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Original Article

# Association of three single nucleotide polymorphisms of *ESR1* with breast cancer susceptibility: a meta-analysis

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## Abstract

Expression of estrogen receptors is correlated with breast cancer risk, but inconsistent results have been reported. To clarify potential estrogen receptor (ESR)-related breast cancer risk, we analyzed genetic variants of *ESR1* in association with breast cancer susceptibility. We performed a meta-analysis to investigate the association between rs2234693, rs1801132, and rs2046210 (single nucleotide polymorphisms of *ESR1*), and breast cancer risk. Our analysis included 44 case-control studies. For rs2234693, the CC genotype had a higher risk of breast cancer compared to the TT or CT genotype. For rs2046210, the AA, GA, or GA + GG genotype had a much higher risk compared to the GG genotype. No significant association was found for the rs1801132 polymorphism with breast cancer risk. This meta-analysis demonstrates association between the rs2234693 and rs2046210 polymorphisms of *ESR1* and breast cancer risk. The correlation strength between rs2234693 and breast cancer susceptibility differs in subgroup assessment by ethnicity.

Keywords: breast cancer, estrogen receptor alpha, meta-analysis, single nucleotide polymorphism

## Introduction

Breast cancer is one of the leading causes of cancer mortality in women worldwide<sup>[1]</sup>. Many environmental exposures contribute to breast cancer risk, including exposure to some organic solvents, polycyclic aromatic hydrocarbons (PAHs), organic chlorine compounds, pesticides, and ingestion of food contaminated by fungus, bacteria, and heavy metals, such as cadmium, chromium, lead, and arsenic<sup>[2-3]</sup>. However, newer genomics technology has also identified genetic variations as risk factors for breast cancer<sup>[4]</sup>. *BRCA1* was the

first gene found to be associated with breast cancer risk<sup>[5]</sup>, although two other well-known genes, *HER2* and *BRCA2*, are also associated with breast cancer risk<sup>[6-7]</sup>.

Khan *et al.* reported that estrogen receptor (ESR) expression is also associated with breast cancer susceptibility<sup>[8]</sup>. Breast tissue exposed long-term to high levels of estrogen may develop cancer, which can result from ESR stimulation by estrogen-mediated aberrant gene expression<sup>[9]</sup>.

More recently, *ESR1*-induced carcinogenesis in mammary tissues has been explained by epigenetic

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mechanisms. Indeed, *ESR1* methylation may influence activity of normal breast tissue<sup>[10]</sup>. ESRs have two typical types, ESR-alpha and ESR-beta, which are encoded by *ESR1* and *ESR2*, respectively. *ESR1* (6q25.1) single nucleotide polymorphisms (SNPs) are associated with tumor carcinogenesis, cell proliferation, and metastasis<sup>[11]</sup>. For example, *PvuII* (rs2234693) and *XbaI* (rs9340799) polymorphisms located in intron 1 are correlated with breast cancer<sup>[12]</sup>, prostate cancer<sup>[13]</sup>, and systemic lupus erythematosus<sup>[14]</sup>.

However, other studies have found inconsistent results. For example, Li et al. found no significant correlation between rs9340799 and breast cancer risk<sup>[15]</sup>. Zhang et al. conducted a meta-analysis of ESR1 SNPs associated with breast cancer risk, although that study did not include rs2046210, an important novel SNP<sup>[16]</sup>. Considering the heterogeneous approaches and limited sample sizes of earlier studies, we performed a larger sample size-based meta-analysis of published reports of three of the most studied ESR1 SNPs: rs2234693, rs1801132, and rs2046210. Our included studies covered reports published in both Chinese and English, since most studies published were conducted by Chinese researchers and the association between rs2046210 and breast cancer risk was first found in China<sup>[17]</sup>.

## Materials and methods

#### Search strategy

We performed a systematic search of English and

Chinese databases, including PubMed, Web of Science, Embase, Springer, China National Knowledge Infrastructure (CNKI) (http://www.cnki.net), Wanfang Data (http://www.wanfangdata.com.cn), and VIP (http:// www.cqvip.com). We searched these databases by using key terms including "ESR1", "ESR-alpha", "ESR  $\alpha$ ", "breast cancer risk", and "breast cancer susceptibility". The most recent search was performed on January 1, 2016.

#### **Data extraction**

Two researchers, H.X. and J.L., independently extracted information from the literature. Entered data were double-checked to ensure accuracy, and inconsistent data were resolved by discussion. In total, 177 studies were related to the key terms. Data were included in the meta-analysis if they met the following criteria (Fig. 1): (i) included recent pathology diagnosed as breast cancer; (ii) reported association between risk of breast cancer and one or more of the four ESR1 polymorphisms; (iii) included case-control studies; (iv) included adult women as study subjects; (v) results were adjusted for age and body mass index; (vii) genotypes of controls followed Hardy-Weinberg equilibrium. Studies were excluded if: (i) the full article was not accessible; (ii) drugs that may be an interactive factor, such as tamoxifen, were included; (iii) results mainly focused on the mechanism of ESR1 influencing breast cancer; (iv) the study based on most samples was selected from overlapped ones.

From each study, the following information was



Fig. 1 Flow diagram of data extraction

A	5	case	9	Cont	rol		Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	A. 2010	69	101	53	90	0.5%	1.51 [0.83, 2.72]	
	A.M. 2008	118	190	2101	3703	2.1%	1.25 [0.93, 1.69]	
	Aesun 2003	126	201	129	190	1.3%	0.79 [0.52, 1.21]	
	Alisa 2007	858	1256	1762	2489	10.1%	0.89 [0.77, 1.03]	
	Alison 2009	3102	4362	3230	4548	24.7%	1.00 [0.92, 1.10]	+
	Bai 2010	106	189	225	374	1.8%	0.85 10.59, 1.211	
	Cao 2014	179	221	203	252	1.0%	1.03 (0.65, 1.63)	
	Deng 2011	105	128	113	130	0.5%	0.69 (0.35, 1.36)	
	Emily 2009	381	539	757	1073	4.0%	1.01 (0.80, 1.26)	
	Jing 2011	506	859	553	877	6.1%	0.84 [0.69, 1.02]	
	Jun 2007	275	392	569	783	3.1%	0.8810.68 1.151	
	Lori 2011	383	612	547	874	4.6%	1.00 [0.81, 1.24]	
	Lu 2005	84	138	90	140	0.9%	0 86 10 53 1 411	
	Luning 2013	501	875	511	886	5 9%	0 98 10 81 1 191	
	N Charlotte 2005	219	308	249	337	1.9%	0.87 10.62 1 23	
	Oundo 2003	654	1069	736	1166	7 4%	0 92 10 78 1 091	
	Rosario 2008	291	444	511	704	3 7%	0.72 10 56 0.931	
	Sara 2004	902	1292	964	1348	7 7%	0.92 (0.78 1.09)	
	Shilpi 2014	203	360	224	360	2 6%	0 79 10 58 1 061	
	Tecc 2013	829	1163	1446	2160	7 9%	1 23 [1 05 1 43]	
	Yueping 2006	140	247	167	2100	1 796	0.07 [0.60 1.20]	
	Thep 2007	74	112	64	112	0.6%	1 45 10 95 2 401	
	211611 2007	14	115	04	115	0.0%	1.45 [0.65, 2.45]	
	Total (95% CI)		15059		22871	100.0%	0.96 (0.92, 1.01)	•
	Total evente	10114		15204			eres feneri us il	
	Heterogeneity Chille	31.37 df	= 21 (P -	0 071 P	= 33%			
	Test for overall effect	7=1 52 /	P=013	0.07,1	- 5570			0.5 0.7 1 1.5 2
	rescior overall effect.	2-1.52(	- 0.13	/				Favours [case] Favours [control]
D		case	e	Cont	rol		Odds Ratio	Odds Ratio
D	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
	A. 2010	4	101	15	90	0.6%	0.21 [0.07, 0.65]	
	A.M. 2008	24	190	453	3703	1.4%	1.04 [0.67, 1.61]	+
	Aesun 2003	35	201	26	190	0.8%	1.33 [0.77, 2.31]	- <del></del>
	Alisa 2007	245	1256	537	2489	10.8%	0.88 [0.74, 1.04]	
	Alison 2009	934	4362	938	4548	26.8%	1.05 [0.95, 1.16]	+
	Bai 2010	15	189	48	374	1.1%	0.59 [0.32, 1.08]	
	Cao 2014	70	221	79	252	1.9%	1.02 (0.69, 1.50)	
	Deng 2011	42	128	52	130	1.3%	0.73 [0.44, 1.22]	
	Emily 2009	108	539	218	1073	4.3%	0.98 [0.76, 1.27]	+
	Jing 2011	107	859	151	877	4.9%	0.68 (0.52, 0.89)	
	Jun 2007	87	392	176	783	3.4%	0.98 [0.74, 1.32]	-
	L ori 2011	93	612	120	874	31%	1 13 10 84 1 511	
	Lu 2005	19	138	21	140	0.7%	0 90 10 46 1 771	
	Luxing 2013	127	875	136	886	4 396	0 94 10 72 1 221	-
	N Charlotte 2005	69	308	96	337	2.6%	0.72 [0.51 1 04]	
	Oiuvin 2003	138	1069	190	1166	5 9%	0.76 (0.60, 0.96)	
	Recorio 2008	82	444	150	704	3.5%	0.94 [0.62, 1.13]	
	Rosano 2008	260	1202	212	1240	0.0%	0.04 [0.02, 1.13]	
	Shiloi 2014	167	260	126	260	2.0%	1 27 10 95 1 721	·
	Tage 2012	244	1162	426	2160	0.0%	1.05 (0.99, 1.25)	+
	Vuening 2006	299	247	430	2100	1 206	0.71 /0.42 1 101	
	Thep 2007	16	112	43	112	0.6%	0.0210.40 1.601	
	211611 2007	10	115	13	115	0.0 %	0.02 [0.40, 1.00]	
	Total (95% CD		15059		22871	100.0%	0 94 10 89 1 001	•
	Total events	2013	15055	4353	22011	100.074	0.54 [0.65, 1.66]	
	Heterogeneity Chiz=	37 12 df	= 21 (P =	= 0.02\· P	= 43%			+ + + + + + + + + + + + + + + + + + + +
	Test for overall effect	7=211/	P=0.04	0.02),1	- 43 70			0.05 0.2 1 5 20
	restion overall effect.	2.11 (	- 0.04	·				Favours [variant] Favours [control]
C		case	a.	Contr	ol		Odds Ratio	Odds Ratio
C	Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixed, 95% CI
	A 2010	4	36	15	52	0.5%	0.31 (0.09. 1.02)	
	A.M. 2008	24	96	453	2055	1.5%	1.18 [0.73, 1.89]	
	Aesun 2003	35	110	26	87	1.0%	1.09 [0.60, 2.01]	<u> </u>
	Alisa 2007	245	643	537	1264	10.8%	0.83 [0.69, 1.01]	-+-
	Alison 2009	934	2194	938	2256	25.6%	1.04 [0.92, 1.17]	+
	Bai 2010	15	98	48	197	1.3%	0.56 [0.30, 1.06]	
	Cao 2014	70	112	79	128	1.3%	1.03 [0.61, 1.74]	
	Deng 2011	42	65	52	69	0.9%	0.60 [0.28, 1.26]	
	Emily 2009	108	266	218	534	4.2%	0.99 [0.73, 1.34]	+
	Jing 2011	107	460	151	475	5.5%	0.65 (0.49, 0.87)	
	Jun 2007	87	204	176	390	3.3%	0.90 [0.64, 1.27]	
	Lori 2011	93	322	120	447	3.4%	1.11 [0.80, 1.52]	
	Lu 2005	19	73	21	71	0.8%	0.84 [0.40, 1.74]	
	Luying 2013	127	501	136	511	4.8%	0.94 [0.71, 1.24]	
	N. Charlotte 2005	69	158	96	184	2.4%	0.71 [0.46, 1.09]	
	Qiuyin 2003	138	553	190	620	6.5%	0.75 [0.58, 0.97]	-
	Rosario 2008	82	235	150	343	3.8%	0.69 [0.49, 0.97]	
	Sara 2004	268	658	313	697	8.7%	0.84 [0.68, 1.05]	
	Shilpi 2014	157	314	136	272	3.5%	1.00 [0.72, 1.38]	-
	Tess 2013	244	578	436	1150	8.1%	1.20 [0.98 1.47]	+
	Yueping 2006	29	127	43	150	1.5%	0.74 [0.43, 1.27]	
	Zhen 2007	16	55	19	68	0.6%	1.06 [0.48. 2.32]	
							the format stored	
	Total (95% CI)		7858		12020	100.0%	0.92 [0.87. 0.98]	•
	Total events	2913	0 0 <b>6 7</b> 0	4353				
	Heterogeneity: Chi#=	35.08. df	= 21 (P	= 0.03)	<sup>2</sup> = 40%			
	Test for overall effect	Z= 249	P=0.01	)				0.1 0.2 0.5 1 2 5 10
								Favours (variant) Favours (control)

*Fig. 2* Forest plot of the association between breast cancer risk and rs2234693 polymorphism in all population. A: dominant model (TT + TC vs. CC), B: recessive model (TT vs. TC + CC), C: homozygous model (TT vs. CC).



*Fig. 3* Forest plot of the association between breast cancer risk and rs1801132 polymorphism in all population. A: dominant model (CC + CG vs. GG), B: recessive model (CC vs. CG + GG), C: homozygous model (CC vs. GG).

extracted: first author's name, year of publication, country of origin, ethnicity, matching criteria, number of cases and controls, and odds ratio (OR) values. If any information was not included in the study, the term "mixed" was used.

## Statistical analysis

Pooled ORs with 95% confidence intervals (CIs) were calculated to assess risk of breast cancer associated with *ESR1* polymorphisms. The  $l^2$  index was used to measure heterogeneity among included studies. An  $l^2 \ge 50\%$  indicated heterogeneity among studies and a DerSimonian and Laird random-effects model was used to analyze data. Otherwise, we used a Mantel–Haenszel fixed-effects model to analyze data. For each SNP in *ESR1*, we analyzed three inheritance models (dominant, recessive, and homozygous models) when possible.

To explore whether there were differences in results of the above meta-analysis in different ethnicities, we performed a subgroup-analysis on each SNP by ethnicity. Asians and/or Han Chinese were regarded as subgroup 1, and Europeans and/or Caucasians as subgroup 2. Publication bias was tested with funnel plots and Egger's test, and Forest plots were used to present pooled results. Sensitivity analysis was used to evaluate the stability of results by removing some of the studies, the sizes of which were significantly larger than others or the results were significantly different from other studies. All analyses, except the Egger's test (using Stata V12.0), were performed using Review Manager V5.3.

# Results

As shown in *Fig. 1*, 177 studies were identified and reviewed. After inclusion and exclusion procedures were applied, 47 studies were included in the metaanalysis, comprising 137,451 cases and 145,391 controls. Details of each included study are described in *Table 1*.

According to  $I^2$  indexes of all three SNPs, we found that heterogeneity existed in dominant (97%), recessive (94%), and homozygous (91%) models of rs2046210, but not in any inheritance models of rs2234693 and rs1801132. Thus, a fixed-effects model was used to analyze studies on rs1801132 and rs2234693. A random-effects model was used for those on rs2046210.

As shown in Fig. 2B-C, we found significant

associations between rs2234693 and breast cancer risk in a recessive model [OR: 0.94, 95%CI (0.89, 0.996)] and homozygous model [OR: 0.92, 95%CI (0.87, 0.98)]. Significant associations were also found for rs2046210 in all three inheritance models (*Fig. 4A-C*). No significant associations were found for rs1801132 (*Fig. 3*).

Funnel plots and Egger's test were used to represent publication bias for the three SNPs (*Fig. 5*). We found no publication bias for any of the three inheritance

Δ		0.00	0	Con	trol		Odde Patio	Odde Patio
1	Study or Subaroun	Funnte	Total	Evente	Total	Woight	M H Random 95% Cl	M.H Bandom 95% Cl
- 1	Aiko 2012	201	607	677	1204	4 604	1 25 11 12 1 62	
- 1	Antonio 2012	4602	0006	6620	0100	4.0 %	0.5210.40.0.66	-
- 1	Depielo 2011	4003	0000	0020	11543	5.170	0.52 [0.49, 0.55]	+
- 1	Damele 2011	49/0	1050	0039	1043	4.70	0.01/0.77 1.07	
- 1	Edward 2012	600	1140	1150	1003	4.770	0.91 [0.77, 1.07]	
- 1	Edward 2012	089	1149	1150	1041	4.8%	0.89 [0.76, 1.03]	
- 1	He 2015	211	253	200	343	3.0%	1.00 (0.05, 1.55)	
- 1	Hui 2012	1004	401	301	037	4.2%	1.42 [1.10, 1.83]	-
- 1	Hyung-cheol 2012	1361	2257	1081	2052	4.9%	1.36 [1.21, 1.54]	
- 1	Jing 2011	5/1	861	503	884	4.5%	1.49 [1.23, 1.81]	
- 1	Lao 2012	430	617	350	597	4.3%	1.70 [1.34, 2.16]	
- 1	Long 2015	300	459	326	549	4.1%	1.29 [1.00, 1.67]	
- 1	Luo 2012	73	114	92	141	2.6%	0.95 [0.57, 1.59]	
- 1	M.Chan 2012	804	1173	819	1417	4.7%	1.59 [1.35, 1.87]	
- 1	Qiuyin01 2011	7788	11996	5587	9748	5.1%	1.38 [1.30, 1.46]	-
- 1	Qiuyin02 2011	2684	43/3	2309	3885	5.0%	1.08 [0.99, 1.18]	
- 1	Rebecca 2012	32883	56281	28585	51428	5.2%	1.12 [1.10, 1.15]	
- 1	Simon01 2010	739	1126	664	1118	4.7%	1.31 [1.10, 1.55]	
- 1	Simon02 2010	4520	7899	6296	11234	5.1%	1.05 [0.99, 1.11]	
- 1	Taeko 2013	255	468	219	463	4.1%	1.33 [1.03, 1.73]	
- 1	Wei 2009	4310	6472	2348	3962	5.0%	1.37 [1.26, 1.49]	
- 1	Wonshik 2011	1991	3251	1907	3493	5.0%	1.31 [1.19, 1.45]	
- 1	Yongdong 2011	297	493	279	510	4.2%	1.25 [0.98, 1.61]	
- 1								
- 1	Total (95% CI)		118653		116631	100.0%	1.18 [1.05, 1.33]	•
- 1	Total events	70876		66791				C 10 1 1 1 10 10
- 1	Heterogeneity: Tau <sup>2</sup> =	0.07; Chi <sup>2</sup>	= 750.05	5, df = 21	(P < 0.00	001); P =	97%	05 07 1 15 2
I	Test for overall effect:	Z= 2.82 (F	P = 0.005	)				Favours Ivarianti Favours Icontroll
n l			-	Con	tral		Odde Datia	Odde Datio
в	Chuche or Codemour	Cas	e Total	Con	Tatal	Mainht	M H Dandem OFM C	Odds Ratio
- 1	Study of Subgroup	Events	Total	Events	Total	weight	M-H, Kandom, 95% C	M-H, Random, 95% CI
- 1	Aiko 2012	79	697	112	1394	4.2%	1.46 [1.08, 1.98]	
- 1	Antonis 2011	1010	8888	1265	8109	5.4%	0.69 [0.63, 0.76]	-
- 1	Daniele 2011	1180	8298	1478	11543	5.4%	1.13 [1.04, 1.23]	
- 1	Dezheng 2012	133	1059	192	1383	4.6%	0.89 [0.70, 1.13]	
- 1	Edward 2012	155	1149	280	1841	4.8%	0.87 [0.70, 1.07]	
- 1	He 2015	90	253	139	343	4.0%	0.81 [0.58, 1.13]	
- 1	Hui 2012	75	461	61	537	3.8%	1.52 [1.05, 2.18]	
- 1	Hyung-cheol 2012	309	2257	200	2052	4.9%	1.47 [1.22, 1.77]	
- 1	Jing 2011	158	861	110	884	4.5%	1.58 [1.21, 2.06]	
- 1	Lao 2012	115	617	83	597	4.2%	1.42 [1.04, 1.93]	
- 1	Long 2015	83	459	74	549	4.0%	1.42 [1.01, 1.99]	
- 1	Luo 2012	26	114	16	141	2.2%	2.31 [1.17, 4.56]	
- 1	M.Chan 2012	231	1173	180	1417	4.8%	1.69 [1.36, 2.08]	
- 1	Qiuyin01 2011	193	11966	147	9748	4.8%	1.07 [0.86, 1.33]	· · · ·
- 1	Qiuyin02 2011	946	4373	1276	3885	5.3%	0.56 [0.51, 0.62]	-
- 1	Rebecca 2012	7238	56281	5786	51428	5.5%	1.16 [1.12, 1.21]	•
- 1	Simon01 2010	193	1126	147	1118	4.7%	1.37 [1.08, 1.72]	
- 1	Simon02 2010	946	7899	1276	11234	5.4%	1.06 [0.97, 1.16]	- +
- 1	Taeko 2013	61	468	34	463	3.3%	1.89 [1.22, 2.94]	
- 1	Wei 2009	1102	6472	536	3962	5.3%	1.31 (1.17, 1.47)	-
- 1	Wonshik 2011	426	3251	376	3493	5.1%	1.25 [1.08, 1.45]	-
- 1	Yonadona 2011	85	493	55	510	3.8%	1.72 (1.20, 2.48)	· · · · · ·
- 1								53
- 1	Total (95% CI)		118623		116631	100.0%	1.19 [1.05, 1.36]	•
- 1	Total events	14834		13823				
- 1	Heterogeneity: Tau <sup>2</sup> =	0.08: Chi <sup>2</sup>	= 374.11	1. df = 21	(P < 0.00	001): P=	94%	
I	Test for overall effect	Z = 2.69 (F	P = 0.007	)				0.2 0.5 1 2 5
				·				Favours (variant) Favours (control)
C		cas	e	Cont	rol		Odds Ratio	Odds Ratio
~	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
I	Aiko 2012	79	385	112	829	4.0%	1.65 (1.20, 2.27)	
I	Antonis 2011	1010	4436	1265	4653	5.8%	0.79 [0.72, 0.87]	+
	Daniele 2011	1180	4502	1478	6382	5.9%	1.18 [1.08, 1.29]	+
- 1	Dezheng 2012	133	575	192	736	4.6%	0.85 [0.66, 1.10]	
I	Edward 2012	155	615	280	965	4.8%	0.82 [0.66, 1.04]	
- 1	He 2015	90	132	139	196	2.8%	0.88 [0.54, 1.42]	
- 1	Hui 2012	75	239	61	297	3.4%	1.77 [1.20, 2.62]	
- 1	Hyung-cheol 2012	309	1205	200	1171	5.1%	1.67 [1.37, 2.04]	
- 1	Jing 2011	158	448	110	497	4.3%	1.92 [1.44, 2.55]	
- 1	Lao 2012	115	296	83	330	3.8%	1.89 [1.34, 2.66]	
- 1	Long 2015	83	242	74	297	3.6%	1.57 [1.08, 2.29]	
I	Luo 2012	26	67	16	65	1.6%	1.94 [0.92, 4.10]	
	M.Chan 2012	231	600	180	778	4.8%	2.08 [1.65, 2.63]	
I	Qiuvin01 2011	1983	6191	1203	5364	5,9%	1.63 [1.50, 1.77]	+
I	Qiuvin02 2011	587	2276	473	2049	5.6%	1.16 [1.01, 1.33]	
I	Rebecca 2012	7239	30636	5786	28629	6.1%	1.22 [1 17 1 27]	•
I	Simon01 2010	192	580	147	601	4.6%	1 54 [1 19 1 99]	
I	Simon02 2010	946	4326	1276	6214	5.8%	1 08 0 99 1 10	+-
I	Taeko 2012	64	274	24	279	3.0%	2 06 (1 20 2 25)	
I	Wei 2009	1102	3264	626	2160	5 7%	1 63 (1 28 1 72)	
I	Wonshik 2011	429	1696	376	1062	5 404	1.03 [1.30, 1.73]	
I	Vonadona 2011	920	264	570	206	3 /04	2 11 [1 42 2 42]	
I	rongoong zorr	00	204	55	200	3.470	2.11 [1.43, 3.13]	
I	Total (95% Ch		63220		64720	100.0%	1 39 14 23 4 543	▲
I	Total events	16265	03220	14070	34123	.00.079	1.50 [ 1.25, 1.54]	•
I	Heterogeneity Tour	- 0.05-05	8- 241	14076	1 /0 - 0 0	00011-12-	- 01%	
I	Tect for everall offer	- 0.05, Ch	P = 241.	0.01	1 (- < 0.0	0001), 1*1	- 3170	0.2 0.5 1 2 5
- 1	restion overall effec	= 3.72	u = 0.00	001)				Favours (variant) Favours [control]

*Fig. 4* Forest plot of the association between breast cancer risk and rs2046210 polymorphism in all population. A: dominant model (GG + GA vs. AA), B: recessive model (GG vs. GA + AA), C: homozygous model (GG vs. AA).

Table 1 Characterist SNP	tics of literatures included in the Author(ref.)	he meta-analysi Year	s. Country	Ethnicity	Matching Criteria	Sample Size	
						Case	Control
rs2234693	Anghel <sup>[18]</sup>	2010	Romania	Caucasian	Ethnicity	101	06
	Gonzalez-Zuloeta <sup>[19]</sup>	2008	Netherlands	Caucasian	Ethnicity	190	3703
	Shin <sup>[20]</sup>	2003	Korea	Asian	Arca	201	190
	Kjaergaard <sup>[21]</sup>	2007	Denmark	Caucasian	Ethnicity	1256	2489
	Dunning <sup>[22]</sup>	2009	Mixed	Mixed	Mixed	4548	4362
	Bai <sup>[23]</sup>	2010	China	Han	Ethnicity	189	374
	Cao <sup>[24]</sup>	2014	China	Asian	Arca	221	252
	Deng <sup>[25]</sup>	2011	China	Asian	Area	128	130
	Sonestedt <sup>[26]</sup>	2009	Sweden	Caucasian	Ethnicity	539	1073
	Han <sup>[27]</sup>	2011	China	Asian	Area	859	877
	Wang <sup>[28]</sup>	2007	USA	Caucasian	Ethnicity	392	783
	Sakoda <sup>[29]</sup>	2011	China	Asian	Area	612	874
	$Lu^{[30]}$	2005	China	Asian	Area	138	140
	Tang <sup>[31]</sup>	2013	China	Asian	Arca	875	886
	Onland-Moret <sup>[32]</sup>	2005	Netherlands	Caucasian	Ethnicity	308	337
	Cai <sup>[33]</sup>	2003	China	Asian	Area	1069	1166
	Gonzalez-Mancha <sup>[34]</sup>	2008	Spain	Caucasian	Ethnicity	444	704
	Wedren <sup>[35]</sup>	2004	Sweden	Caucasian	Ethnicity	1292	1348
	Chattopadhyay <sup>[36]</sup>	2014	India	Asian	Area	360	360
	Clendenen <sup>[37]</sup>	2013	Sweden	Caucasian	Ethnicity	1163	2106
	Shen <sup>[38]</sup>	2006	China	Asian	Area	247	274
	Hu <sup>[39]</sup>	2007	China	Asian	Area	113	113
rs1801132	Anghel <sup>[18]</sup>	2010	Romania	Caucasian	Ethnicity	103	88
	Awatif <sup>[40]</sup>	2008	Sudan	Caucasian	Ethnicity	79	85
	$\operatorname{Han}^{[27]}$	2011	China	Asian	Area	865	885
	Wang <sup>[28]</sup>	2007	NSA	Caucasian	Ethnicity	393	789
	Fernandez <sup>[41]</sup>	2006	Spain	Caucasian	Ethnicity	529	545
	Ding <sup>[42]</sup>	2010	India	Asian	Area	934	1544
	Jeon <sup>[43]</sup>	2009	Korean	Asian	Area	746	655
	Gallicchio <sup>[44]</sup>	2006	USA	Caucasian	Ethnicity	90	1298

Sample Size	Case Control	697 1394	8896 8109	8298 11543	1059 1383	1149 1841	253 343	461 537	2257 2052	617 597	459 549	114 141	1173 1417	861 884	9748 9748	4373 3885	56281 51428	1126 1118	7899 11234	468 463	6472 3962	3251 3493	493 510
Matching Criteria		Area	Ethnicity	Area	Ethnicity	Ethnicity	Area	Ethnicity	Area	Area	Area	Area	Area	Area	Area	Area	Ethnicity	Area	Area	Area	Area	Area	Area
Ethnicity		Asian	Caucasian	European	African	African–American	Asian	Han	Asian	Asian	Asian	Asian	Asian	Asian	Asian	European	Mixed	Asian	European	Asian	European	Asian	Asian
Country		Japan	USA	Germany	USA	USA	China	China	Korea	China	China	China	China	China	Mixed	Mixed	Mixed	Mixed	Mixed	Japan	USA	Korea	China
Year		2012	2011	2011	2012	2012	2015	2012	2012	2012	2015	2012	2012	2011	2011	2011	2012	2010	2010	2013	2009	2011	2011
Author(ref.)		Sueta <sup>[45]</sup>	Antoniou <sup>[46]</sup>	Campa <sup>[47]</sup>	Huo <sup>[48]</sup>	Ruiz-Narvaez <sup>[49]</sup>	He <sup>[50]</sup>	Guo <sup>[51]</sup>	Kim <sup>[52]</sup>	Lao <sup>[53]</sup>	Zhou <sup>[54]</sup>	Luo <sup>[55]</sup>	Chan <sup>[56]</sup>	Han <sup>[27]</sup>	Cai01 <sup>[57]</sup>	Cai02 <sup>[57]</sup>	Hein <sup>[58]</sup>	Stacey01 <sup>[59]</sup>	Stacey02 <sup>[59]</sup>	Mizoo <sup>[60]</sup>	Zheng <sup>[17]</sup>	Han <sup>[61]</sup>	Jiang <sup>[62]</sup>
SNP		Rs2046210																					



*Fig.* 5 Funnel plots of the association between breast cancer risk and all three polymorphisms in all populations. (A) dominant model, (B) recessive model, (C) homozygous model, (a) rs2234693, (b) rs1801132, (c) rs2046210. Two symmetric oblique dotted lines was used to mark Mantel–Haenszel fixed-effects models.

models of rs1801132 (P = 0.272, 0.493, and 0.631, for dominant, recessive, and homozygous model, respectively) and rs2046210 (P = 0.568, 0.489, and 0.196, respectively). For rs2234693, we observed possible bias in the recessive model (P = 0.553, 0.045, and 0.053, respectively).

**Tables 2-4** show the results of our subgroup analyses. For rs2234693, subgroup 1 retained strong association with breast cancer susceptibility, and heterogeneity was low among the studies (three  $I^2$  values were all less than 50%). In subgroup 2, only the homozygous model showed strong association with low heterogeneity

(*Table 2*); no significant correlation was shown in the other two groups. In addition, for rs1801132, the results for the two subgroups were negative (*Table 3*); thus, independent of subgroup, the rs1801132 polymorphism might not have significance for breast cancer risk. For rs2046210, the two subgroups both had strong positive results (*Table 4*); thus, correlation between rs2046210 and breast cancer risk was not affected by ethnicity.

Finally, we performed sensitivity analysis to evaluate whether our results were stable. First, we removed the study from Anghel *et al.*<sup>[18]</sup> for its significant OR values (0.68, 2.59, 2.35, *Fig. 3*) and re-analyzed the associa-

Subgroup <sup>\$</sup>	Dominan	t model		Recessiv	e model		Homozyg	gous model	
	$I^{2}(\%)$	Ph*	OR (95%CI)	$I^{2}(\%)$	${\rm Ph}^{*}$	OR(95%CI)	$I^{2}(\%)$	Ph*	OR(95%CI)
1	0	0.75	0.92 (0.85, 0.99)	11	0.33	0.85 (0.76, 0.95)	43	0.06	0.89 (0.80, 0.99)
2	63	0.006	0.98 (0.86, 1.11)	52	0.03	0.89 (0.77, 1.04)	35	0.14	0.91 (0.84, 0.99)

tion between rs1801132 and breast cancer risk in all three models. Still, no significant correlation was found (P = 0.966, 0.514 and 0.474 for the dominant, recessiveand homozygous models, respectively). Besides, we also re-analyzed the association between rs2234693 and breast cancer risk in the recessive model by removing the Anghel *et al.* study<sup>[18]</sup> due to its potential influence on publication bias. The publication bias no longer existed (P = 0.140) and the association between rs2234693 and breast cancer risk in the recessive model was marginally significant [OR: 0.95, 95%CI (0.90, 1.0004)]. Given that the effect size only changed slightly, we concluded that the results of our metaanalysis were stable.

# Discussion

The association between *ESR1* polymorphisms and breast cancer risk has attracted increasingly more attention<sup>[8-9]</sup>. Although there have been several genetic variations reportedly associated with breast cancer risk, our meta-analysis is the first to include these three polymorphisms of *ESR1*. Among the 44 studies included in our meta-analysis, 29 include Asian populations and 17 include Caucasian populations. The meta-analysis found that a variant genotype (AG or AA) of rs2046210 and one (CC) of rs2234693 were associated with increased risk of breast cancer. However, we did not find associations between breast cancer risk and another *ESR1* SNP, rs1801132.

Previous studies have found that variants of *ESR1* are associated with endometriosis, uterine fibroids, breast cancer, and osteoporosis<sup>[19–21,63–65]</sup>. ESR and progesterone receptor (PR) status is also important for clinicians to determine whether a patient needs adjuvant therapy and, if so, what type is needed<sup>[22,66]</sup>. The

mechanism for this influence of ESR may be through estrogen, which generally stimulates ESR-mediated transcription, thereby increasing the number of errors during DNA replication as well as rate of cell proliferation<sup>[23,67]</sup>.

Rs2234693 is intronic and possibly affects receptor function *via* altered pre-mRNA splicing. Herrington *et al.* found that the C allele of rs2234693 produces a functional binding site for transcription factor B-Myb, significantly increasing transcription of a downstream reporter construct compared to the T allele<sup>[24,68]</sup>, which may explain its high correlation with breast cancer risk.

Rs2046210, located upstream of ESR1, is strongly and consistently associated with breast cancer risk in a three-stage genome-wide association study<sup>[17]</sup>. It should be noted that rs2046210 is also associated with bone mineral density, a trait that is affected by estrogen<sup>[25]</sup>. In our analysis, rs2046210 was significantly associated with risk of breast cancer in all three models, indicating that variant A carriers have a higher risk of breast cancer compared to GG homozygotes. Stacey et al. hypothesized that it was the polymorphism itself or causal variants in linkage disequilibrium that might regulate ESR1 expression and elevate susceptibility to breast cancer<sup>[29,59]</sup>. However, direct evidence of whether rs2046210 affects ESR1 expression is lacking; therefore, further investigations are required<sup>[27,70]</sup>. Sun et al.<sup>[28,71]</sup> found that SNP rs2046210 may increase expression of AKAP12, a functional gene located ~26.8 kb upstream of SNP rs2046210 that is associated with malignancy and metastasis in many cancer types, including breast cancer<sup>[29,72]</sup>, expression in both normal tissues and tumor tissues. This regulation may explain how the genetic variations in this locus play a role in multiple stages of breast cancer development, including initiation, progression, and metastasis.

Subgroup <sup>s</sup>	Domina	int model		Recessi	ve model		Homozy	gous mo	del
	$I^{2}(\%)$	Ph*	OR (95%CI)	$I^{2}(\%)$	Ph*	OR (95%CI)	$I^{2}(\%)$	Ph*	OR (95%CI)
	0	0.6	1.03 (0.91, 1.16)	0	0.4	1.03 (0.91, 1.16)	0	0.45	1.04 (0.90, 1.21)
	0	0.77	0.93 (0.80, 1.09)	0	0.64	1.15 (0.79, 1.68)	0	0.63	1.12 (0.77, 1.65)

Table 4 Sub	ogroup m	ieta-analysis o	f the association l	between	the rs20462	10 polymorphism	and bro	east cancer ris	k.	
Subgroup <sup>\$</sup>	bgroup <sup>8</sup> Dominant model Recessive model Homozygous model									
	$I^{2}(\%)$	Ph <sup>*</sup>	OR (95%CI)	$I^{2}(\%)$	Ph <sup>*</sup>	OR (95%CI)	$I^{2}(\%)$	Ph <sup>*</sup>	OR (95%CI)	
1	73	< 0.00001	1.34 (1.24, 1.44)	66	0.0002	1.37 (1.23, 1.53)	76	< 0.00001	1.62 (1.44, 1.83)	
2	90	< 0.00001	1.14 (1.03, 1.27)	65	0.03	1.15 (1.05, 1.25)	85	0.0001	1.22 (1.06, 1.41)	
*P-value from h	heterogene	ity test; <sup>\$</sup> Subgro	up 1: Asian and/or H	Han popul	ation, 2: Euroj	pean and/or Caucasia	an populat	ion.		

Interestingly, rs1801132 is reported to influence mRNA stability and translation efficiency and predict exonic splicing enhancers<sup>[30,73]</sup>. However, we found no significant association in this meta-analysis. Hence, it is implied that there are some other unknown metabolisms contributing to the varying influence of different SNPs on ESR1 expression.

Zhang et al. performed a meta-analysis on associations between rs2234693 and rs1801132 and breast cancer and found that individuals with a TT + TC or TTgenotype in rs2234693 had a higher risk of developing breast cancer than those with a CC genotype<sup>[16]</sup>, which is consistent with our results. However, we also provided a subgroupanalysis with more details. For rs2234693, Caucasian patients were likely to develop breast cancer in a homozygous model, indicating that the association between rs2234693 and breast cancer risk was stronger in Asians, but not non-correlated in Caucasians as previously reported. Our negative result on rs1801132 also gave a further justification to Zhang et al. and Sun et al. [31,74], but is inconsistent with Li et al. <sup>[32,75]</sup>, which may be due to its limited sample sizes and different inclusion or exclusion criteria with ours.

Possible bias was observed for rs2234693 in the recessive model, which may be due to the significantly lower OR value reported by Anghel *et al.* <sup>[18]</sup>. Through the sensitivity analysis, we found that the upper bound of 95%CI was changed to 1.0004 after removing the study of Anghel *et al.* We concluded that the influence of publication bias was limited as our results are stable.

To the best of our knowledge, this meta-analysis included the most recently published articles reporting the association between *ESR* gene SNPs with breast cancer. We believe that our study provided more evidence supporting further investigation on *ESR* gene. We acknowledge that there were some limitations of our study. For rs1801132, our sample size was limited. However, as most studies did not report smoking, blood pressure, or other environmental factors for subgroups, it was not possible for us to perform stratified analyses.

In conclusion, our meta-analysis demonstrated a link between the rs2234693 and rs2046210 polymorphisms of *ESR1* and breast cancer risk. In addition, the correlation strength between rs2234693 and breast cancer susceptibility differs in subgroup assessment by ethnicity. Based on a much larger sample size, our results gave further justifications and supplements to previous works and clarified the inconsistency of their contradictory results.

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