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META-ANALYSIS

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Association Between ESR1 PvuII, XbaI, and P325P Polymorphisms and Breast Cancer Susceptibility: A Meta-Analysis

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Background: Breast cancer is one of the leading causes of cancer-related deaths for women. Numerous studies have shown that single-nucleotide polymorphisms (SNPs) on the ESR1 gene are associated to this disease. However, data and conclusions are inconsistent and controversial.

Material/Methods: To investigate the association between PvuII (rs2234693), XbaI (rs9340799) and P325P (rs1801132) polymorphisms of ESR1 gene with the risk of breast cancer under different population categorizations, we searched multiple databases for data collection, and performed the meta-analysis on a total of 25 case-control studies. Three different comparison models – dominant model, recessive model, and homozygote comparison model – were applied to evaluate the association.

Results: Our results indicated that people with TT+TC or TT genotype were at a greater risk of developing breast cancer than those with CC genotype in the PvuII polymorphism. While for XbaI and P325P polymorphisms, no significance was found using any of the 3 models. Furthermore, the data were also stratified into different subgroups according to the ethnicity (white or Asian) and source of controls (hospital-based or population-based), and separate analyses were conducted to assess the association. The ethnicity subgroup assessment showed that the higher risk of breast cancer for TT genotype of PvuII polymorphism than CC genotype only occurred in Asian people, but not in white populations. For the source-stratified subgroup analysis, significant association suggested that people with TT + TC genotype were at a greater risk of developing breast cancer than those with CC genotype in the hospital-based subgroup.

Conclusions: Thus, this meta-analysis clarified the inconsistent conclusions from previous studies, conducted analyses for the entire population as well as for different subgroups using diverse population categorization strategies, and has the potential to help provide a personalized risk estimate for breast cancer susceptibility.

MeSH Keywords: Estrogen Receptor Modulators • Meta-Analysis • Polymorphism, Genetic

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Background

Breast cancer (BC) is the most common malignant tumor for women worldwide [1]. Similar to other cancer types, genetic factors play a central role in the development and progression of breast cancer [2]. Studies show that excessive estrogen from the exogenous source can have pathological consequences in human cell, and result in the alteration of tumors, including the occurrence of breast cancer [3]. Two major types of estrogen receptors (ESRs), named as ESR1 and ESR2, act as the key regulators in controlling the actions of estrogen. The ESR1 gene encodes a transcription factor with an estrogen-binding domain, an activation domain, and an estrogen response element (ERE) DNA-binding domain. By regulating the cell proliferation and differentiation via paracrine mechanism, ESR1 is believed to be tightly associated with breast cancer [4]. Therefore, genetic variations in the ESR1 gene, which can lead to disordered estrogen activity, become a potential risk for breast cancer. Single-nucleotide polymorphisms (SNPs) of ESR1 have been studied in numerous clinical studies. Many association studies on this gene have been confined to 2 SNPs (originally detected with the restriction enzymes PvuII and XbaI [5]), which are located in the first intron of ESR1. The ESR1 PvuII and XbaI polymorphisms have been associated to tumorigenesis and many other diseases [6], involving heterogeneous conclusions. The meta-analysis conducted by Li et al. concluded that the PvuII polymorphism of ESR1 was a risk factor for prostate cancer development [7], while the meta-analysis conducted by Gu et al. found no association between frequencies of the PvuII (C>T) polymorphism and prostate cancer susceptibility, but found a positive correlation between XbaI (A>G) polymorphism and the risk of prostate cancer [8]. A recent study showed that the ESR1 PvuII CC/CT and XbaI GG/GA genotypes could increase susceptibility to systemic lupus erythematosus (SLE) [9]. Several other meta-analyses suggested that the PvuII variant, instead of XbaI, was negatively associated with Alzheimer's disease (AD) in white populations, especially in southern European people, but not in Asian populations [7,10]. The risk of idiopathic scoliosis was not obviously associated with the ESR1 PvuII or XbaI polymorphism [11]. It has been also frequently reported that the PvuII and XbaI polymorphisms of the ESR1 gene are related to breast cancer [12,13]. Li and Xu reported that ESR1 PvuII (C>T) polymorphism placed pre-menopausal women at risk for breast cancer, but XbaI (A>G) polymorphism is not associated with the risk of breast cancer [14]. P325P polymorphism in the exon 4 of ESR1 gene has been found to be associated with bone mineral density in post-menopausal women [15]. Korean women carrying both the ESR1 P325P CC and CDK7 Ex2-28C>T (rs2972388) TT genotypes have been shown to be at increased breast cancer risk [16]. However, because of the heterogeneous of data sources and analysis methods, the conclusions in many of these studies were inconsistent and controversial. Although 2 studies have been conducted on this issue, both of them have some drawbacks. Specifically, Li et al. narrowed the population to Asian women [14]. Hu et al. focused on some of SNPs in ESR1, but SNPs like P325P, which is also associated with the risk of breast cancer, was not included in their articles [17]. In this study, we performed an updated meta-analysis by involving as many data as possible from published studies, to provide a more precise estimation of the potential association between ESR1 PvuII, XbaI, and P325P polymorphisms and the risk of breast cancer. We collected all related studies from online databases to assess the association between 3 SNPs on ESR1 and breast cancer susceptibility. In addition, the analyses were conducted for the entire population, as well as for different subgroups using diverse population categorization strategies.

Material and Methods

Search strategy

We performed an online search of PubMed, Elsevier, Science Direct, Karger, Web of Science, Wiley Online Library, and Springer databases for eligible studies on the association between ESR1 PvuII, XbaI, and P325P polymorphisms with breast cancer susceptibility. The related terms, including"ESR1", "rs2234693", "rs9340799", "rs1801132", "polymorphism","breast cancer" and "BC" were used for searching. The literature search was updated on September 2014.

Data collection

A total of 91 results were found in the literature search. Among these studies, only ones which meet the following criteria were included in our meta-analysis: (i) case-control study that focused on breast cancer and ESR1 gene polymorphisms; (ii) ethnicity and source information was available for case and control; (iii) the diagnosis of breast cancer was confirmed by pathological or histological examination; (v) were published in English language. Studies were excluded when they were: (i) irrelevant articles, duplicated articles; (ii) not case-control study; (iii) genotype frequency information was not accessible; and (iv) meta-analysis, letters, reviews, or editorial articles. As a result, 25 articles were eventually included in the meta-analysis. In our data collection procedure we restricted the time frame from Jan. 2000 to Sept. 2014. Since there was no eligible study prior to 2003, all included studies were published later than 2003. For each article, the following data were collected: the first author's last name, year of publication, country of origin, ethnicity, source of controls, and the number and frequency of ESR1 PvuII, XbaI, and P325P polymorphisms of cases or controls.

Statistical methods

We used STATA software (version 12.0) for all analyses. The strength of the association between ESR1 polymorphisms and

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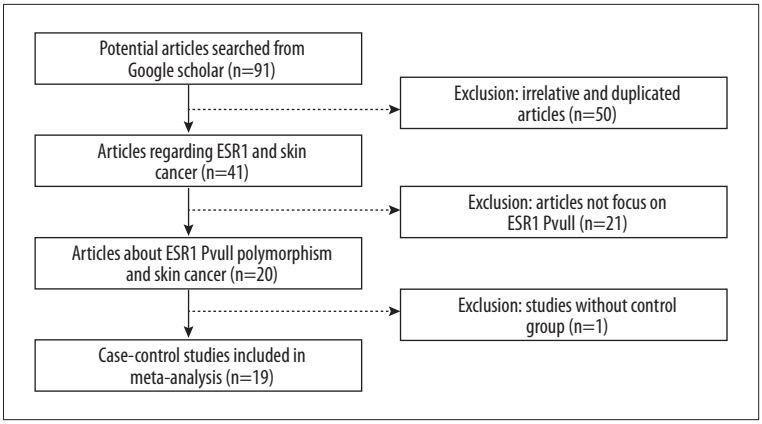

Figure 1. Flow diagram of studies included in the meta-analysis.

breast cancer susceptibility was assessed using all databases by pooled odds ratios (ORs) with 95% confidence intervals (CIs). Three models were used to evaluate the association: dominant model, recessive model, and homozygote comparison model. We also performed subgroup analyses by ethnicity (white or Asian) and source of controls (hospital-based or population-based). The heterogeneity assumption was assessed by I^2 index. Higher I^2 indicates more significant heterogeneity. I^2=50% represents the dividing point between low and high heterogeneity. When $I^2 \leq 50\%$, we assumed that there was no significant heterogeneity between pooled data. Correspondingly, $I^2 > 50$ was treated as significant heterogeneity. Moreover, based on the I^2 index, we chose a different model in analysis: Mantel-Haenszel (M-H) fixed-effects model was used to analyze datasets without significant heterogeneity and DerSimonian and Laird (D-L) random-effects model was used to analyze datasets showing obvious heterogeneity. In our meta-analysis, we used M-H fixed-effects model to test the heterogeneity first, and then chose different models based on the testing results. ORs were calculated with each model within 95% confidence intervals. Forest plots were generated to summarize the results. Potential publication bias was assessed by the Begg's funnel plots and the Egger's test. All reported P values were for a two-tailed test.

Results

We performed an online search of multiple databases for eligible studies on the association between ESR1 polymorphisms and breast cancer susceptibility. The procedure of article collection is shown in Figure 1. By excluding irrelevant articles, duplicated articles, and articles not focused on ESR1 polymorphisms and breast cancer, we found a total of 25 case-control studies covering 24 740 cases, and 38 866 controls were eligible [12,13,16–38], main characteristics of which are shown in Table 1. For the ethnicity distribution, there were 8 studies of Asians and 15 studies of whites. For the source of controls, 14 studies used population-based controls and 11 studies used hospital-based controls.

To choose a proper model for the study, we first used the I^2 indexes to evaluate the heterogeneity of the data for all 3 SNPs. As shown in Table 2, for PvuII, the I^2 indexes ranged from 36% to 48%, and for XbaI and P325P, the I^2 values were mostly equal to 0% in all 3 tested genetic models. Statistically significant heterogeneities were only observed for PvuII in dominant model TT *vs.* (TC+CC) and homozygote model (TT *vs.* CC). The PvuII polymorphism showed a relative higher I^2 index than the other 2 SNPs mainly because more studies were included in the PvuII analysis. Nevertheless, all of the I^2 indexes were smaller than 50%, which can be still considered as non-significant heterogeneity. Therefore, the statistical power was still acceptable in our study. Since the I^2 indexes were smaller than 50%, M-H fixed-effects models were used for all of the 3 SNPs. The forest plots for PvuII, XbaI, and P325P are shown in Figures 2–4, respectively. Overall, we found significant associations between ESR1 PvuII polymorphism and breast cancer susceptibility in both recessive model ((TT+TC) *vs.* CC: OR=1.08, 95% CI (1.02–1.14), p=0.01, Figure 2B) and homozygote model (TT *vs.* CC: OR=1.10, 95% CI (1.03–1.18), p=0.03, Figure 2C), but not in dominant model (TT *vs.* (TC+CC): OR=1.05, 95% CI (1.00–1.10), p=0.05, Figure 2A). These results indicated that the people with TT or TC genotype were at a greater risk of developing breast cancer than those with CC genotype in the ESR1 PvuII polymorphism. On the other hand, for XbaI and P325P, no significance was found for all 3 models (GG *vs.* GA+AA: OR=1.05, 95% CI (0.94–1.18), p=0.37, Figure 3A; GG+GA *vs.* AA: OR=1.05, 95% CI (0.98–1.12), p=0.15, Figure 3B; GG *vs.* AA: OR=1.08, 95% CI (0.96–1.21), p=0.22, Figure 3C; CC *vs.* CG+GG: OR=1.01, 95% CI (0.91–1.11), p=0.90, Figure 4A; CC+CG *vs.* GG: OR=0.97, 95% CI (0.86–1.09), p=0.60, Figure 4B; CC *vs.* GG: OR=0.96, 95% CI (0.84–1.10), p=0.56, Figure 4C). We found that there was no significant publication bias based on funnel plot for all 3 SNPs (Figures 5–7). Egger's and Begg's tests also indicated that there was no obvious bias for publications investigating the relationship of ESR1 polymorphisms with breast cancer risk, as shown in Table 2.

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

Author	Year	Case				Control				Country	Ethnicity	Source*	Age	Genotyping method	Premeno-pausal proportion
PvuII		**CC**	**CT**	**TT**	**Total**	**CC**	**CT**	**TT**	**Total**						
Madeira	2014	9	49	6	64	8	39	25	72	Brazil	Caucasian	HB	Median: 55	PCR-RFLP	Mixed
Chattpoad-hyay	2014	39	164	157	360	62	162	136	360	India	Caucasian	PB	<50: 44%	PCR-RFLP	49%
Tang	2013	127	374	293	875	136	375	334	886	China	Asian	HB	Mean: 49	MALDI-TOF	50%
Lu	2013	57	228	227	542	137	454	425	1016	China	Asian	PB	Mean: 49	PCR-RFLP	N/A
Sakoda	2011	93	290	229	612	120	427	327	874	China	Asian	PB	<50: 51.7%	SNaPshot assays	55%
Han	2011	107	399	353	859	151	402	324	877	China	Asian	HB	Mean: 51	TaqMan	48%
Sonestedt	2009	108	273	158	539	218	539	316	1073	Sweden	Caucasian	PB	Mean: 57	SEQUENOM	N/A
Dunning	2009	938	2164	1260	4362	934	2296	1318	4548	UK	Caucasian	PB		PCR-RFLP	
Ladd	2008	24	94	72	190	453	1648	1602	3703	Nether-lands	Caucasian	PB	Mean: 70	N/A	0%
Gonzalez-Mancha	2008	82	209	153	444	150	361	193	704	Spain	Caucasian	HB	Mean: 58	PCR-RFLP	
Wang	2007	87	188	117	392	176	393	214	783	USA	Caucasian	PB		PCR-MPLA	
Kjaergaard	2007	245	613	398	1256	537	1225	727	2489	Denmark	Caucasian	HB		TaqMan	25%
Hu	2007	16	58	39	113	19	45	49	113	China	Asian	HB	<50: 73%	PCR-RFLP	72%
Shen	2006	29	120	98	247	43	124	107	274	China	Asian	PB	<50: 79%	PCR-RFLP	
Onland-Moret	2005	69	150	89	308	96	153	88	337	Nether-lands	Caucasian	PB	Mean: 57	PCR-RFLP	
Modugno	2005	80	115	53	248	1272	1810	819	3901	USA	Caucasian	PB	Mean: 71	PCR-MPLA	
Wedren	2004	268	634	390	1292	313	651	384	1348	Sweden	Caucasian	PB	50-74	PCR–RFLP	0%
Shin	2003	35	91	75	201	26	103	61	190	Korea	Asian	HB		PCR-RFLP	
Cai	2003	138	516	415	1069	190	546	430	1166	China	Asian	PB	Mean: 47	PCR-RFLP	64%
XbaI		**GG**	**GA**	**AA**	**Total**	**GG**	**GA**	**AA**	**Total**						
Madeira	2014	12	47	5	64	14	58	0	72	Brazil	Caucasian	HB	Median: 55	PCR-RFLP	Mixed
Sakoda	2011	22	197	395	614	30	277	569	876	China	Asian	PB	<50: 51.7%	SNaPshot assays	55%
Dunning	2009	521	1967	1682	4170	526	2048	1873	4447	UK	Caucasian	PB		PCR-RFLP	
Wang	2007	19	137	237	393	29	299	461	789	USA	Caucasian	PB		PCR-MPLA	
Slattery	2007	52	235	287	574	61	313	351	725	USA	Caucasian	PB		PCR-RFLP	

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Table 1 continued. Characteristics of literatures included in the meta-analysis.

Author	Year	Case				Control				Country	Ethnicity	Source*	Age	Genotyping method	Premeno-pausal proportion
Shen	2006	14	84	149	247	21	87	168	276	China	Asian	PB	<50: 79%	PCR–RFLP	
Cai	2003	36	497	536	1069	49	507	610	1166	China	Asian	PB	Mean: 47	PCR-RFLP	64%
P325P		**CC**	**CG**	**GG**	**Total**	**CC**	**CG**	**GG**	**Total**						
Han	2011	208	441	216	865	232	452	201	885	China	Asian	HB	Mean: 51	TaqMan	48%
Ding	2010	241	468	225	934	402	751	391	1544	China	Asian	HB		Taqman	
Jeon	2009	218	311	217	746	182	288	185	655	Korea	Asian	HB	Mean: 47	MALDI-TOF	
Sidding	2008	55	23	1	79	56	27	2	85	Sudan	Caucasian	HB	Mean: 46	PCR-SSCP	67%
Wang	2007	237	137	19	393	461	299	29	789	USA	Caucasian	PB		PCR-MPLA	
Gallicchio	2006	52	31	7	90	794	440	64	1298	USA	Caucasian	PB	Mean: 54	TaqMan	26.2%
Fernandez	2006	355	156	18	529	356	167	22	545	Spain	Caucasian	HB	<50: 27%	Taqman	15%

* HB – hospital-based; PB – population-based.

Table 2. Meta-analysis for all population with Dominant model, Recessive model and homozygote comparison.

Analysis model	Analysis method	Heterogeneity		OR				Publication bias	
		I^2 (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
PvuII									
TT *vs.* TC+CC	Fixed	43.6	0.02	1.05	1.00	1.10	0.05	0.48	0.47
TT+TC *vs.* CC	Fixed	36.8	0.06	1.08	1.02	1.14	0.01	0.94	0.15
TT *vs.* CC	Fixed	48.1	0.01	1.10	1.03	1.18	0.03	0.68	0.62
XbaI									
GG *vs.* GA+AA	Fixed	3.5	0.40	1.05	0.94	1.18	0.37	0.76	0.73
GG+GA *vs.* AA	Fixed	0.0	0.86	1.05	0.98	1.12	0.15	0.55	0.19
GG *vs.* AA	Fixed	0.0	0.51	1.08	0.96	1.21	0.22	0.76	0.87
P325P									
CC *vs.* CG+GG	Fixed	0.0	0.82	1.01	0.91	1.11	0.90	0.76	0.74
CC+CG *vs.* GG	Fixed	0.0	0.63	0.97	0.86	1.09	0.60	0.76	0.68
CC *vs.* GG	Fixed	0.0	0.64	0.96	0.84	1.10	0.56	1.00	0.83

Furthermore, we performed subgroup analysis, and results are shown in Tables 3–5. For the subgroup analysis by ethnicity, the I^2 indexes for PvuII were larger than 50% in both dominant model and homozygote model for white subgroups, indicating a high heterogeneity in these 2 genetic models (Table 3). Correspondingly, we used the random-effects model for assessing the association in these high-heterogeneity cases, and used the fixed-effects model in other cases. Although the above analysis showed that TT genotype of PvuII had higher risk of breast cancer than CC genotype in all populations, further subgroup assessment demonstrated that only Asians followed this trend (TT *vs.* CC: OR=1.18, 95% CI (1.04–1.33), p=0.01), while whites did not (TT *vs.* CC: OR=1.13, 95% CI (0.98–1.29), p=0.09). For the source-stratified subgroup analysis, significant

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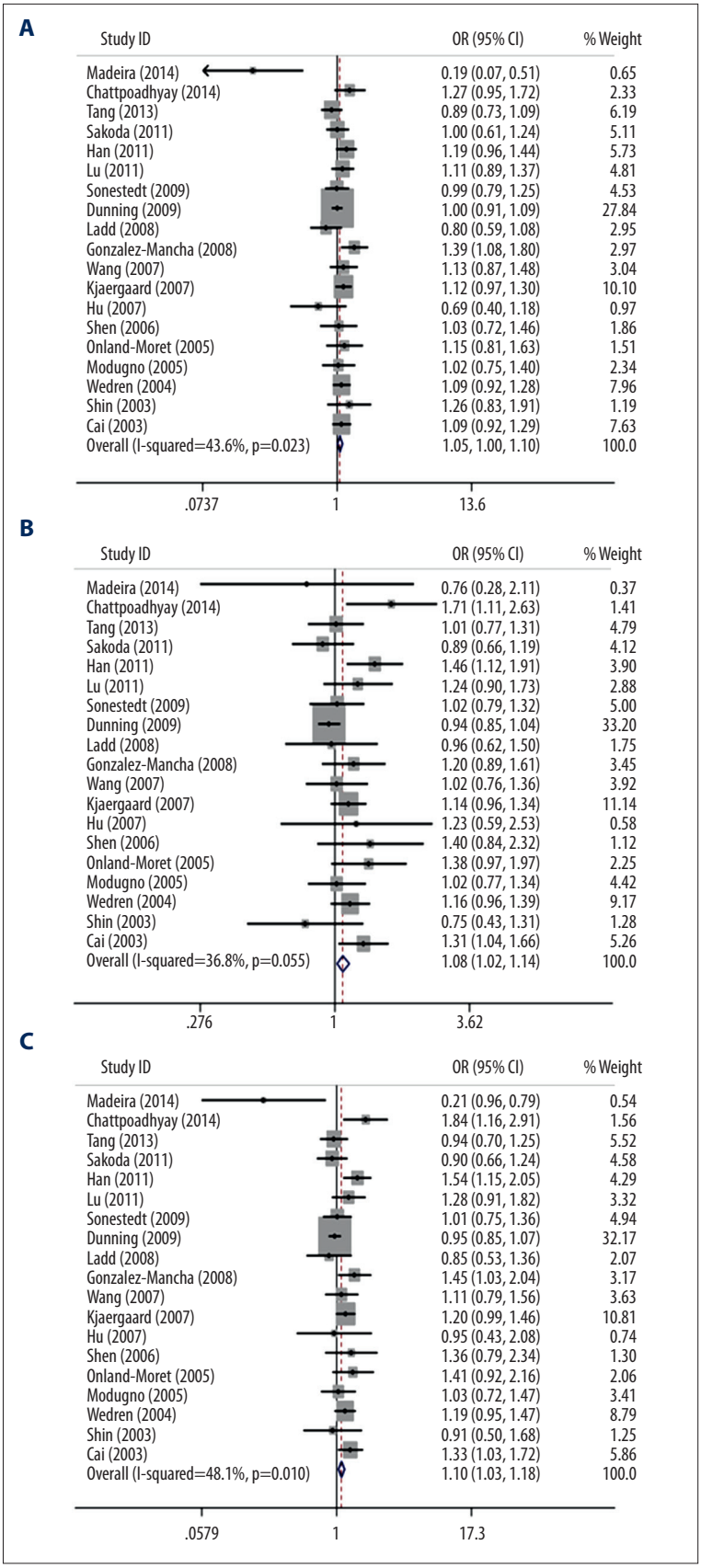

Figure 2. Forest plot of the association between breast cancer risk and ESR1 PvuII polymorphism in all population with respect to (**A**) dominant model (TT *vs.* TC+CC), (**B**) recessive model (TT+TC *vs.* CC), and (**C**) homozygote model (TT *vs.* CC).

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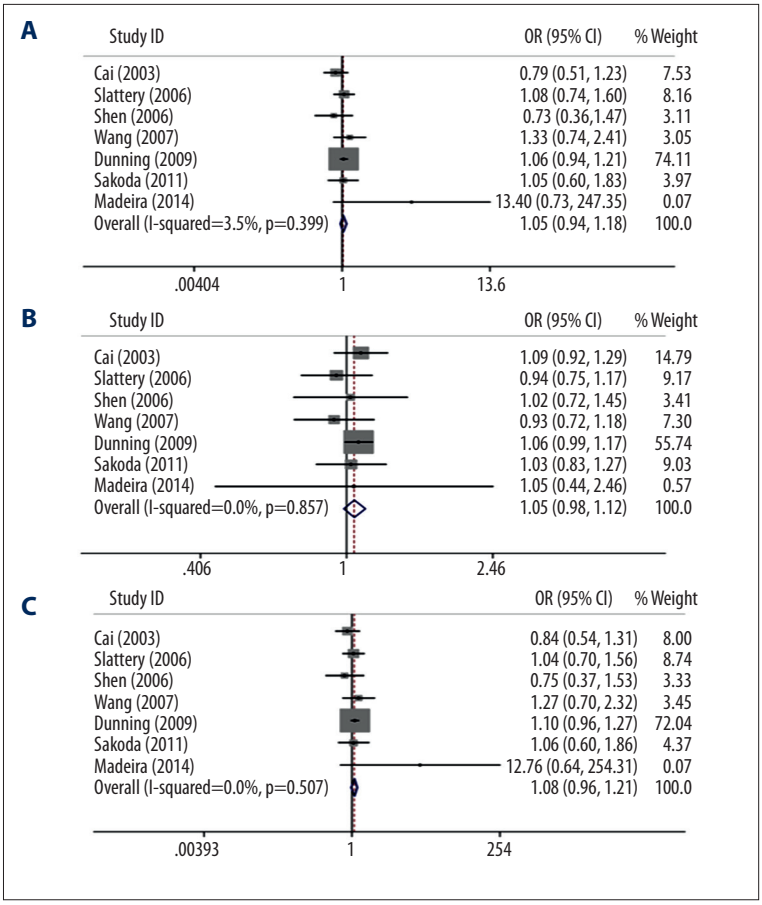

Figure 3. Forest plot of the association between breast cancer risk and ESR1 XbaI polymorphism in all population with respect to (**A**) dominant model (GG *vs.* GA+AA), (**B**) recessive model (GG+GA *vs.* AA) and (**C**) homozygote model (GG *vs.* AA).

association was observed in the recessive model of hospital-based subgroup (TT+TC *vs.* CC: OR=1.15, 95% CI (1.03–1.28), p=0.02), suggesting that the people with TT + TC genotype were at a greater risk of developing breast cancer than those with CC genotype in the hospital-based subgroup. On the other hand, similar with the results obtained by using the entire population, analysis on XbaI (Table 4) and P325P polymorphisms (Table 5) showed that there was almost no heterogeneity for any of the subgroup cases, with I^2 being equal to 0 for all tests except for XbaI in the white group. In addition, no statistical significant association was found between XbaI and P325P polymorphisms and breast cancer susceptibility in any of the subgroups. Given these results, we conclude that only TT genotype in PvuII was associated with the risk of breast cancer for Asians, and polymorphisms in the other 2 SNPs in ESR1 had little influence on breast cancer.

Discussion

In recent years, the association of genetic susceptibility to cancers has drawn more and more attention to the study of polymorphisms of genes involved in tumorigenesis and other diseases. Numerous studies have been conducted to investigate the association between breast cancer susceptibility with 3 SNPs on ESR1: PvuII, XbaI, and P325P. However, because of the heterogeneous of data and methods, the conclusions in these studies are inconsistent and controversial. For example, some studies concluded that the PvuII CC and CT genotype significantly increased the risk of breast cancer [12,13]. Some studies claimed that T allele of PvuII conferred a higher risk of breast cancer [18,24,32]. Other studies showed that ESR1 PvuII polymorphism did not have any significant effect on breast cancer [19,21,25,27,28]. Given these results, it is necessary to perform a meta-analysis to clarify this issue, which can rapidly and effectively increase sample size by combining data of association studies, thus enhancing the statistical power of analysis to estimate the genetic effects. Pooling data from different studies also has the advantage of reducing random errors. With the accumulation of the studies over the years, we performed an updated meta-analysis, by including 3 SNPs of ESR1 and by involving as many data as possible from published studies, to provide a more comprehensive and reliable estimation of the potential association correlation between ESR1 PvuII, XbaI, and P325P polymorphisms and the risk of breast cancer. In the present study, our results showed that genotype TT+TC or TT in ESR1 PvuII were significantly associated with increased breast cancer risk in overall population compared

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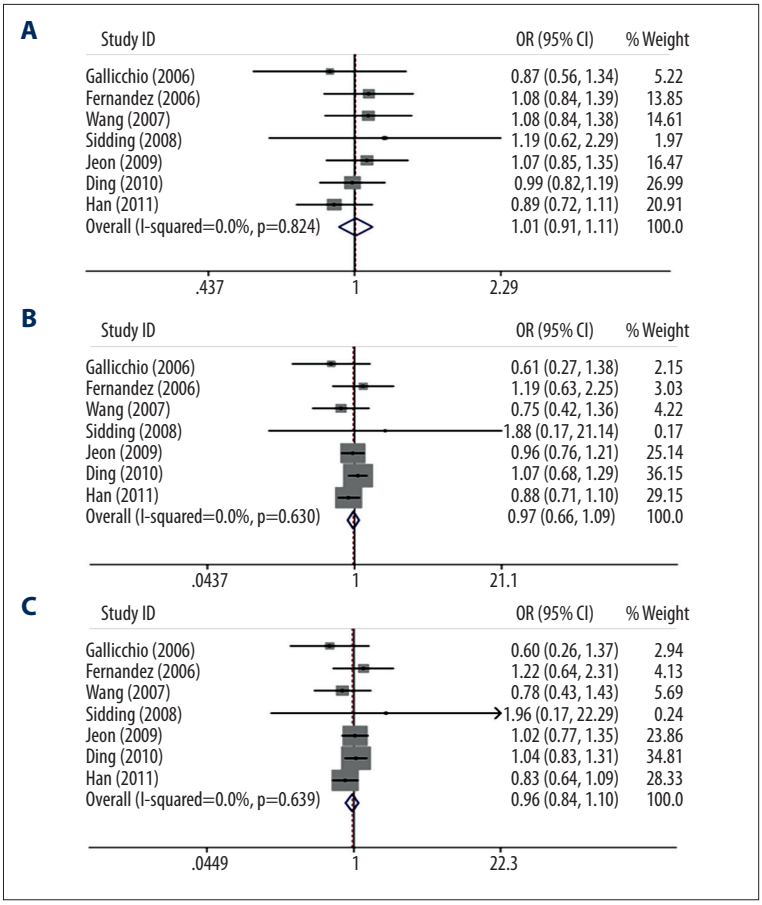

Figure 4. Forest plot of the association between breast cancer risk and ESR1 P325P polymorphism in all population with respect to (**A**) dominant model (CC *vs.* CG+GG), (**B**) recessive model (CC+CG *vs.* GG) and (**C**) homozygote model (CC *vs.* GG).

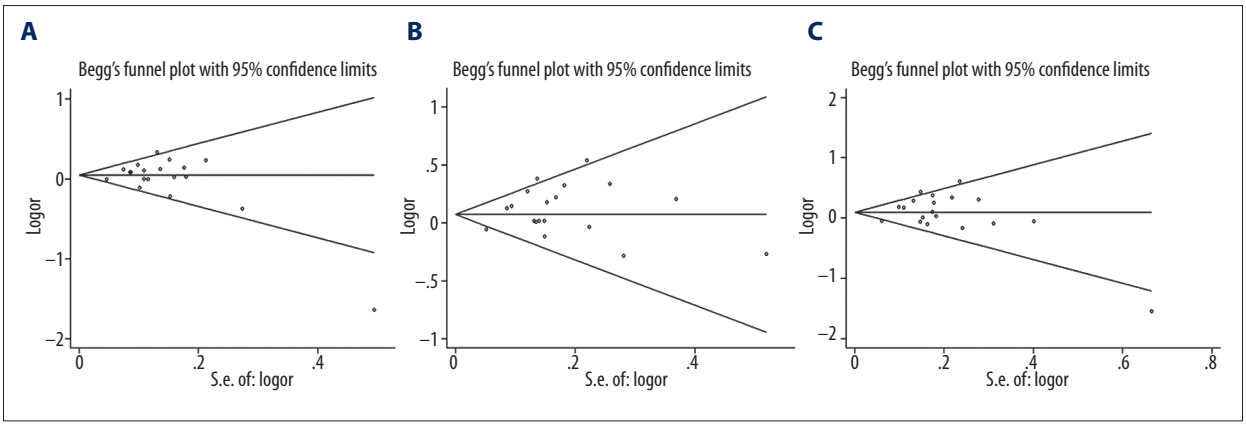

Figure 5. Funnel plot of the association between breast cancer risk and ESR1 PvuII polymorphism in all population with respect to (**A**) dominant model (TT *vs.* TC+CC), (**B**) recessive model (TT+TC *vs.* CC) and (**C**) homozygote model (TT *vs.* CC).

with CC genotype. The ESR1 PvuII polymorphism is intronic and possibly affects receptor function by changing ESR1 expression levels or altering its pre-mRNA splicing. Herrington et al. found that the C allele of PvuII produced a functional binding site for a transcription factor B-Myb, which resulted in significantly increasing transcription of a downstream reporter construct compared to the T allele [39]. This indicates that CC genotype correlates with a higher ESR1 transcriptional level and may explain our observation that TT+TC or TT genotypes were associated with higher breast cancer risk than was CC genotype, but further functional studies are needed to investigate the functions of these alleles.

It is likely that the tumorigenesis of breast cancer is affected by many factors such as age, ethnicity, environment, and other variables. We therefore performed subgroup analysis

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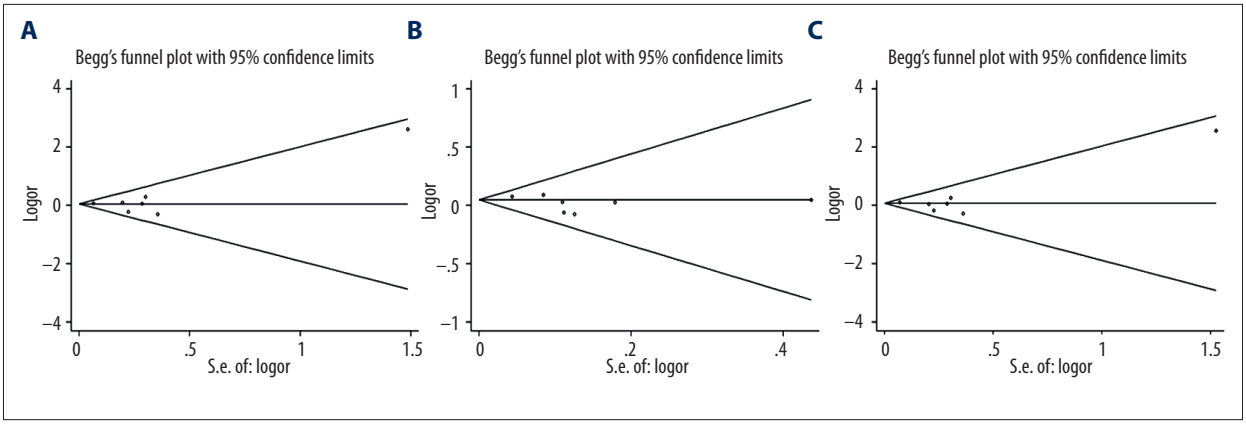

Figure 6. Funnel plot of the association between breast cancer risk and ESR1 XbaI polymorphism in all populations with respect to (**A**) dominant model (GG *vs.* GA+AA), (**B**) recessive model (GG+GA *vs.* AA), and (**C**) homozygote model (GG *vs.* AA).

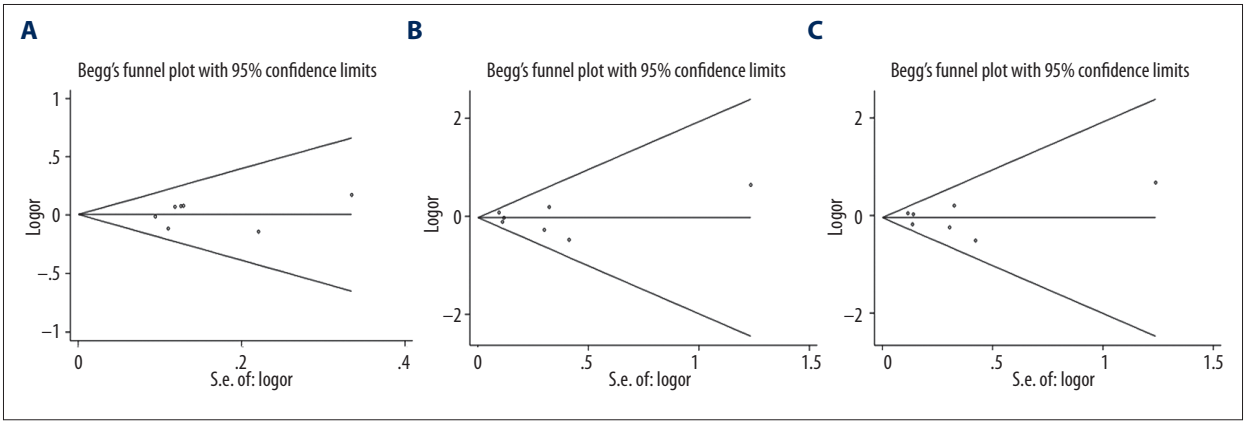

Figure 7. Funnel plot of the association between breast cancer risk and ESR1 P325P polymorphism in all populations with respect to (**A**) dominant model (CC *vs.* CG+GG), (**B**) recessive model (CC+CG *vs.* GG), and (**C**) homozygote model (CC *vs.* GG).

Table 3. Subgroup meta-analysis of the association between ESR1 PvuIIpolymorphisms and breast cancer risk.

Subgroup	TT *vs.* TC+CC				TT+TC *vs.* CC				TT *vs.* CC			
	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*
Ethnicity												
Caucasian	58.5	0.01	1.06 (0.95–1.18)	0.28	31.9	0.14	1.05 (0.98–1.12)	0.16	56.1	0.01	1.13 (0.98–1.29)	0.09
Asian	10.0	0.35	1.05 (0.97–1.14)	0.24	38.0	0.01	1.17 (1.04–1.31)	0.12	33.8	0.16	1.18 (1.04–1.33)	0.01
Source												
HB	74.6	<0.01	1.02 (0.83–1.26)	0.83	15.0	0.32	1.15 (1.03–1.28)	0.02	58.9	0.02	1.13 (0.90–1.43)	0.28
PB	0.0	0.77	1.04 (0.98–1.10)	0.23	44.2	0.05	1.05 (0.99–1.12)	0.13	81.3	<0.01	0.78 (0.64–0.94)	0.01

P-value from heterogeneity test; * P-value from OR test.

based on ethnicity of samples. We found only Asians with TT genotype of ESR1 PvuII polymorphism had a higher risk of breast cancer than people with CC genotype, while whites did not show this trend. This may be attributable to genetic heterogeneity among different populations. We could not rule out the possibility of gene-gene interactions or the possibility of linkage disequilibrium between polymorphisms. Further studies of multiple polymorphisms in ESR1 [40,41] or different genes or gene regulators such as microRNAs [42–44] are needed to address this question. In addition, it is also possible

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Table 4. Subgroup meta-analysis of the association between ESR1 Xbalpolymorphisms and breast cancer risk.

Subgroup	GG *vs.* GA+AA				GG+GA *vs.* AA				GG *vs.* AA			
	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*
Ethnicity												
Caucasian	11.9	0.33	1.09 (0.96–1.22)	0.17	0.0	0.51	1.04 (0.97–1.13)	0.27	0.0	0.41	1.11 (0.98–1.26)	0.10
Asian	0.0	0.67	0.85 (0.62–1.16)	0.30	0.0	0.89	1.06 (0.94–1.20)	0.34	0.0	0.73	0.88 (0.64–1.20)	0.42
Source												
PB	0.0	0.66	1.04 (0.93–1.17)	0.46	0.0	0.76	1.05 (0.98–1.12)	0.15	0.0	0.75	1.07 (0.95–1.20)	0.27

P-value from heterogeneity test; * P-value from OR test; ** Analysis on HB is not performed due to the lack of study.

Table 5. Subgroup meta-analysis of the association between ESR1 P325Ppolymorphisms and breast cancer risk.

Subgroup	CC *vs.* CG+GG				CC+CG *vs.* GG				CC *vs.* GG			
	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*	I^2 (%)	ph#	OR (95%CI)	pOR*
Ethnicity												
Caucasian	0.0	0.81	1.06 (0.90–1.24)	0.50	0.0	0.51	0.88 (0.60–1.29)	0.52	0.0	0.50	0.90 (0.61–1.33)	0.60
Asian	0.0	0.51	0.98 (0.87–1.10)	0.70	0.0	0.43	0.98 (0.87–1.11)	0.73	0.0	0.42	0.97 (0.84–1.12)	0.67
Source												
HB	0.0	0.72	1.00 (0.90–1.12)	0.98	0.0	0.67	0.99 (0.88–1.11)	0.83	0.0	0.64	0.98 (0.85–1.13)	0.81
PB	0.0	0.39	1.03 (0.83–1.27)	0.82	0.0	0.70	0.71 (0.44–1.14)	0.16	0.0	0.60	0.72 (0.44–1.18)	0.19

P-value from heterogeneity test; * P-value from OR test.

that differences in environment and lifestyle between different populations may affect the tumorigenesis of breast cancer.

The heterogeneity between studies could also be from the heterogeneous controls. Therefore, we also conducted a source-stratified subgroup analysis on 14 studies of population-based controls and 11 studies of hospital-based controls, and found significant association in the recessive model of the hospital-based subgroup. Interestingly, we also noticed that TT genotype of ESR1 PvuII polymorphism in the population-based subgroup decreased the risk of breast cancer more than CC genotype. The inconsistent results between different subgroups could come from the possible non-differential misclassification bias because the hospital-based controls might develop more breast cancer than healthy populations in subsequent years. For P325P, only 2 studies were included in subgroup analysis for PB. Given this small sample size, the statistical power is limited. More studies should be conducted to provide a more precise result.

Conclusions

Our study provided a systematic review and updated meta-analysis of genetic association between ESR1 PvuII, XbaI and P325P polymorphisms and the risk of human breast cancer. Using 3 models (dominant model, recessive model, and homozygote comparison model), we confirmed that only PvuII polymorphism was a risk factor for breast cancer susceptibility in the overall population, but not XbaI and P325P SNPs. Moreover, our results suggest that subgroup assessment by ethnicity of samples and source of controls yields results that are different from those using the overall population. Thus, we believe our study clarifies the inconsistent conclusions from previous studies, and will shed some light on future breast cancer-related research.

Conflict of interest statement

No conflict of interest.

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