

Angiotensin Converting Enzyme Insertion/Deletion Polymorphism is Associated with Breast Cancer Risk: A Meta-Analysis

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Abstract

Background: A number of case-control studies were conducted to investigate the association of angiotensin converting enzyme insertion/deletion (ACE I/D) polymorphism with breast cancer. But the results remain controversial. This meta-analysis aims to comprehensively evaluate the association of ACE I/D polymorphism with breast cancer. **Method:** A comprehensive literature search on PubMed, Google Scholar, SCOPUS and ISI Web of Knowledge databases for studies published up to June 01, 2018 was performed. Summary odds ratios (ORs) and 95% confidence intervals (CI) were estimated. Publication bias of literatures was evaluated using funnel plots and Egger's test. **Results:** A total of 20 studies including 2846 breast cancer cases 9299 controls meeting the predefined criteria were involved in the meta-analysis. Overall, the ACE I/D polymorphisms was significantly associated with breast cancer under the allele model (I vs. D: OR= 0.803, 95% CI 0.647-0.996, p=0.046), the homozygote model (II vs. DD: OR= 0.662, 95% CI 0.462-0.947, p=0.024), the heterozygote model (ID vs. DD: OR= 0.707, 95% CI 0.528-0.946, p=0.020), the dominant model (II+ID vs. DD: OR= 0.691, 95% CI 0.507-0.941, p=0.019). In the subgroup analysis by ethnicity, a significant association was found among Asian and Caucasian populations, but not among mixed populations. **Conclusions:** This meta-analysis suggests that ACE I/D polymorphism may be associated with increased risk of breast cancer, especially among Asian and Caucasians. However, well-designed studies with larger sample size and more ethnic groups are needed to further validate the results.

Keywords: Breast cancer- ACE I/D- genetic polymorphism- cancer- Meta-analysis- susceptibility

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Introduction

Breast cancer is the most frequently diagnosed cancer among women, which contributed to 25% of all cancer cases in women worldwide (Nedooshan et al., 2017; Yazdi et al., 2015). The etiology of breast cancer is still not fully understood. It is a heterogeneous disease in regard to its clinical, histological, and molecular profile (Kamali et al., 2017; Kamali et al., 2017). At present, genetic polymorphisms are increasingly recognized as contributors to breast cancer risk. Numerous breast cancer risk factors such as age, age at menarche, age at first childbirth, and number of first-degree female relatives with breast cancer have been identified (Shiryazdi et al., 2015; Shiryazdi et al., 2015). The heritable defects of BRCA1 and BRCA2 are identified in less than 50% of

hereditary breast cancer cases (Forat-Yazdi et al., 2015; Forat-Yazdi et al., 2017; Neamatzadeh et al., 2015). Several epidemiological and molecular studies indicates ACE I/D gene polymorphism as a risk factor involved in the initiation and progression of different disease such as diabetic nephropathy, end-stage renal disease (ESRD) and cancer (Buraczynska et al., 2006; Singh et al., 2018).

The ACE, a zinc metalloenzyme, is a member of renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II (Fagyas et al., 2014). The ACE gene (Gene ID: 1636; also known as: DCP; ACE1; DCP1; CD143) is localized in human chromosomes 17q23, comprises 26 exons, spans about 21 kb and more than 13 polymorphisms in this gene have

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been identified with susceptibility to different disease such as ACE I/D (rs 1799752), A240A>T (rs4291), 2350G>A (rs4344), and 17888C>T (rs4359) (Sayed-Tabatabaei et al., 2006). The ACE insertion/deletion (I/D) polymorphism is a nonsense and 287 bp Alu repeat sequence of DNA in the intron 16 of ACE gene, which represented by “Insertion” or “I”, and absence of the same denotes “Deletion” or “D” (Mahjoub et al., 2016).

To date, several studies have evaluated the association between ACE I/D polymorphism and breast cancer risk. However, the results are inconsistent and inconclusive, with some studies found significant association, while others were not. Although previous meta-analyses has tried to explore the whether the ACE I/D polymorphism is associated with increased risk of breast cancer, recently, new case-control studies in different ethnicities have been published. Therefore, we pooled all eligible studies in the present meta-analysis to evaluate the association of ACE I/D polymorphism with the risk of breast cancer.

Materials and Methods

Search Strategy

Electronic databases of PubMed (Medline), EMBASE and Google Scholar, ISI Web of Knowledge, Chinese National Knowledge Infrastructure database (CNKI), and Chinese Biomedical Literature Database (CBM) were used to identify all studies that evaluate the associations of ACE I/D polymorphism with breast cancer up to June 01, 2018. The key words used for search were: (breast, cancer, carcinoma, tumor, neoplasm, malignancy) and (angiotensin converting enzyme insertion/deletion, ACE I/D) and (polymorphism, mutation, variant, SNP). In addition, we have hand searched reference list of all eligible studies and related reviews for additional suitable studies. Studies in English, Persia, chinses and Portuguese languages were included to the meta-analysis. In addition, we have not set any restriction on time period, sample size, and ethnicity.

Data extraction

Two authors reviewed and extracted data independently in accordance with the inclusion criteria. The results were compared, and if any disagreement appeared, a third investigator was invited to evaluate such studies, and then the discrepancy was resolved by discussion. The following data were extracted: the name of first author, year of publication, country, ethnicity, sample size, allele numbers and genotype distributions in cases and controls, and the results of Hardy-Weinberg equilibrium (HWE) test.

Inclusion and exclusion criteria

The studies included in this meta-analysis had to meet the following criteria: (1) only case-control or cohort studies; (2) evaluation of the ACE I/D polymorphism and breast cancer risk; (3) provided sufficient genotyping data to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). On the other side, the major reasons for study exclusion were: (1) studies were not relevant to ACE I/D polymorphism or breast cancer; (2) studies did not report genotype frequencies; (3) case only studies and

control group including malignant tumor patients; (4) the design were based on sibling pairs or linkage studies; (5) reviews, case reports, abstracts, posters, letter and animal studies; and (6) overlapped or duplicated publications. When, more than one of the same populations was included in several studies, the most recently published study or the largest study with extractable data was selected. If original necessary data were unavailable in the selected studies, we have sent a request to the corresponding author for additional data.

Statistical analysis

Pooled ORs with corresponding 95% CIs were calculated to evaluate the association between ACE I/D polymorphism and breast cancer risk. We have used the Z-test to assess the significance of the pooled OR, in which $P < 0.05$ was considered as statistically significant. Pooled ORs was calculated under the following five genetic models: the allele model (I vs. D), the homozygote model (II vs. DD), the heterozygote model (ID vs. DD), the dominant model (II+ID vs. DD), and the recessive model (II vs. ID+DD). The Q-test was used to evaluate between-study heterogeneity, was considered significant when $p\text{-value} < 0.05$. Additionally, the I² statistics was used to quantify or describe the percentage of between-study heterogeneity, which was considered as significant when $I^2 > 50\%$ ($I^2 < 25\%$ indicating low heterogeneity; 25%-50% indicating moderate heterogeneity; and $> 50\%$ indicating high heterogeneity) (Sobhan et al., 2018; Yazdi et al., 2017). Therefore, a fixed-effects model (the Mantel-Haenszel method) as used to calculate pooled OR in the absence of heterogeneity (Mantel and Haenszel, 1959). Otherwise, the random-effects model (the DerSimonian and Laird method) was used (DerSimonian and Laird 1986). The control genotypes were tested for Hardy-Weinberg equilibrium (HWE) using the Goodness of fit Chi-square test. The heterogeneity was adjusted by subgroup analysis and meta-regression. Sensitivity analyses were conducted to evaluate the effect of individual study on pooled ORs and assess the stability of results. The evidence of potential publication bias was evaluated by the funnel plot and Egger's test, in which $P < 0.01$ was considered as statistically significant. In addition, publication bias was assessed using visual inspection an asymmetric plot (Begg and Mazumdar, 1994; Egger et al., 1997). When publication bias observed, the Duval and Tweedie non-parametric “trim and fill” method was applied to adjust for it. The Comprehensive Meta-Analysis (CMA) Version 2.2 software program (Biostat, USA) was used to perform all statistical analysis, and all the P values were two sided.

Results

According to the present meta-analysis selection criteria, a total of 127 articles were retrieved by literatures search of online databases and hand searching. After review of titles and abstracts, 139 publications were excluded because were reviews, duplication and overlapping data, non-case-control studies, not relevant to ACE I/D polymorphism and breast cancer risk. Finally,

Table 1. Characteristics of the Studies Included in the Meta-analysis

First Author	Country	Ethnicity	Case	Control	Cases					Control					HWE
					Genotypes			Alleles		Genotypes			Alleles		
					DD	ID	II	D	I	DD	ID	II	D	I	
Koh 2003	Singapore	Asian	182	643	23	80	79	126	238	56	305	282	417	869	0.036
Haiman 2003a		African Americans	257	631	77	118	62	272	242	221	310	100	752	510	0.614
Haiman 2003b	Japan	Asian	284	357	37	128	119	202	366	43	160	154	246	460	0.884
Haiman 2003c		Mixed	249	652	49	127	73	225	273	162	301	189	463	679	0.055
Haiman 2003d		Caucasians	292	402	84	129	79	297	287	124	187	91	435	369	0.204
Ladd 2005	Netherlands	Caucasians	114	4203	37	55	22	129	99	1133	2192	878	4458	3948	0.002
Yaren 2006	Turkey	Caucasians	44	46	25	17	2	67	21	28	12	6	68	24	0.028
Yaren 2007	Turkey	Caucasians	57	52	31	24	2	85	28	33	12	7	78	26	0.005
Van der 2008	Netherlands	Caucasians	153	655	54	67	32	175	131	185	329	141	699	470	0.815
Alves Corrêa 2009	Brazil	Mixed	101	307	61	20	20	142	60	141	113	53	395	219	≤0.001
Namazi 2010	Iran	Asian	70	70	20	42	8	82	58	29	34	7	92	48	0.514
Siddiqi 2010	India	Asian	130	228	62	43	25	167	93	96	107	25	299	157	0.552
Mendizábal-Ruiz 2011	Mexico	Mixed	63	288	53	6	4	112	14	63	151	74	277	299	0.394
Felipe 2011	Colombia	Mixed	50	50	10	23	17	43	57	10	24	16	44	56	0.854
Fishchuk 2013	Ukraine	Caucasians	131	102	41	53	37	135	127	21	50	31	92	112	0.918
Xiaomei 2014	China	Asian	123	72	61	32	30	154	92	36	19	17	91	53	≤0.001
El-Sharkawy 2014	Egypt	African	70	50	29	28	13	86	54	21	21	8	63	37	0.483
Ghosh 2015	India	Asian	108	128	62	28	18	152	64	32	50	46	114	142	0.017
Kumar 2016	India	Asian	213	213	35	86	92	156	270	24	77	112	125	301	0.061
Singh 2018	India	Asian	155	150	86	59	10	231	79	29	74	47	132	168	0.989

HWE, Hardy Weinberg Equilibrium

a total of 20 case-control studies (Alves Corrêa et al., 2009; Felipe et al., 2011; Fishchuk and Gorovenko, 2013; Ghosh Roy et al., 2015; Gonzalez-Zuloeta Ladd et al., 2005; Haiman et al., 2003; van der Knaap et al., 2008; Koh et al., 2003; Kumar et al., 2016; Mendizábal-Ruiz et al., 2011; Namazi et al., 2010; El Sharkawy et al., 2014; Siddiqi et al., 2010; Singh et al., 2018; Xiaomei et al., 2014; Yaren et al., 2007, 2006) were included in our meta-analysis, consisting of 2,846 cases 9,299 controls. The detailed characteristics of the included studies are listed in Table 1. The original populations contain Singapore, Japan, Netherlands, Turkey, Brazil, Iran, India, Mexico, Colombia, Ukraine, china, and Egypt. There were 8 studies of subjects of Asians, 7 studies of subjects of Caucasian descent, 4 studies of subjects with mixed-ethnicity studies, and one study of subjects of African descent. All the genotype distributions of control subjects were in agreement with HWE for ACE I/D polymorphism except for 7 case-control studies (Table 1).

Quantitative Data Synthesis

In the overall analysis, statistically significant association between ACE I/D polymorphism and breast cancer susceptibility was observed under the allele model (I vs. D: OR= 0.803, 95% CI 0.647-0.996, p=0.046, Figure 1A), the homozygote model (II vs. DD: OR=0.662, 95% CI 0.462-0.947, p=0.024), the heterozygote model (ID vs. DD: OR= 0.707, 95% CI 0.528-0.946, p=0.020), the dominant model (II+ID vs. DD: OR= 0.691, 95% CI 0.507-0.941, p=0.019), but not under the recessive model (II vs. ID+DD: OR=0.841, 95% CI 0.663-1.067, p=0.154, Figure 1B). When stratified, the association between ACE

I/D polymorphism and breast cancer risk was observed among Asian populations under the heterozygote model (ID vs. DD: OR= 0.655, 95% CI 0.436-0.984, p=0.041) and Caucasian populations under the allele model (I vs. D: OR= 1.115, 95% CI 1.002-1.241, p=0.046), but not among mixed populations. In the subgroup analysis by studies quality (fulfilling HWE or not), a significant association between the ACE I/D polymorphism and breast cancer risk was observed under the heterozygote model (ID vs. DD: OR= 0.656, 95% CI 0.454-0.946, p=0.024).

Heterogeneity Test

We observed high to extreme heterogeneities under all genetic model including the allele model (I vs. D: I²= 88.84% and PH≤0.001), the homozygote model (II vs. DD: I²= 83.10% and PH≤0.001), the heterozygote model (ID vs. DD: I²= 81.79% and PH≤0.001), the dominant model (II+ID vs. DD: I²= 86.52% and PH≤0.001), and the recessive model (II vs. ID+DD: I²= 74.01% and PH≤0.001, Table 2). In the subgroup analysis by ethnicity, results were similar in the Asians and mixed population. While, in the Caucasians, between study heterogeneity was significantly reduced under the allele model (I vs. D: I²= 51.31% and PH=0.055), the heterozygote model (ID vs. DD: I²= 47.68% and PH=0.075), and the dominant model (II+ID vs. DD: I²= 46.81% and PH=0.080).

Sensitivity Analysis

To evaluate the robustness of the association results, a meta-analysis was performed repeatedly with each study removed. The results indicated that

Table 2. Summary Risk Estimates for Association between ACE I/D Polymorphism and Risk of Breast Cancer

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio (OR)					Publication Bias	
			I ² (%)	P _H	OR	95% CI	Z _{OR}	P _{OR}	P _{Beggs}	P _{Eggers}	
Overall	I vs. D	Random	88.84	≤0.001	0.803	0.647-0.996	-1.992	0.046	0.035	0.048	
	II vs. DD	Random	83.10	≤0.001	0.662	0.462-0.947	-2.256	0.024	0.030	0.024	
	ID vs. DD	Random	81.79	≤0.001	0.707	0.528-0.946	-2.332	0.020	0.528	0.233	
	II+ID vs. DD	Random	86.52	≤0.001	0.691	0.507-0.941	-2.348	0.019	0.363	0.157	
	II vs. ID+DD	Random	74.01	≤0.001	0.841	0.663-1.067	-1.427	0.154	0.234	0.048	
By Ethnicity											
Asian	I vs. D	Random	90.25	≤0.001	0.735	0.512-1.055	-1.668	0.095	0.710	0.606	
	II vs. DD	Random	86.73	≤0.001	0.578	0.303-1.103	-1.663	0.096	0.710	0.657	
	ID vs. DD	Random	74.70	≤0.001	0.655	0.436-0.984	-2.040	0.041	0.265	0.494	
	II+ID vs. DD	Random	84.71	≤0.001	0.628	0.388-1.015	-1.899	0.058	0.536	0.705	
	II vs. ID+DD	Random	82.10	≤0.001	0.739	0.483-1.131	-1.394	0.163	0.265	0.513	
Caucasian	I vs. D	Fixed	51.31	0.055	1.115	1.002-1.241	1.992	0.046	0.133	0.232	
	II vs. DD	Random	62.26	0.014	0.913	0.620-1.343	-0.462	0.644	0.367	0.064	
	ID vs. DD	Fixed	47.68	0.075	0.925	0.778-1.099	-0.885	0.376	1.000	0.587	
	II+ID vs. DD	Fixed	46.81	0.080	0.964	0.821-1.132	-0.443	0.658	0.548	0.800	
	II vs. ID+DD	Random	54.24	0.041	1.044	0.772-1.414	0.282	0.778	0.035	0.018	
Mixed	I vs. D	Random	94.34	≤0.001	0.582	0.262-1.293	-1.329	0.184	0.308	0.299	
	II vs. DD	Random	88.51	≤0.001	0.562	0.195-1.618	-1.068	0.286	0.734	0.308	
	ID vs. DD	Random	91.16	≤0.001	0.410	0.107-1.564	-1.306	0.192	0.734	0.330	
	II+ID vs. DD	Random	95.17	≤0.001	0.450	0.126-1.611	-1.227	0.220	0.734	0.427	
	II vs. ID+DD	Random	68.67	0.023	0.819	0.466-1.439	-0.694	0.488	0.308	0.422	

the fixed-effect estimates before or after the deletion of any single study were generally similar, suggesting a high stability of the meta-analysis results (data not shown). After excluding studies which not fulfilling HWE the pooled ORs were materially altered under the allele model (I vs. D: OR= 0.814, 95% CI 0.608-1.090, p=0.167), the homozygote model (ID vs. DD: OR= 0.709, 95% CI 0.439-1.147, p=0.161), and the dominant model (II+ID vs. DD: OR= 0.672, 95% CI 0.438-1.029, p=0.064; data not shown). The sensitivity analyses substantially alter the pooled ORs except heterozygote model in overall populations, suggesting that the results of this

meta-analysis were generally robust.

Publication bias

Publication bias were qualitatively assessed by Begg's funnel plot and quantitatively assessed by Egger's test. A significant publication bias was detected by Egger's test under the allele model (P_{Beggs} = 0.035, P_{Eggers} = 0.048, Figure 2), the homozygote model (P_{Beggs} = 0.030, P_{Eggers} = 0.024) and the recessive model (P_{Beggs} = 0.234, P_{Eggers} = 0.048). In the stratified analysis by ethnicity, still obvious publication bias were found among Caucasians under the recessive model (P_{Beggs} = 0.035, P_{Eggers} = 0.018). Thus,

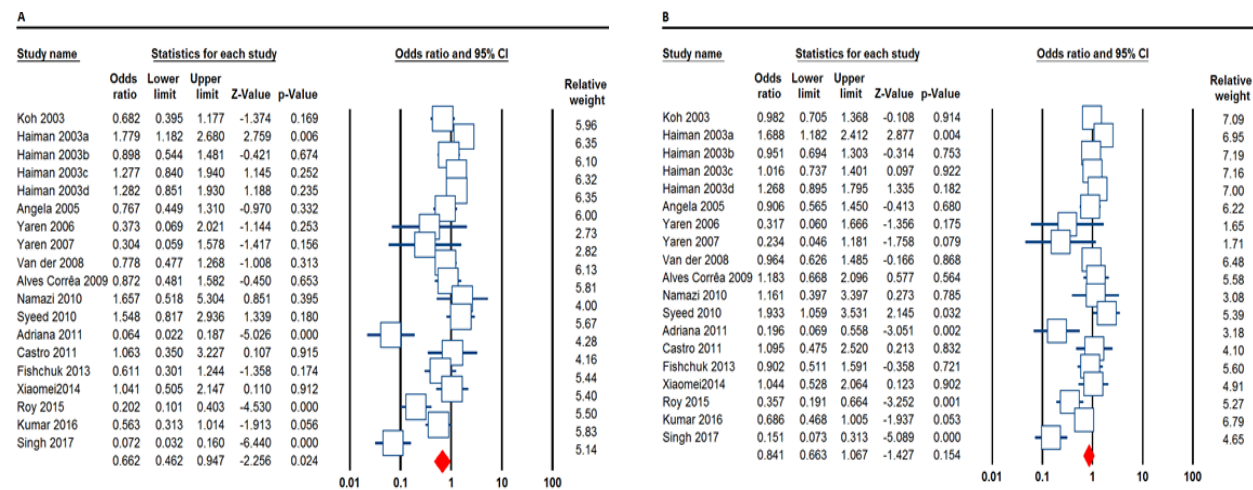


Figure 1. Forest Plots for Association between ACE I/D Polymorphism and Breast Cancer Risk. A, the allele model (I vs. D) and B, the recessive model (II vs. ID+DD).

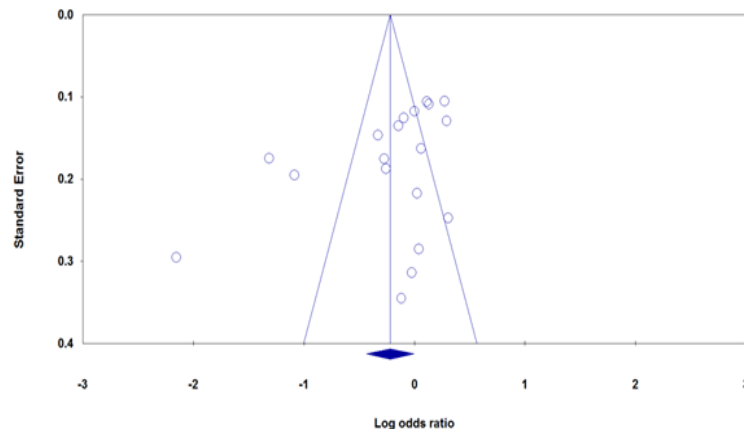


Figure 2. Begg's Funnel Plots for the Association between ACE I/D Polymorphism and Breast Cancer under the Allele Model (I vs. D).

we have repeated meta-analysis with the “trim and fill” method to adjust publication bias under the three genetic models. Adjusting these three genetic models by “trim and fill” method did not influence the conclusion, which indicated the robustness our results (data not shown).

Discussion

ACE is well known to be a key part of the RAS that regulates blood pressure through conversion of the angiotensin I to the angiotensin II by removing the two C-terminal amino acids. The ACE I/D polymorphism, the most widely studied polymorphism within ACE gene, which individuals carrying the D allele have higher ACE activity. Rigat et al has initially detected ACE I/D polymorphism by restriction fragment length polymorphism (RFLP) analysis (Rigat et al., 1990). There have been a few meta-analyses focusing on association of ACE I/D polymorphism with breast cancer risk. However, most of these analyses wrongly not included all published studies and a new meta-analysis is needed to give a comprehensive conclusion due to the increasing data of case-control studies.

This present meta-analysis, including 2846 breast cancer cases and 9,299 controls from 20 case-control studies, explored the association between the ACE I/D polymorphism and breast cancer risk. This is the largest scale meta-analysis so far. Our results suggested that the ACE I/D polymorphism was significantly associated with increased risk of breast cancer. To further elucidate the association between the ACE I/D and the risk of breast cancer, we have performed subgroup analysis. In subgroup analysis by ethnicity, we found a marginal association of ACE I/D and breast cancer among Asian populations under the heterozygote model (ID vs. DD: OR= 0.655, 95% CI 0.436-0.984, p=0.041) and Caucasian populations under the allele model (I vs. D: OR= 1.115, 95% CI 1.002-1.241, p=0.046), but not among mixed populations. The inconsistency of genetic effects across the ethnicities was detected for breast cancer, and it showed that Asian populations had a greater genetic risk in developing depression on account of genetic variation in this locus than White populations. Results of

this meta-analysis indicated that there was a significant association of ACE I/D polymorphism with increased risk of breast cancer. The present meta-analysis results are inconsistent with all previous the meta-analysis (Li et al., 2015; Pei and Li, 2012; Xi et al., 2011; Zhang et al., 2011). The inconsistent results between ours and previous meta-analyses might mainly be due to relevant smaller sample size from previous meta-analyses. Furthermore, most studies included in the present meta-analysis performed among Asians, while previous meta-analyses only had very limited Asian populations.

The great discrepancy among different studies indicated the existence of between-studies heterogeneity and it is generally introduced that meta-analyses should assess heterogeneity (Abedinzadeh et al., 2015; Nedooshan et al., 2017). There are several factors responsible for such heterogeneity such as the study designs, ethnicity of cases and controls, genotyping method, sample size, selection criteria and etc., (Mehdinejad et al., 2017; Sobhan et al., 2017). In the present meta-analysis, there was an extreme heterogeneity ($I^2 = 75\%$ to 100%) under all five genetic models in overall estimations. Thus, we have performed stratified analysis by ethnicity to identify possible sources for the observed heterogeneity. However, after stratified analysis, there were still heterogeneities in Asian and mixed populations.

To our best knowledge, the present meta-analysis is the most comprehensive, latest one and has the largest sample size. Thus, the statistical power of our analyses was noticeably increased as a large sample size pooled from different studies, and has more statistical powerful than any single case-control study and previous meta-analyses. However, the conclusions of this meta-analysis should be interpreted cautiously due to some limitations. First, the number of published studies was not sufficiently large for stratified analyses by ethnicity. Because of limited available data for mixed population and Africans, our results should be interpreted with caution. Therefore, larger studies are required to explore the association ACE I/D polymorphism with susceptibility to the breast cancer in different ethnicities, especially among mixed population and Africans. Second, there was a significant between

study heterogeneity under all five genetic models in overall estimations. One possible reason for such heterogeneity is a wide variation in various included ethnicities. Therefore, we have performed subgroup analysis by ethnicity to eliminate heterogeneity. However, the results showed that the heterogeneity did not reduced or disappeared significantly. Third, there was a significant publication bias under three genetic models which could influence the results of our meta-analysis. However, adjusting pooled ORs for these genetic models by “trim and fill” method did not influence the conclusion, which indicated the robustness our results. Forth, we included only published studies, so there was space for publication bias, which in fact was confirmed by formal statistical tests. Finally, lacking the original data for the included studies limited our further evaluation of potential interactions among gene–gene, gene–environment, or even different polymorphism loci of the ACE gene.

In summary, the present meta-analysis suggested that suggest that the ACE I/D polymorphism is significantly associated with risk of breast cancer. Considering the limited sample size among different ethnicities included in the present meta-analysis, further well-designed and unbiased studies with larger sample studies are needed to confirm our results.

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