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EPIDEMIOLOGY

Association between a novel polymorphism (rs2046210) of the 6q25.1 locus and breast cancer risk

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Abstract The novel single nucleotide polymorphism (SNP), rs2046210, was identified in a breast cancer genome-wide association study of Chinese women. The SNP is located on 6q25.1 in proximity to the *C6orf97* and estrogen receptor 1 (*ESR1*) genes. To replicate this susceptibility, a number of case–control studies have been conducted in various populations. However, some results were inconclusive due to the restriction of sample size or ethnic diversity. To derive a more precise estimation of the relationship between rs2046210 and genetic risk of breast cancer, we performed the first comprehensive meta-analysis which included 121,494 cases and 119,295 controls from 14 published studies. Overall, significant increased risk between the A allele of rs2046210 and breast cancer was found in the total population (allelic model: OR = 1.16, 95 %CI = 1.11–1.21, $P_{\text{heterogeneity}} < 0.0001$; dominant model: OR = 1.22, 95 %CI = 1.14–1.29, $P_{\text{heterogeneity}} < 0.0001$; recessive model: OR = 1.21, 95 %CI = 1.13–1.29, $P_{\text{heterogeneity}} < 0.0001$). When stratified by ethnicity, significant elevated risk was found among Europeans and Asians. However, no significant association was detected in African descent population. In the subgroup analyses according to estrogen receptor (ER) positive/negative status, our results suggested that this polymorphism tended to increase breast cancer risk in ER negative tumors by a greater magnitude compared to ER positive tumors. In addition, our subgroup analysis also indicated that this SNP was significantly associated with the risk of breast cancer for *BRCA1* mutation carriers and exhibited weaker association with the risk for *BRCA2* mutation carriers. Substantial heterogeneity was present in the overall analysis, but largely disappeared after stratification by ethnicity. Despite some limitations, this meta-analysis demonstrates that the rs2046210 polymorphism may be a risk factor associated with increased breast cancer risk. However, the association varies in different ethnicities.

Keywords rs2046210 · 6q25.1 · Polymorphism · Variant · Breast cancer and meta-analysis

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Introduction

Breast cancer, one of the most common malignancies among women worldwide, is a complex polygenic disease in which genetic factors play a significant role in the disease etiology [1, 2]. Given its position as one of the leading health problems for women, breast cancer has been the target of numerous candidate gene studies since the 1980s.

However, the susceptibility genes identified so far by this method, such as the *BRCA1* and *BRCA2* genes, explain only about 25 % of the familial risk and less than 5 % of the total breast cancer incidence [3, 4]. Genome-wide association studies (GWAS) have recently identified several common, low-penetrance genetic variants that are associated with the risk of breast cancer [5–14]. Because minor allele frequencies of single nucleotide polymorphisms (SNPs) are highly variable and the linkage disequilibrium patterns differ between ethnicities, it is important to confirm the effects of the variants identified in GWAS studies in different ethnic populations.

Recently, a GWAS study in Chinese women by Zheng et al. [14] identified a novel breast cancer susceptibility locus at 6q25.1. The most strongly associated SNP was rs2046210 A/G, with an estimated per-allele odds ratio (OR) of 1.29 [95 % confidence interval (CI) = 1.21–1.37, $P = 10^{-15}$] in Chinese population. In addition, Zheng et al. evaluated rs2046210 in association with breast cancer risk among cases and controls of European ancestry, which found out that this SNP was associated with an elevated risk of breast cancer in European women as well (allelic OR = 1.15, 95 % CI = 1.03–1.28, $P = 0.01$). This SNP is located upstream of the estrogen receptor 1 (*ESR1*) gene and downstream of *C6orf97*. Although the function of *C6orf97* has not yet been elucidated, the *ESR1* gene has been a focus of attention because of the roles of estrogen in risk of breast cancer, osteoporosis and other conditions. Many studies have been conducted to investigate for risk associations with sequence variants in *ESR1*, generally with equivocal results [15]. Comprehensive tag-SNP and meta-analyses also found little evidence of the associations between breast cancer risk and variants in the *ESR1* gene itself [16, 17].

Since then, a lot of researches have been carried out to examine the relationship between rs2046210 and breast cancer susceptibility in diverse populations, including Asian, European, and African population. However, these have produced conflicting results. This may be due to insufficient statistical power, population stratification, or small effect of single SNP on the risk of breast cancer. Moreover, with increasing studies among different populations, there is a need to reconcile these data. Therefore, we performed a systematic meta-analysis of published studies to establish a comprehensive picture of the relationship between rs2046210 and the risk of breast cancer.

Materials and methods

Literature search

We searched PubMed, EMBASE, and ISI Web of Science up to November 30th 2012 for all English language publications using combination of following keywords: rs2046210, 6q25, *ESR1*, *C6orf97*, polymorphism, variant, and breast cancer. Studies using overlapping samples were excluded. In addition, reviews and editorials were not included.

Inclusion criteria

Only those studies assessing the association between rs2046210 and the risk of breast cancer were included, and their references were reviewed to identify other relevant publications. For inclusion, eligible studies had to meet all of the following criteria: (1) be published in a peer-reviewed journal; (2) be a case–control or cohort study; (3) have original data being independent from other studies; (4) have sufficient data to calculate the OR with its 95 % CI and *P* value; (5) describe the genotyping methods used or provide corresponding reference to them; and (6) the diagnosis of the patients with breast cancer was confirmed histologically or pathologically.

Data extraction

Information was carefully extracted from all eligible publications independently by two participants, and potential disagreements were resolved by consensus. The following data were collected: first author's surname, journal, year of publication, diagnosis criteria, study design, age, ethnicity, genotyping method, Hardy–Weinberg equilibrium (HWE) status, source of control, estrogen receptor (ER) status, premenopausal and postmenopausal status, *BRCA1* and *BRCA2* mutation status, total number of cases and controls, and genotype counts among cases and controls.

Statistical analysis

OR with its 95 % CI was used to assess the strength of association between rs2046210 and breast cancer risk. The per-allele OR of the risk allele was compared between cases and controls. And we then used dominant and recessive genetic models to estimate the risk of the genotypes on breast cancer. Possible heterogeneity across individual studies was calculated with the Cochran's Chi square-based *Q* statistic test and was considered significant when $P < 0.05$. ORs were pooled according to the method of DerSimonian and Laird [18], and 95 % CI was constructed by Woolf's method [19]. The *Z* test was used to determine the significance of the pooled OR. The Chi square (χ^2) test was used to examine for deviation from HWE.

In addition, subgroup analyses were performed according to ethnicity (i.e., Asian, Caucasian, and African), ER positive/negative status, premenopausal/postmenopausal

status, and *BRCA1/2* mutation status. In addition, ethnicity, sample size (<2000, 2000–10000, >10000), genotyping method, mean age of cases, and source of controls were analyzed as covariates in meta-regression.

To assess the stability of the results, sensitivity analysis was performed by removing each individual study in turn from the total and re-analyzing the remainder. Begg's funnel plot and Egger's regression test were used to assess publication bias. All analyses were carried out using the STATA software package v.11.0. The type I error rate was set at 0.05. All *P* values were two tailed.

Results

A total of 14 eligible studies [14, 20–32] were included in the meta-analysis involving 121,494 cases and 119,295 controls. The literature selection process was showed in Fig. S1. The main study characteristics and the main results of this meta-analysis were summarized in Tables 1 and 2, respectively. In terms of ethnicity, eight studies involved European subjects, nine involved Asian subjects, and three involved African subjects. The genotype distributions among the controls of all studies were in accord with HWE except for the studies by Cai et al. [21] and Stacey et al. [30] (the latter did not provide genotype information for the calculation). In order to ensure no overlapping samples included, two studies [14, 31] were excluded in the overall analysis for the association between rs2046210 and breast cancer risk. Instead, the data from these two studies were only used for subgroup analysis, in which other studies using the potential same sample source were not included.

Meta-analysis results

The main outcomes of this meta-analysis for the rs2046210 polymorphism are presented in Table 2. Overall, there was evidence indicating that the A allele was associated with a significantly increased risk for breast cancer in the total population (allelic model: OR = 1.16, 95 %CI = 1.11–1.21, $P_{\text{heterogeneity}} < 0.0001$; dominant model: OR = 1.22, 95 %CI = 1.14–1.29, $P_{\text{heterogeneity}} < 0.0001$; recessive model: OR = 1.21, 95 %CI = 1.13–1.29, $P_{\text{heterogeneity}} < 0.0001$) as shown in Figs. 1, 2, and 3. In the subgroup analysis by ethnicity, statistically significant associations were detected among Europeans (allelic model: OR = 1.09, 95 %CI = 1.06–1.12, $P_{\text{heterogeneity}} = 0.036$) and among Asians (allelic model: OR = 1.30, 95 %CI = 1.25–1.35, $P_{\text{heterogeneity}} = 0.203$), but not for African population in any genetic model (Table 2). In meta-regression analysis, we assessed the source of heterogeneity by ethnicity, sample size, genotyping method, mean age of cases, and source of controls. As a result, ethnicity ($P = 0.002$), but not sample size

Table 1 Main characteristics of the included studies on rs2046210 and breast cancer risk

Study	Years	Ethnicity	No. of case/control	Source of control	Genotyping method	HWE status
Antoniou et al. [20]	2011	European	8,896/8,109	Population and hospital	Taqman and iPLEX	Y
Cai et al. [21]	2011	Asian, European and African–American	11,901/12,049	Population and hospital	Taqman, Affymetrix SNP array, Sequenom and iPLEX	N
Campa et al. [22]	2011	European	8,298/11,543	Population	Taqman	Y
Chan et al. [23]	2012	Asian	1,173/1,417	Hospital	Dynamic Array and Taqman	Y
Han et al. [24]	2011	Asian	3,251/3,493	Population	Taqman	Y
Hein et al. [25]	2012	Asian and European	56,281/51428	Population and hospital	Taqman	Y
Jiang et al. [26]	2011	Asian	492/510	Population	SNaPshot SNP assay	Y
Kim et al. [27]	2012	Asian	2,257/2,052	Hospital	Affymetrix SNP array	Y
Mulligan et al. [28]	2011	European	7,744/6,826	Hospital	Taqman and iPLEX	Y
Ruiz-Narvaez et al. [29]	2012	African–American	1,149/1,841	Population	iPLEX	Y
Stacey et al. [30]	2010	Asian, European and African–American	10,176/13,286	Population and hospital	Nanogen Centaurus assay and sequencing	NA
Stevens et al. [31]	2011	European	2,707/1,385	Population and hospital	iPLEX and Illumina SNP array	Y
Sueta et al. [32]	2012	Asian	697/1,394	Hospital	Taqman	Y
Zheng et al. [14]	2009	Asian and European	6,472/3,962	Population	Affymetrix SNP array	Y

Y yes, *N* no, *NA* not available

($P = 0.19$), genotyping method ($P = 0.52$), mean age of cases ($P = 0.14$), and source of controls ($P = 0.33$), was found to be significantly correlated with the heterogeneity, which explained 27 % of the heterogeneity.

To investigate whether the polymorphism was associated with particular subtypes of breast cancer and menopausal status, we analyzed the associations between rs2046210 and the risk of breast cancer according to ER positive/negative, premenopausal/postmenopausal, and *BRCA1/2* mutation status. The rs2046210 polymorphism was statistically significantly associated with both risks of ER + breast cancer (allelic model: OR = 1.18, 95 %CI = 1.08–1.28, $P_{heterogeneity} < 0.0001$) and ER − breast cancer (allelic model: OR = 1.27, 95 %CI = 1.16–1.38, $P_{heterogeneity} < 0.0001$) (Fig. 4). When stratified by menopausal status, significantly elevated risks were found among both premenopausal (allelic model: OR = 1.21, 95 %CI = 1.16–1.26, $P_{heterogeneity} = 0.869$) and postmenopausal patients (allelic model: OR = 1.25, 95 %CI = 1.21–1.30, $P_{heterogeneity} = 0.471$) (Fig. 5). In addition, we found that this SNP was significantly associated with the risk of breast cancer for *BRCA1* mutation carriers (allelic model: OR = 1.17, 95 %CI = 1.13–1.22, $P_{heterogeneity} = 0.837$), and exhibited weaker association with the risk for *BRCA2* mutation carriers (allelic model: OR = 1.06, 95 %CI = 1.00–1.12, $P_{heterogeneity} = 0.488$) (Fig. 6).

Sensitivity analysis and potential bias

The results of all genetic models were not changed substantially by the removal of any data set according to sensitivity analysis. Begg's funnel plot and Egger's regression test were performed to assess publication bias of the included literatures. The inverted funnel plots were symmetrical as shown in Fig. S2. Egger's test also indicated no evidence of publication bias among included studies ($P > 0.05$).

Discussion

The study of gene polymorphisms potentially involved in tumorigenesis has attracted growing attention in recent years. Meta-analysis with a large sample of different ethnicities may assist in estimating the population-wide effects of a genetic risk factor in cancer and may help to unveil the potential relationship between candidate locus and the risk of cancer.

This is the first systematic meta-analysis examining the correlation between 6q25.1–rs2046210 and breast cancer susceptibility. The results demonstrated that the rs2046210 polymorphism is a risk factor for developing breast cancer, however, this genetic susceptibility may vary among different ethnic groups. When stratified by ethnicity, significant associations were detected among Caucasians and Asians in all genetic models. However, there is no evidence of association found in African descent population. This may result from ethnic differences in genetic backgrounds. The frequency of the risk allele is much higher in African population (60.7–71.6 %) [29, 30] than that among Caucasian (33.8–36.8 %) [28, 30] or Asian populations (34.8–39.3 %) [23, 24]. In addition, different lifestyles and environmental factors which may interact with genetic factors to influence the risk of cancer development [33, 34], could also contribute to the different association results. Although meta-analysis is often dominated by a few studies with large sample sizes, there was no statistically significant difference between the result of large studies and that of small ones in this study.

Our data indicated that the association of rs2046210 with breast cancer risk appeared to be stronger for ER− tumors than ER+ tumors. In general, previous studies among women of European origins showed that breast cancer-associated SNPs increased risks in ER+ tumors by a greater magnitude than in ER− tumors [10, 11, 35]. However, other studies conducted in Chinese women have reported that rs2046210 was more closely related to ER−

Table 2 Meta-analysis of the rs2046210 polymorphism on breast cancer risk

Subgroup analysis	No. of study	A allele		No. of study	Dominant model		No. of study	Recessive model	
		OR(95 % CI)	$P_{heterogeneity}$		OR(95 % CI)	$P_{heterogeneity}$		OR(95 % CI)	$P_{heterogeneity}$
Overall association	14	1.16 (1.11–1.21)	<0.0001	9	1.22 (1.14–1.29)	<0.0001	8	1.21 (1.13–1.29)	<0.0001
Stratified by ethnicity									
Caucasian	6	1.09 (1.06–1.12)	0.036	5	1.13 (1.08–1.17)	0.024	5	1.10 (1.08–1.12)	0.412
Asian	8	1.30 (1.25–1.35)	0.203	6	1.36 (1.30–1.43)	0.340	5	1.38 (1.27–1.48)	0.200
African	3	0.99 (0.89–1.10)	0.102	5	1.38 (1.27–1.48)	0.200	1	0.99 (0.81–1.17)	NA
Stratified by sample									
<2,000	4	1.31 (1.12–1.50)	0.002	3	1.54 (1.36–1.71)	0.681	2	1.48 (1.05–1.91)	0.107
2,000–10,000	5	1.16 (1.10–1.21)	0.005	4	1.18 (1.12–1.25)	0.044	4	1.16 (1.10–1.21)	0.697
>10,000	3	1.10 (1.09–1.12)	0.862	2	1.12 (1.10–1.15)	0.366	2	1.16 (1.12–1.20)	0.831

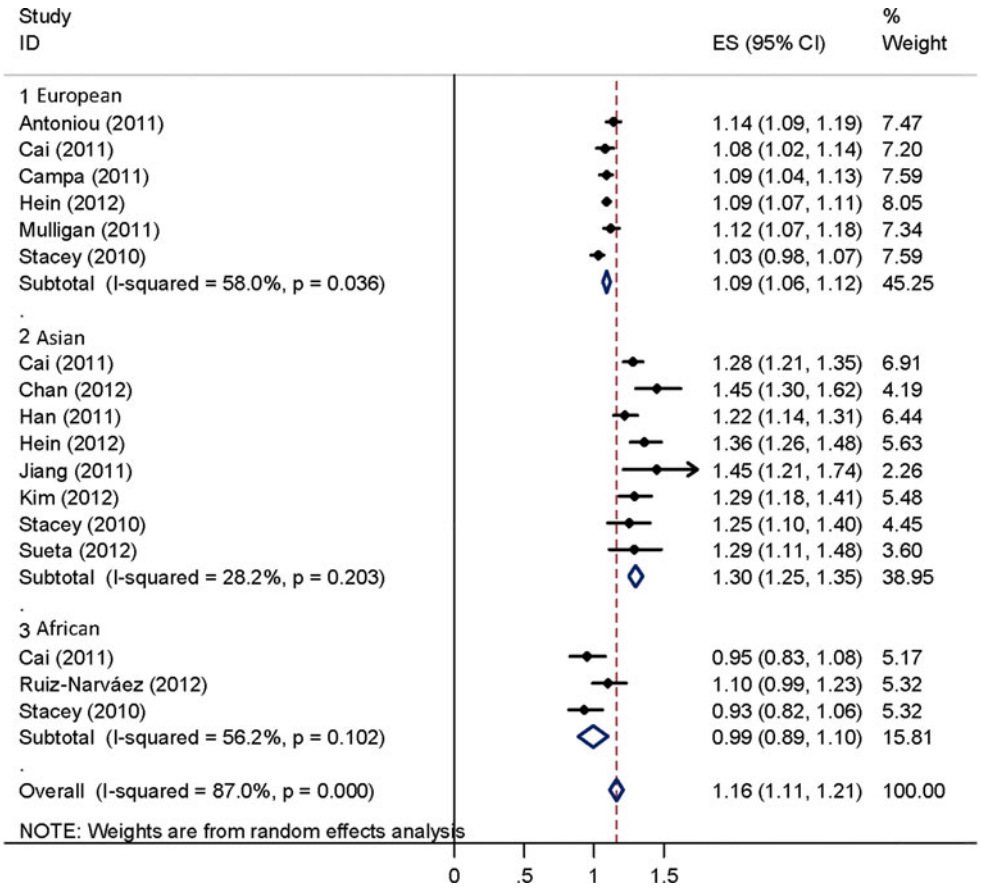

Fig. 1 Meta-analysis of the association between the rs2046210 polymorphism and breast cancer risk (allelic model)

than ER+ breast cancer [14, 23, 36]. Several genes are located in the 1 Mb region centered on this polymorphism [14], among which the *ESR1* gene is perhaps of particular interest to breast carcinogenesis. The *ESR1* gene encodes estrogen receptor α (ERα) that regulates signal transduction of estrogen, which plays a central role in the etiology of breast cancer [37]. Considering its relatively close location to the *ESR1* gene and the biological function of ERα, it is possible that rs2046210 may modify the expression of the *ESR1* gene and affect the susceptibility to breast cancer.

In the subgroup analysis based on pre- and postmenopausal status, greater risk was detected in postmenopausal women, however, the difference is not statistically significant. Besides, we performed the subgroup analysis according to *BRCA1/2* mutation status. Significant association was observed for *BRCA1* mutation carriers, but no significant association was found for *BRCA2* mutation carriers. This finding suggested that rs2046210 may be predominantly associated with the risk of breast cancer for *BRCA1* mutation carriers. It has been reported that *BRCA1*-associated tumors are more likely to be ER, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) negative [15, 16], while *BRCA2*-associated tumors are more often ER+ [17]. This is consistent with our result that stronger association was found for ER− breast cancer compared with ER+ breast cancer. Previous GWASs have identified several common alleles as modifiers of cancer risk for *BRCA1* and *BRCA2* mutation carriers. SNPs in *FGFR2*, *TOX3/TNRC9*, *MAP3K1*, *LSP1*, 2q35, *SLC4A7/NEK10*, and 5p12 have been shown to be associated with breast cancer risk for *BRCA2* mutation carriers, whereas SNPs in *TOX3/TNRC9* and 2q35 were correlated with the risk for *BRCA1* mutation carriers [38–40]. These findings, combined with our results, could be useful to improve risk prediction and clinical management in *BRCA1* and *BRCA2* mutation carriers.

Despite the considerable efforts to examine the potential association between the rs2046210 polymorphism and the risk of breast cancer, some limitations should be acknowledged. Firstly, our results were based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available, which would allow for an adjustment estimate (i.e., age, drinking status, cigarette consumption, and other risk factors). Secondly, subgroup analyses were based on studies with relevant information available. Owing to the lack of detailed information in most studies, the analysis for *BRCA1/2* mutation carriers consisted of only two studies [20, 28], which might not be sufficient to reach a reliable

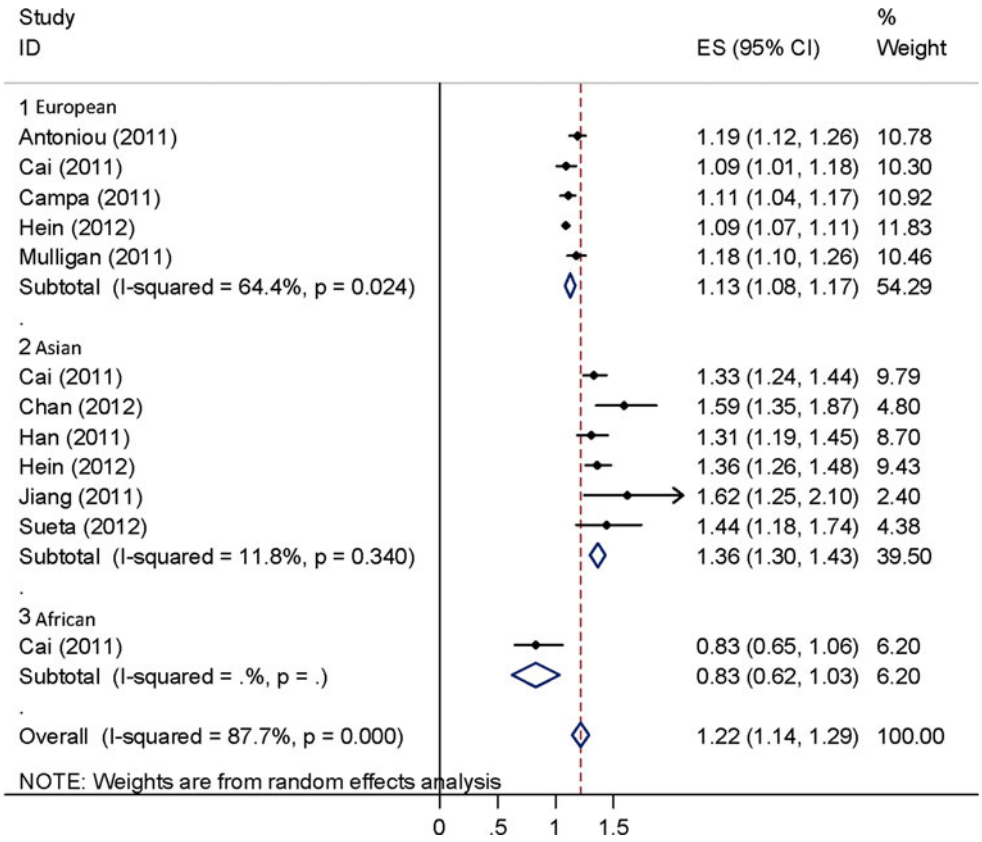

Fig. 2 Meta-analysis of the association between the rs2046210 polymorphism and breast cancer risk (dominant model)

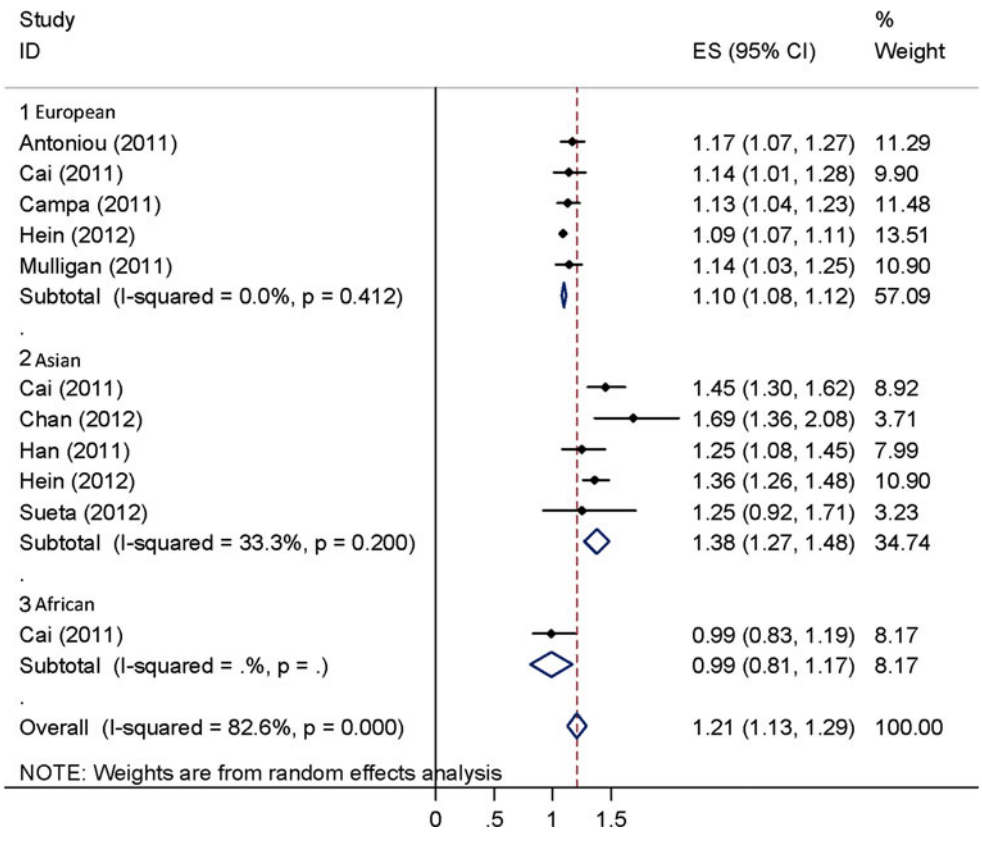

Fig. 3 Meta-analysis of the association between the rs2046210 polymorphism and breast cancer risk (recessive model)

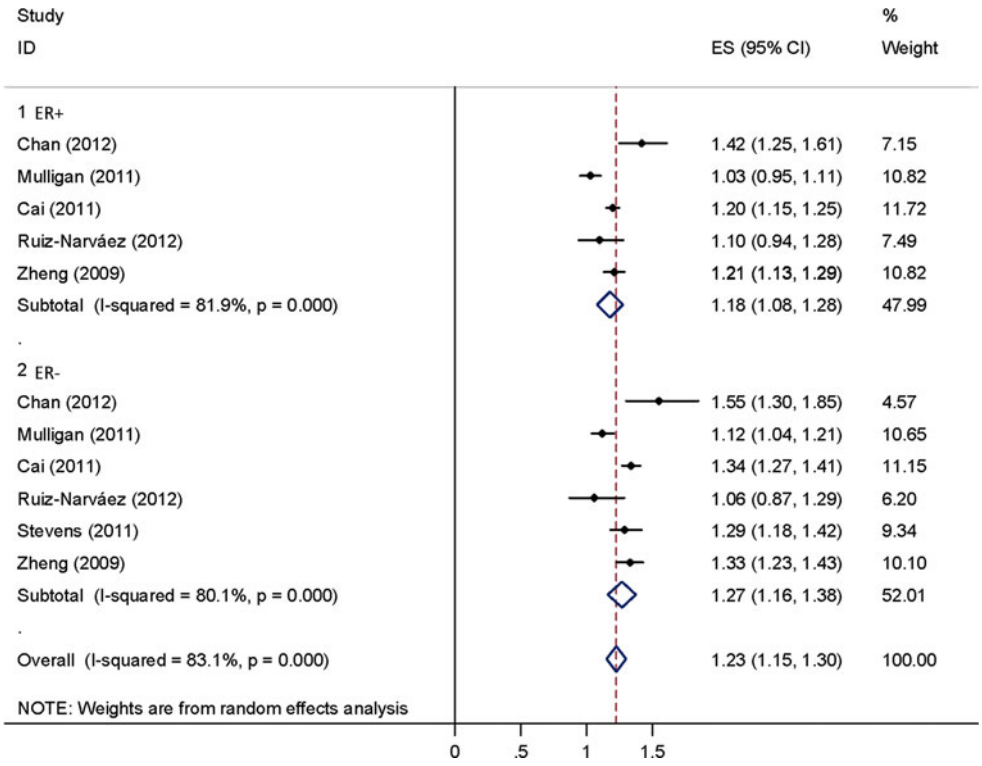

Fig. 4 Subgroup analysis of the association between the rs2046210 polymorphism and breast cancer risk (based on ER+/ER− status)

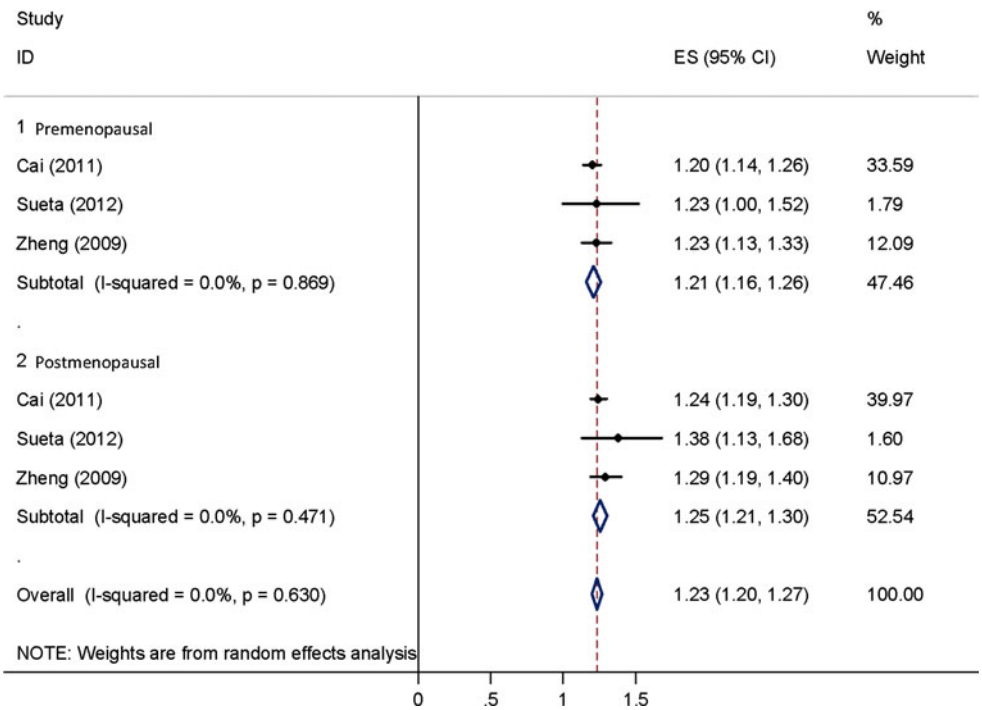

Fig. 5 Subgroup analysis of the association between the rs2046210 polymorphism and breast cancer risk (based on premenopausal/postmenopausal status)

conclusion. Thirdly, studies in African descent populations are still limited. Therefore, further studies investigating the role of this polymorphism on breast cancer risk in these populations are needed.

To conclude, this meta-analysis suggested that the rs2046210 polymorphism was significantly associated with increased risk of breast cancer, especially in Caucasian and Asian population. In the future, association studies with more individual information (including ER positive/negative status, premenopausal/postmenopausal status, and *BRCA1/2* mutation status) and larger sample size of different ethnic populations will be needed to further validate the results of our meta-analysis. Moreover, the interactions between gene–gene and gene–environment should also be

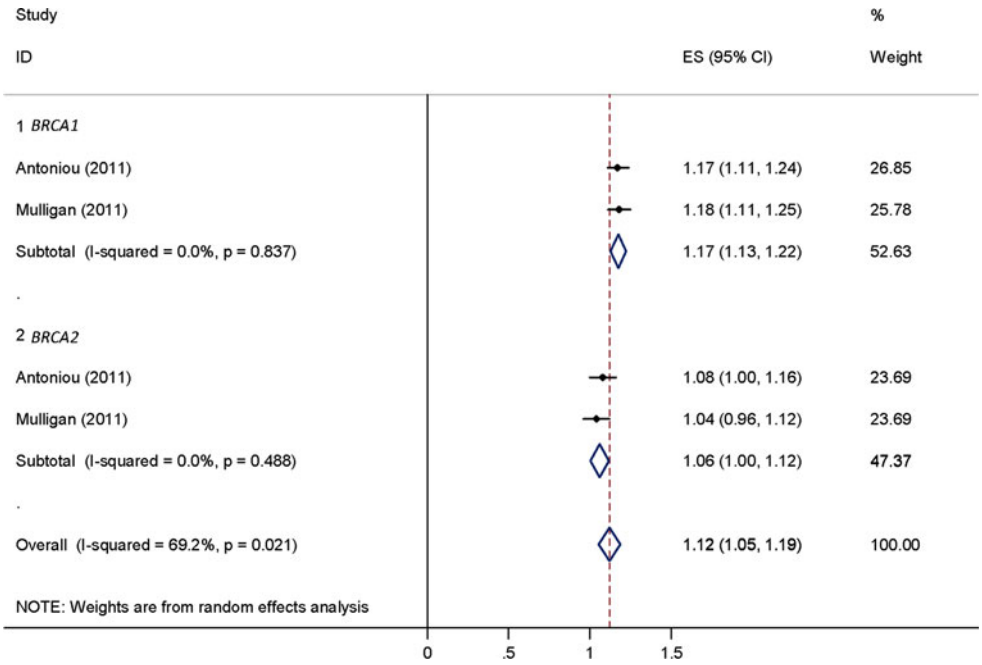

Fig. 6 Subgroup analysis of the association between the rs2046210 polymorphism and breast cancer risk (based on *BRCA1/2* mutation status)

evaluated to unveil the underlying relationship between the rs2046210 polymorphism and the risk of breast cancer.

Conflict of interest The authors declare that they have no conflict of interest.

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