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Association between ERα gene Pvu II polymorphism and breast cancer susceptibility

A meta-analysis

Zhen-lian Zhang, MD[a], Cui-zhen Zhang, MD[b], Yan Li, MD[c], Zhen-hui Zhao, MD[c], Shun-e Yang, MD[a,*]

Abstract

Background: Estrogen has played an important role in the development of breast cancer. ER-α PvuII gene polymorphism is in close association with the occurrence risk of breast cancer, but no consensus has been achieved currently.

Methods: PubMed, Embase, China National Knowledge Infrastructure (CNKI) database, Wanfang database, and VIP database were retrieved to collect the case–control studies on association between *ERα* gene Pvu II polymorphism and breast cancer risk published before September 1, 2017. Newcastle–Ottawa Scale (NOS) was used to assess the quality of the literatures, Stata 14.0 software was applied for meta-analysis, and the pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated. The subgroup analysis was performed to assess the confounding factors, followed by assessment of publication bias and sensitivity analysis.

Results: A total of 26 studies were enrolled in the analysis based on inclusion criteria, which included 15,360 patients and 26,423 controls. The results demonstrated that *ERα* gene Pvu II polymorphism was in significant association with the decrease of breast cancer risk in 3 genetic models (C vs T, OR = 0.962, 95% CI = 0.933–0.992, *P* = .012; CC vs TT, OR = 0.911, 95% CI = 0.856–0.969, *P* = .003; CC vs TT/CT, OR = 0.923, 95% CI = 0.874–0.975, *P* = .004). Subgroup analysis was conducted on the basis of ethnicity and source of controls, whose results illustrated that *ERα* gene Pvu II polymorphism was in significant association with the decrease of breast cancer risk in Asians rather than in Caucasians (CC vs TT, OR = 0.862, 95% CI = 0.750–0.922, *P* = .038; CC vs TT/CT, OR = 0.851, 95% CI = 0.755–0.959, *P* = .008). In population-based subgroup rather than in hospital-based subgroup, *ERα* gene Pvu II polymorphism was in significant association with the decrease of breast cancer risk in the allele model, homozygous model, dominant model, and recessive model (C vs T, OR = 0.943, 95% CI = 0.911–0.977, *P* = .001; CC vs TT, OR = 0.878, 95% CI = 0.817–0.944, *P* = .000; CC/CT vs TT, *OR* = 0.936, 95% CI = 0.881–0.994, *P* = .031; CC vs TT/CT, OR = 0.902, 95% CI = 0.847–0.960, *P* = .001).

Conclusion: *ERα* gene Pvu II polymorphism exerts an important function in the progression of breast cancer.

Abbreviations: CBM = China Biomedicine, CI = confidence interval, CNKI = China National Knowledge Infrastructure, ER = estrogen receptors, ERα = estrogen receptor α, ERE = estrogen response element, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, MALDI-TOF = matrix-assisted laser desorption ionization time-of-flight, NOS = Newcastle–Ottawa Scale, OR = odds ratio, PB = population-based study, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SNPs = single nucleotide polymorphisms.

Keywords: breast cancer, *ERα* gene, meta-analysis, polymorphism, Pvu II

1. Introduction

According to the global data statistics on cancer in 2012, breast cancer had become the most common malignancy and the leading cause for cancer-related death in females, and about 1,700,000 had been diagnosed with breast cancer, and 521,900 died of breast cancer annually.[1] In China, new cases with breast cancer account for 15% in females, with morbidity and mortality increasing annually.[2] At present, multiple studies have shown that genetic mutation, menopause status, family history, fertility, alcoholic consumption, smoking, and exposure to estrogen are risk factors for women with breast cancer, and play important roles in the pathogenesis and progression of breast cancer.[3–5]

Estrogens exert great functions in the development and progression of breast cancer, whose effects are mainly mediated by intracellular estrogen receptors (ERs). ER-α and ER-β, 2 types of ER, are important regulators for the actions of estrogens, in which *ER-α* gene can encode a transcription factor with an estrogen response element (ERE) DNA-binding domain and an estrogen-binding domain.[6] *ERα* gene, as a steroid hormone receptor gene, is located in chromosome 6 at 6p25.1, and *ERα* gene mutation can induce cell proliferation, regulate cell apoptosis by affecting protein expression, so as to participate

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[a] Department of Lymphoma, The Third Clinical Medicine College of Xinjiang Medical University, Xinjiang, [b] Department of Medical Laboratory, Chengdu Shuangliu District Maternal and Child Health Hospital, Sichuan, [c] Department of Mastology, The Third Clinical Medicine College of Xinjiang Medical University, Xinjiang, China.

[*] Correspondence: Shun-e Yang, Department of Lymphoma, The Third Clinical Medicine College of Xinjiang Medical University, 789 Suzhou East Road, Xinshi District, Urumqi, Xinjiang 830000, China (e-mail: yangshune@yeah.net).

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in the development and progression of breast cancer.[7] Multiple single nucleotide polymorphisms (SNPs) in ER-α, as located in intron 1 of ER-α, have been studied in numerous clinical studies and have become one of the hot topics on tumor susceptibility, including rs2234693, also termed as *ERα* gene PvuII.[8] ER-α PvuII SNPs have found to be associated with numerous carcinoma included prostate cancer,[9] systemic lupus erythematosus,[10] Alzheimer disease,[11] etc. And ER-α PvuII polymorphisms have been verified to be in close connection with tumorigenesis. It has also been found that ER-α PvuII and Xbal polymorphisms are closely related with breast cancer,[12] in which ER-α PvuII polymorphism is proved to play an important role in breast cancer risk in pre-menopausal females .[13]

Although the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility has been extensively reported currently, there are great differences among study conclusions. Atoum et al[14] did not found any correlation between *ERα* gene Pvu II polymorphism and breast cancer risk in Jordaneses, but some investigators discovered that there was a significant correlation between *ERα* gene Pvu II polymorphism and breast cancer risk in Brazilians and Northern Indians and patients with p allele had lower morbidity of breast cancer.[15,16] Although meta-analysis have been conducted in pre-studies,[13,17–19] there are still new literatures on the association between *ERα* gene Pvu II polymorphism and breast cancer risk published. Considering the timeliness of meta-analysis and to provide a more accurate estimation of the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility, an updated meta-analysis on related case–control studies published in Open Access journals was conducted to further determine the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility by involving as many data as possible from published studies.

2. Materials and methods

2.1. Literature retrieval

Case–control studies on the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility included in medical databases such as PubMed, Embase, China Biomedicine (CBM) database, Wanfang database, VIP database, and China National Knowledge Infrastructure (CNKI) database were retrieved using terms such as "estrogen receptor α," " ERα," "Pvu II," "rs2234693," "polymorphism," "single nucleotide polymorphism," "variation," "breast carcinoma," "breast cancer," and "BC." Simultaneously, references in corresponding literatures included in above databases were retrieved artificially based on the title of the literatures in order to screen more applicable literatures.

2.2. Inclusion and exclusion criteria

Inclusion criteria included studies published in English or Chinese language before September 1, 2017; case–control studies; studies that enrolled healthy populations in the control group; studies with full texts; studies on the distribution frequency of *ERα* gene Pvu II or studies that provided corresponding odds ratio (OR) value with clearly described data; studies focused on the association between breast cancer risk and *ERα* gene Pvu II polymorphism. Exclusion criteria included studies with incomplete data; studies in which patients with fibroadenoma of breast or nonbreast cancer were selected as study subjects; studies that focused on exploring the association between gene polymorphism and other factors such as disease progression, disease severity, phenotype modification, sensitivity to clinical treatment, or survival, etc; studies on family association; and studies in which systematic reviews or meta-analysis were also excluded. In overlapping studies, those with large sample size were selected.

2.3. Data extraction

In this study, the *ERα* gene Pvu II polymorphism in enrolled population was set as the primary index. Two researchers were assigned to collect literatures independently based on above inclusion criteria, exclusion criteria, and data extraction criteria, with following variables extracted from each study: the year of publication, name of the first author, source of the controls, ethnicity of enrolled population, gene detection method, and phenotype distribution data, etc. The disagreement in data extraction should be resolved by discussion or a third-party researcher when necessary. The data involving different ethnicities should be extracted independently based on ethnicity. The ethnicities included in this study contained Caucasians, Asians, and others.

2.4. Quality assessment

The quality of the case–control studies enrolled in this study was assessed by 2 investigators using Newcastle–Ottawa Scale (NOS). Primary contents to be assessed include selection of study subjects (4 scores in total); inter-group comparability (2 scores in total); exposure factors or outcomes (3 scores in total). Low-quality studies: 0 to 4 points; high-quality studies: 5 to 9 points.

2.5. Statistical data analysis

STATA 14.0 software was used to analyze the extracted data. Hardy–Weinberg equilibrium (HWE) analysis was performed using χ^2 test. Allele model, homozygous model, dominant model, and recessive model were used, and pooled OR values and 95% confidence intervals (95% CIs) were used to assess the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility. The heterogeneity was assessed by Q and I^2 statistics. There was no heterogeneity if $P > .1$ or $I^2 < 50\%$, for which fixed-effect model (Mantel–Haenszel method) was used. There was heterogeneity if $P < .1$ and $I^2 > 50\%$, for which random-effect (DerSimonian Laird) model was used for analysis. Subgroup analysis was performed on the basis of ethnicity and source of controls. Funnel plot was applied to detect whether there was publication bias in the enrolled literatures. There was publication bias if the funnel plot was asymmetric. Egger test was adopted to test the severity of publication bias. The stability of results was analyzed and assessed by sensitivity analysis. Two-tailed test was applied, with a $P < .05$ level of significance.

3. Results

3.1. General information of enrolled literatures

A total of 409 articles were retrieved using the keywords, as shown in Fig. 1. A total of 367 articles were excluded according to the titles and abstracts, among which 211 were significantly irrelevant, 146 were overlapped, 5 were reviews, and 5 were animal or cell experiments; 7 were about meta-analysis and 9 were not related with Pvu II polymorphisms. Finally, 26 full-text articles with detailed study information enrolling 15,360 cases and 26,423 controls were obtained. The primary

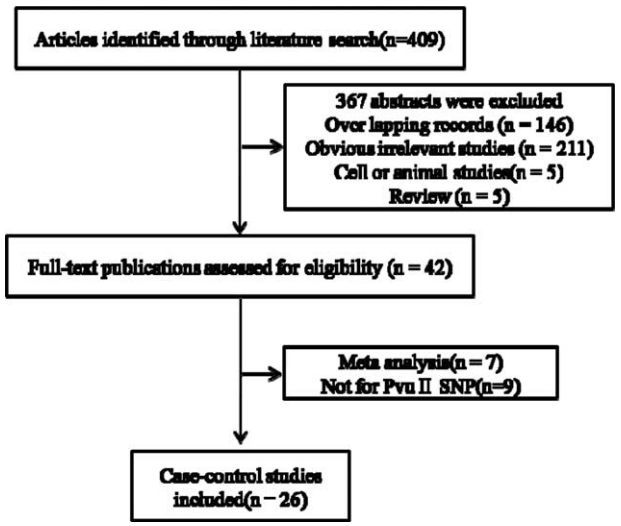

Figure 1. Retrieval flow chart of eligible case–control studies enrolled in the meta-analysis.

information of studies enrolled in this meta-analysis is summarized in Table 1.[20–40]

3.2. Meta-analysis results

The meta-analysis results indicated that a significant association between ERα gene Pvu II polymorphism and the decrease of breast cancer risk was found in allele model, homozygous model, and recessive model (C vs T, OR = 0.962, 95% CI = 0.933–0.992, $P = .012$; CC vs TT, OR = 0.911, 95% CI = 0.856–0.969, $P = .003$; CC vs TT/CT, OR = 0.923, 95% CI = 0.874–0.975, $P = .004$) rather than in dominant model (CC/CT vs TT, OR = 0.970, 95% CI = 0.927–1.015, $P = .187$), as shown in Fig. 2.

Subgroup analysis was conducted based on ethnicity, and the results suggested that in Asians, a significant association between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk was shown in homozygous model and recessive model, whereas in Caucasians, no association was found between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk. In population-based subgroup rather than in hospital-based subgroup, the results of analysis based on the source of healthy controls demonstrated that a significant association between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk was found in allele model, homozygous model, dominant model, and recessive model, as summarized in Table 2.

3.3. Analysis of publication bias and sensitivity

Funnel plot and Egger test were used to analyze the publication bias in above 4 models, but no significant publication bias was found, as shown in Fig. 3A and B. The Egger results were C vs T: $t = 0.71$, $P = .487$; CC vs TT: $t = 0.56$, $P = .582$; CC/CT vs TT: $t = 0.74$, $P = .465$; CC vs TT/CT: $t = 0.53$, $P = .601$. The sensitivity analysis also indicated stable results, as shown in Fig. 3C.

4. Discussion

Breast cancer is the most common malignancy in females, which affect females' physiological and psychological health seriously.

Table 1

Characteristics of literatures enrolled in the meta-analysis.

Authors	Year	Country	Ethnicity	Source of controls	Genotype methods	Sample size Case/Control	HWE	Quality score
Atoum and Alzoughool[14]	2017	Jordanians	Caucasian	HB	TaqMan	156/142	Y	6
Sun et al[20]	2015	China	Asians	HB	MassARRAY IPLEX platform	481/463	Y	5
Madeira et al[15]	2014	Brazil	Caucasian	HB	PCR-RFLP	64/72	Y	5
Chattopadhyay et al[16]	2014	India	Caucasian	PB	PCR-RFLP	360/360	Y	6
Cao* et al[21]	2014	China	Asians	HB	PCR-RFLP	221/252	Y	5
Tang et al[12]	2013	China	Asians	HB	MALDI-TOF	794/845	Y	6
Lu and Xu[13]	2013	China	Asians	PB	PCR-RFLP	542/1016	Y	8
Ramalhinho et al[22]	2013	Portuguese	Caucasian	HB	PCR-RFLP	107/121	Y	6
Han et al[23]	2011	China	Asians	PB	TaqMan	859/877	Y	7
Sakoda et al[24]	2011	China	Asians	PB	SNaPshot assays	612/874	Y	7
Deng* and Lu[25]	2011	China	Asians	HB	PCR-RFLP	128/130	Y	6
Bai* et al[26]	2010	China	Asians	HB	PCR-RFLP	189/374	Y	5
Dunning et al[27]	2009	UK	Caucasian	PB	PCR-RFLP	4362/4548	Y	5
Sonestedt et al[28]	2009	Sweden	Caucasian	PB	SEQUENOM	539/1073	Y	6
González-Mancha et al[29]	2008	Spain	Caucasian	PB	PCR-RFLP	444/704	Y	5
Ladd et al[30]	2008	Netherlands	Caucasian	PB	NA	190/3703	Y	5
Hu et al[31]	2007	China	Asians	HB	PCR-RFLP	113/113	Y	5
Wang et al[32]	2007	USA	Caucasian	PB	PCR-MPLA	392/783	Y	5
Kjaergaard et al[33]	2007	Denmark	Caucasian	HB	TaqMan	1256/2489	Y	5
Surekha et al[34]	2007	India	Caucasian	HB	TaqMan	249/248	Y	6
Shen et al[35]	2006	China	Asians	PB	PCR-RFLP	247/274	Y	5
Modugno et al[36]	2005	USA	Caucasian	PB	PCR-RFLP	248/3901	N	5
Onland-Moret et al[37]	2005	Netherlands	Caucasian	PB	PCR-RFLP	308/337	Y	4
Lu* et al[38]	2005	China	Asians	HB	PCR-RFLP	138/140	Y	5
Wedrén et al[39]	2004	Sweden	Caucasian	PB	PCR-RFLP	1292/1418	Y	7
Cai et al[40]	2003	China	Asians	PB	PCR-RFLP	1069/1166	Y	6

HB = hospital-based, MALDI-TOF = matrix-assisted laser desorption ionization time-of-flight, PB = population-based, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.
* Published in Chinese journals.

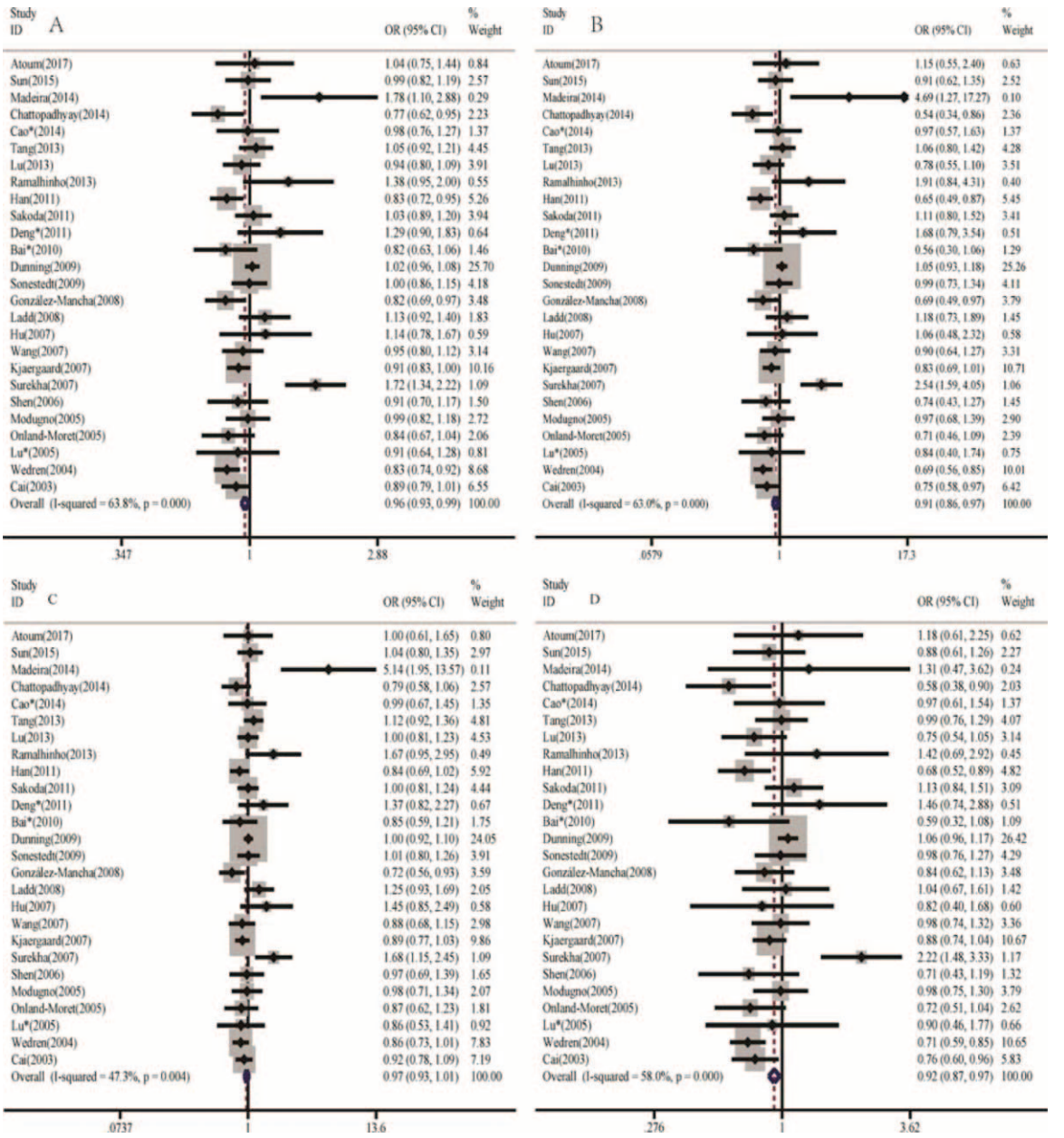

Figure 2. Significant association between *ERα* gene Pvu II polymorphism and breast cancer risk. (A) Allele model (C vs T, $P = .012$), (B) Homozygote model (CC vs TT, $P = .003$), (C) Dominant model (CC/CT vs TT, $P = .187$), and (D) Recessive model (CC vs TT/CT, $P = .004$).

At present, genetic polymorphism has become one of the hot topics in the studies on risk factors of breast cancer. Although the association between *ERα* gene PvuII polymorphism and breast cancer risk has been reported widely, the conclusions vary in different studies due to the difference of study design, study methods, regions and ethnicities, etc. Multiple studies have reported that patients carried with T allele exhibit relatively low morbidity of breast cancer.[15,16,22] However, Cai et al[40] pointed out that TT could increase the risk of breast cancer. Some researchers believed that there was no association between *ERα* gene PvuII polymorphism and breast cancer risk.[14,20] Therefore, this study mainly analyzed 26 studies on the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility through meta-analysis, and obtained more accurate and objective conclusion by reducing randomization error and increasing the power of test.

This meta-analysis mainly enrolled 15,360 cases and 26,423 controls, and the results revealed that the breast cancer susceptibility decreased significantly in people carried with *ERα* gene Pvu II CC genotype or C allele, which was similar to the conclusions of Lu et al,[13] Zhang et al,[17] and Li et al.[18] However, how *ERα* gene intron Pvu II affect the receptor function to participate in the pathogenesis of breast cancer is still unclear. A study has shown that Pvu IIare near to *ERα* gene promotor, which may impact the stability of other genes or mRNA transcription so as to affect the expressions of other genes.[41] In addition, some introns may regulate the expression levels of proteins by regulating the gene transcription.[42] Another study has reported that compared with T allele, C allele could produce the function-binding site of transcription factor B-myb, so as to influence the transcription level of *ERα* gene.[43] Liu et al[44] reported that ERα played an important role in the active

Table 2

Meta-analysis results of association between *ERα* gene Pvu II polymorphism and breast cancer risk.

Contrast model	Studies	Subjects (cases/controls)	OR (95% CI)	P^*	I^2 (%)	$P^\dagger$
Total studies						
C vs T	26	15,360/26,423	0.962 (0.933–0.992)	.012	63.8	.000
CC vs TT	26	15,360/26,423	0.911 (0.856–0.969)	.003	63.0	.000
CC/CT vs TT	26	15,360/26,423	0.970 (0.927–1.015)	.187	47.3	.004
CC vs TT/CT	26	15,360/26,423	0.923 (0.874–0.975)	.004	58.0	.000
Subgroup analysis						
Caucasians						
C vs T	14	9967/19,899	0.970 (0.934–1.006)	.103	76.4	.000
CC vs TT	14	9967/19,899	0.937 (0.870–1.009)	.087	74.4	.000
CC/CT vs TT	14	9967/19,899	0.965 (0.912–1.022)	.221	65.6	.000
CC vs TT/CT	14	9967/19,899	0.954 (0.895–1.017)	.148	69.5	.000
Asians						
C vs T	12	5393/6524	0.950 (0.894–1.010)	.102	18.9	.258
CC vs TT	12	5393/6524	0.862 (0.750–0.992)	.038	26.9	.180
CC/CT vs TT	12	5393/6524	0.978 (0.908–1.054)	.560	0.0	.574
CC vs TT/CT	12	5393/6524	0.851 (0.755–0.959)	.008	18.1	.266
Subgroup analysis						
HB						
C vs T	14	5199/6970	1.019 (0.960–1.082)	.535	68.6	.000
CC vs TT	14	5199/6970	1.015 (0.897–1.147)	.817	68.6	.000
CC/CT vs TT	14	5199/6970	1.408 (0.959–1.145)	.298	61.7	.003
CC vs TT/CT	14	5199/6970	0.991 (0.888–1.106)	.871	52.9	.016
PB						
C vs T	12	10,161/19,453	0.943 (0.911–0.977)	.001	55.8	.006
CC vs TT	12	10,161/19,453	0.878 (0.817–0.944)	.000	58.9	.003
CC/CT vs TT	12	10,161/19,453	0.936 (0.881–0.994)	.031	13.6	.304
CC vs TT/CT	12	10,161/19,453	0.902 (0.847–0.960)	.001	61.9	.001

HB = hospital-based study, PB = population-based study.

* *P* value of *OR*.

† *P* value of I^2.

regulation of p53, as the combination of ERα and p53 could inhibit the function of wild p53 so that the wild p53could not suppress the tumor growth and metastasis of ERα-positive breast cancer. However, whether CC phenotype participates in the development and progression of breast cancer via these pathways needs to be further studied and verified.

Factors such as ethnicity, region, living environment, and age exert certain function in the development and progression of breast cancer. We found in the subgroup analysis based on ethnicity that there was significant association between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk in Asians rather than in Caucasians. Lu et al,[13] Zhang et al,[17] and Li et al[18] also reported the significant association between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk in Asians. This difference might be caused by the genetic heterogeneity among different ethnicities, or was connected with interaction between genes, the linkage disequilibrium between SNPs sites, regions, living environment, and lifestyles. There are significant differences in the distribution of Pvu II polymorphism in European, Asian, and African populations. Most genetic phenomenon, such as natural selection, mutation, random shift, genetic hitchhiking, or gene flow, can cause large amount of linkage disequilibrium, which may also occur in different ethnicities or populations. In addition, intergenetic interaction and gene–environment interaction may also trigger distinct contributions of gene to tumorigenesis among different ethnicities.[45]

The difference in selection of controls may lead to between-study heterogeneity. Therefore, this study conducted a subgroup analysis based on the source of controls, and the results illustrated that in population-based subgroup rather than hospital-based subgroup, there was a significant association between *ERα* gene Pvu II polymorphism and the decrease of breast cancer risk. The morbidity of breast cancer may increase greatly in hospital-based controls in the future, which may trigger significant difference between different subgroups. However, Li et al[13] did not show that the association between Pvu II polymorphism and breast cancer risk was in any association with the source of controls.

Although researchers in pre-study have reported the association between *ERα* gene Pvu II polymorphism and breast cancer risk,[13,18,24] this study was more in the number of articles enrolled and larger in sample size, which comparatively reduced the influence of contingency on the results of meta-analysis. Therefore, the conclusions of this study were more persuasive and accurate.

However, this study also had some limitations described as follows. First, the studies enrolled lacked of data of family history, smoking, alcoholic consumption, age, and other environmental exposure factors; therefore, its OR values were nonadjusted data. Second, stratified analysis was not conducted based on pathological patterns, as the studies enrolled lacked of complete data on pathological patterns. Third, this study did not analyze the influence of interaction of different genes and interaction of genes with environment on the association of gene polymorphism and breast cancer risk. Fourth, the selection bias of controls by researchers in studies could not be avoided. Therefore, a comprehensive analysis of larger sample size and sample information is needed in the future so as to obtain more accurate conclusion on the association between *ERα* gene Pvu II polymorphism and breast cancer susceptibility.

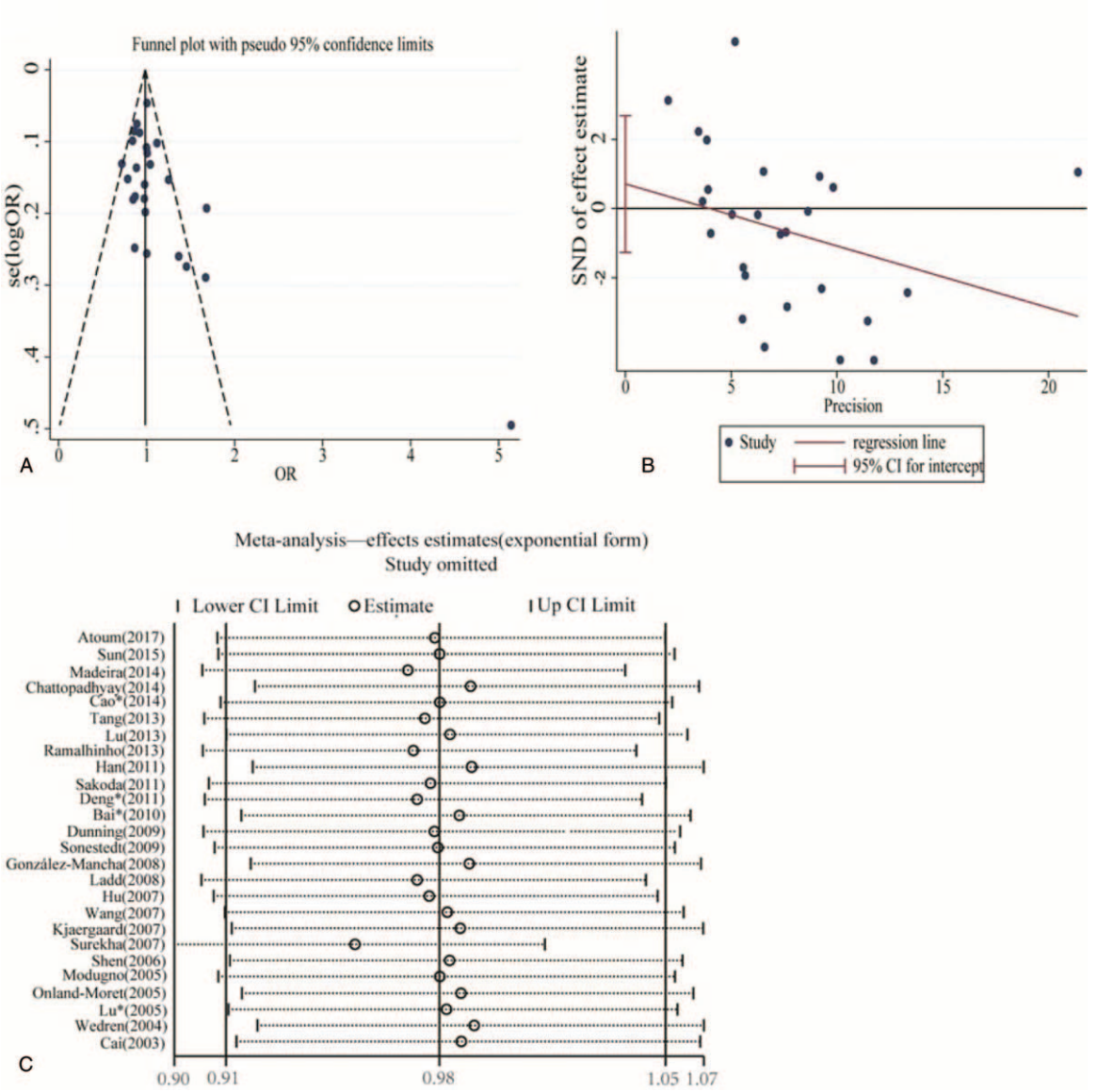

Figure 3. Publication bias and sensitivity analysis of studies included in the meta-analysis of dominant model. (A) Funnel plot, (B) Egger test ($P = .465$), (C) Sensitivity analysis.

In conclusion, this meta-analysis has found that *ERα* gene Pvu II polymorphism has participated in the development and progression of breast cancer. However, larger sample size, more accurate sample information, and more strict and reasonable study design are needed in the future to comprehensively verify the association between *ERα* gene Pvu II polymorphism and breast cancer risk.

Author contributions

Conceptualization: Shun-e Yang.
Data curation: Yan Li.
Formal analysis: Shun-e Yang.
Investigation: Zhen-hui Zhao.
Methodology: Cui-zhen Zhang.
Resources: Zhen-hui Zhao, Shun-e Yang.
Software: Zhen-hui Zhao.
Supervision: Zhen-hui Zhao, Shun-e Yang.
Validation: Zhen-hui Zhao, Shun-e Yang.
Visualization: Shun-e Yang.
Writing – original draft: Zhen-Lian Zhang.

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