–1.39	–	–	–
	African	1	1.45	0.97–2.18	–	–	–
	All	6	1.05	0.73–1.52	Random	65.0	0.014

[a] P value for heterogeneity based on Q test

[b] Results after the study by Koh et al. [15] deviated from Hardy–Weinberg equilibrium were excluded

Table 4 Summary ORs and 95% CI of the association between AGTR1 A1166C polymorphism and breast cancer risk

Genetic models	Ethnicity	No. of studies	OR	95% CI	Statistical model	I^2 (%)	P^a
Co-dominant model							
CC vs. AA	Caucasian	3	0.50	0.23–1.06	Fixed	0.0	0.378
	Caucasian[b]	2	0.31	0.10–0.99	Fixed	0.0	0.403
AC vs. AA	Caucasian	3	0.64	0.46–0.89	Fixed	12.3	0.320
	Caucasian[b]	2	0.73	0.46–1.16	Fixed	36.6	0.209
Dominant model	Caucasian	3	0.62	0.45–0.86	Fixed	0.0	0.483
	Caucasian[b]	2	0.66	0.43–1.03	Fixed	21.1	0.260
Recessive model	Caucasian	3	0.59	0.28–1.26	Fixed	17.6	0.297
	Caucasian[b]	2	0.36	0.12–1.13	Fixed	0.0	0.332

[a] P value for heterogeneity based on Q test

[b] Results after the study by Alves Corrêa et al. [22] deviated from Hardy–Weinberg equilibrium were excluded

with the II genotype was found to have a marginally significant increase in breast cancer risk (II vs. DD: OR = 1.30, 95% CI 1.05–1.61) [16]. Another study showed ID genotype carriers were 3.1 times less likely to develop breast cancer than those with II/DD genotypes in Brazilians [22]. However, recently, one study in Iranian population, suggested that I/D polymorphism had no effect on breast cancer risk ($P = 0.15$) [24]. Our present meta-analysis suggested that *ACE* I/D polymorphism might not be a strong predictor of breast cancer risk. A recent meta-analysis of the association between *ACE* I/D polymorphism and cancer risk also showed that there was no statistically significant association between this polymorphism and breast cancer risk in all combined populations ($P > 0.05$),

although a statistically significant association was observed in all postmenopausal women based on only two published studies ($P < 0.05$) [30].

So far, there are only three studies [22–24] that have evaluated the association between *AGTR1* A1166C polymorphisms and breast cancer, but also yielded inconsistent results. Our meta-analysis showed that CC homozygote might be a protective factor of breast cancer development in Caucasians (CC vs. AA: OR = 0.31, 95% CI 0.10–0.99). However, a recent meta-analysis showed that *AGTR1* A1166C allele conferred an increased risk of hypertension (OR = 1.14; 95% CI 1.00–1.30). Therefore, further studies are necessary to explore the association with breast cancer risk for this polymorphism. Other polymorphisms in *AGTR1* with breast cancer risk have also been investigated. Three polymorphisms (A168G, C535T, and T825A) in the 5′ region were found positively to be associated breast cancer in a Chinese population [14], while C573T polymorphism was not significantly associated with increased breast cancer risk in a Caucasian population [25].

For *AGT* M235T polymorphism, González-Zuloeta Ladd et al. [25] reported that MM genotype carriers had higher risk of developing breast cancer (MM vs. MT + TT: OR = 1.4, 95% CI 1.1–1.9), while Mendizábal-Ruiz et al. [23] did not found significant association (MM vs. MT + TT: OR = 1.97, 95% CI 0.87–4.42). Further combined results yielded positive associations, suggesting that *AGT* M235T polymorphism might be implicated in the development of breast cancer.

In addition, there are several studies investigating the association between *ACE* gene polymorphism and risk of other cancers, such as gastric cancer [31–34], colorectal cancer [21, 35–37], lung cancer [21, 38, 39], and prostate cancer [21, 40–42]. The results have also been inconsistent. Besides breast cancer, the disparate findings for various cancers could be partly explained by the gene–gene/environment interactions. It is well accepted that dietary and other environmental factors (e.g., use of ACE inhibitor and green tea intake) could influence the association between RAS genes and breast carcinogenesis [14, 17]. In addition, difference in linkage disequilibrium between populations might also explain the conflicting associations [16].

The current meta-analysis has some advantages compared to other individual studies; however, it does have some limitations. First, the present meta-analysis was based primarily on unadjusted effect estimates and CIs (since most studies did not provide the adjusted OR and 95% CI controlling for potential confounding factors), so the effect estimates were relatively imprecise. Second, the effect of gene–gene/gene–environment interactions was not addressed in this meta-analysis. Third, the results of subgroup analysis should be interpreted with caution because of limited statistical power. Fourth, the potential publication bias was not assessed for *ACE* A240T, *AGTR1* A1166C, or *AGT* M235T polymorphism because of limited number of studies. Thus, we can not exclude the possibility of publication bias for these polymorphisms.

In summary, ACE gene I/D and A240T polymorphisms might not be a good predictor of breast cancer risk, while *AGTR1* A1166C and *AGT* M235T polymorphisms might be implicated in the pathogenesis of breast cancer. However, given the limited data, it is not possible to draw conclusions on the exact risk of breast cancer associated with RAS genes, which warrant further investigation.

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