RESEARCH ARTICLE

The AURKA Gene rs2273535 Polymorphism Contributes to Breast Carcinoma Risk - Meta-analysis of Eleven Studies

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Abstract

   The rs2273535 polymorphism in the AURKA gene had proven to be associated with breast carcinoma susceptibility. Nevertheless, the results of different studies remain contradictory. A meta-analysis covering 28,789 subjects from eleven different studies was here carried out in order to investigate the association in detail. The random effects model was used to analyze the pooled odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). A significant relationship between the rs2273535 polymorphism and breast tumors was found in an allelic genetic model (OR: 1.076, 95% CI: 1.004-1.153, $p=0.040$, $P_{heterogeneity}=0.002$). No significant association was detected in a homozygote model (OR: 1.186, 95% CI: 0.990-1.423, P=0.065, $P_{heterogeneity}=0.002$), a heterozygote model (OR: 1.016, 95% CI: 0.959-1.076, $p=0.064$, $P_{heterogeneity}=0.000$), a dominant genetic model (OR: 1.147, 95% CI: 0.992-1.325, $p=0.217$, $P_{heterogeneity}=0.294$) and a recessive genetic model (OR: 1.093, 95% CI: 0.878-1.361, $p=0.425$, $P_{heterogeneity}=0.707$). A significant relationship between the rs2273535 polymorphism in the AURKA gene and breast tumor in Asian group was found in an allelic genetic model (OR: 1.124, 95% CI: 1.003-1.29, $p=0.044$, $P_{heterogeneity}=0.034$), a homozygote model (OR: 1.229, 95% CI: 1.038-1.455, $p=0.016$, $P_{heterogeneity}=0.266$) and a recessive genetic model (OR: 1.227, 95% CI: 1.001-1.504, $p=0.049$, $P_{heterogeneity}=0.006$). A significant association was thus observed between the rs2273535 polymorphism in the AURKA gene and breast cancer risk. Individuals with the rs2273535 polymorphism in the AURKA gene have a higher risk of breast cancer in Asian populations, but not in Caucasians.

Keywords: Breast carcinoma - STK-15 polymorphism - cancer risk - meta-analysis,

Introduction

   Cancer is an important public health problem in the world. According to the report from American Cancer Society, breast cancer alone is expected to account for 29% (232, 670) of all new cancers among women in America (Siegel et al., 2013). Approximately 232,340 new cases of invasive breast cancer and 39, 620 breast cancer deaths are expected to occur among US women in 2013 (DeSantis et al., 2014). Breast cancer incidence rates increased slightly among African American women. Among females, breast cancer ranks first in women aged 20 years to 59 years, and lung cancer causes the most cancer deaths in those aged 60 years and older (Siegel et al., 2014).

   According to the report from the National Office for Cancer Prevention and Control of China in 2013, the estimated number of female breast cancer cases was about 208 thousand. And the overall crude incidence rate was 32.43 per 100, 000, accounting for 16.20% of all cancer cases in women, ranking first among all cancer incidences (Zeng et al., 2014). The incidence rates in the eastern area and Middle area were similar, but in western areas, the incidence rate of the disease was 23.47 per 100,000, lowest among all areas (Wu et al., 2014).

   The primary risk factors for breast cancer are female sex and older age. Other potential risk factors are as follows: genetics, lack of childbearing or lack of breastfeeding, higher levels of certain hormones, certain dietary patterns, and obesity. Recent studies have indicated that exposure to light pollution is a risk factor for the development of breast cancer.

   Some genetic susceptibility may have a minor role in most cases. Overall, however, genetics is considered to be the foremost cause of 5-10% of all cases. In those with zero, one or two affected relatives, the risk of breast cancer before the age of 80 is 7.8%, 13.3% and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively. Of those with a first degree relative

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with the disease, the risk of breast cancer between the age of 40 and 50 is double that of the general population. In less than 5% of cases, genetics plays a more important role by causing a hereditary breast-ovarian cancer syndrome. This includes those who carry the BRCA1 and BRCA2 gene mutation. These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60-80% for those affected. Other significant mutations include: p53, PTEN, and STK11, CHEK2, ATM, BRIP1, PALB2 and CXCL12 (Xia et al., 2014). In 2012, researchers said that there are four genetically distinct types of breast cancer and that in each type, hallmark genetic changes lead to many cancers.

Recently, some studies have reported increasing breast cancer risks associated with single nucleotide polymorphisms (SNPs) of Aurora kinase A (AURKA) gene (rs2273535, rs8173). AURKA (also referenced as Aurora-A, STK15, Aurora 2 and BTAK) is a serine/threonine kinase that plays a crucial part in regulation of mitotic chromosomal segregation and centrosome function. The AURKA gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, mosquito, C.elegans, M.oryzae, A.thaliana, rice, and frog.

A functional polymorphism 91T→A in exon 4 (rs2273535) in the AURKA gene has been identified which causes an amino acid substitution changing phenylalanine to isoleucine. The 91A allele has been involved in increased risk of breast cancer, colorectal cancer, ovarian cancer and esophageal squamous cell carcinoma.

The association of STK15 polymorphism with breast cancer risk has been investigated in several studies, while the conclusion is still inconclusive. For example, data from Egan's study provide the first evidence that polymorphic variations in STK15 are a genetic susceptibility factor in breast cancer (Egan et al., 2004), but Tchatchou et al. found the rs2273535 polymorphism is neither associated with familial breast cancer risk in the German population nor was it associated with breast cancer (Tchatchou et al., 2007).

To ascertain the relationship between the rs2273535 polymorphism in the AURKA gene and breast cancer risk, we performed this meta-analysis by pooling all the eligible studies.

Materials and Methods

Publication Search and Inclusion Criteria

The following keywords were searched in PubMed database without a language limitation: "cancer of breast", "breast cancer", "breast carcinoma", "carcinoma of breast'', "breast neoplasms'', "breast neoplasms'', "STK15", "Aurora", "BTAK", "rs2273535", "genetic variation'' and ''polymorphism''. Additional relevant studies were also found in the indexed references of the retrieved literatures. The latest research was updated on June 3, 2014, with publication years ranging from 1997 to 2014.

The studies were selected based on the following inclusion criteria: studies that evaluate rs2273535 gene polymorphism and breast cancer, studies that diagnosis
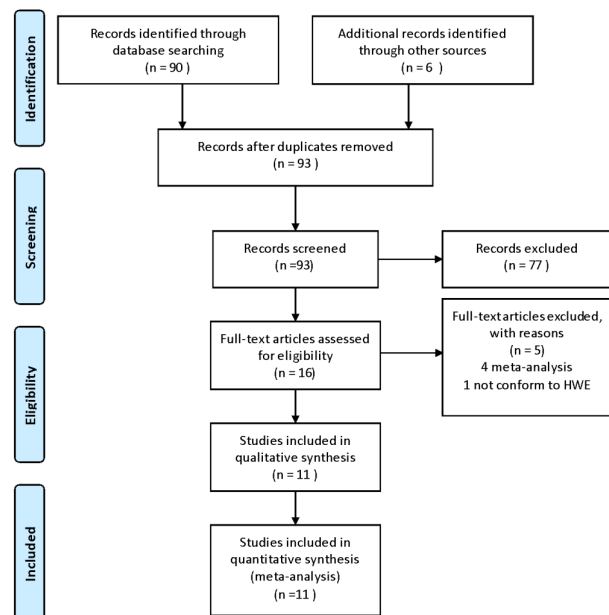

Figure 1. Flow Chart of the Study Selection Process

of cancer was confirmed by a histopathological analysis, case-control or cohort studies published in official journals, and studies that conform to the Hardy-Weinberg equilibrium (HWE). All records were selected by two authors independently according to the inclusion criteria and reached consensus on each record.

Data extraction

The data were abstracted according to a standard protocol. Studies that did not follow the inclusion criteria, those considered double publications, or those that provided inadequate data were excluded. If the same data appeared in different studies, the data were intended for use only once. The abstracted data comprised the following items: the first author's name, publication year, region, the number of genotypes, genotyping, study design, total number of cases and controls and HWE.

Statistical analyses

Five genetic models were used, including allelic (distribution of allelic frequency of the rs2273535 polymorphism in the AURKA gene, allelic model: A allele vs T allele), homozygous (AA vs TT), heterozygous (AT vs TT) and recessive (AA vs AT+TT) and dominant (AA+AT vs TT) models (Thakkinstian et al., 2005). The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were used to compare the association between the rs2273535 polymorphism in the AURKA gene and breast cancer. Chi-square-based Q-tests were used to calculate the heterogeneity between the individual studies with significance set at the $p<0.05$ level (Cochran, 1968). The random-effect model was used to assess the pooled OR (Der Simonian and Laird method) if there was heterogeneity among the individual studies (Mantel and Haenszel, 1959). Otherwise, the fixed-effect model was used (the Mantel Haenszel method). The pooled OR was determined through Z test with significance set at $p<0.05$ level.

Fisher's exact test was used to evaluate the HWE, and

Table 1. Characteristics of Studies of The rs2273535 Polymorphism Included in this Pooled Analysis

Author	Year	Ethnicity	Case AA	Case AT	Case TT	Control AA	Control AT	Control TT	Genotyping	Study design	Sample size Case	Sample size Control	HWE
Shi	2011	Caucasian	514	222	27	967	478	71	Direct sequencing	Case-control	763	1516	Yes
Ruan	2011	Asian	167	568	599	161	691	716	TaqMan	Case-control	1334	1568	Yes
Consortiuma	2010	Caucasian	107	1096	1873	249	1927	3290	MALDI-TOF MS	Case-control	3076	5466	Yes
Vidarsdottir	2007	Caucasian	42	288	429	21	231	401	TaqMan	Case-control	759	653	Yes
Tchatchou	2007	Caucasian	433	257	37	485	287	47	TaqMan	Case-control	727	819	Yes
Fletcher	2006	Caucasian	18	154	335	48	280	547	PCR-RFLP	Case-control	507	875	Yes
Cox	2006	Caucasian	66	401	774	65	571	1075	TaqMan	Case-control	1241	1711	Yes
Lo	2005	Asian	348	288	71	886	887	196	TaqMan	Case-control	707	1969	Yes
Dai	2004	Asian	490	491	121	534	503	149	TaqMan	Case-control	1102	1186	Yes
Sun	2004	Asian	256	214	50	192	262	66	PCR-RFLP	Case-control	520	520	Yes
Egan	2004	Caucasian	50	331	559	31	283	516	Direct sequencing	Case-control	940	830	Yes

MALDI–TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium

Table 2. Meta-Analysis of The Association between The rs2273535 Polymorphism in The AURKA Gene and Breast Cancer Risk

Polymorphism	Population	Number of studies	OR	95% CI	*P* value	Model	*P* value	I²
A verse T	Caucasian	7	1.047	0.959-1.145	0.305	REM	0.013	62.80%
	Asian	4	1.124	1.003-1.29	0.044	REM	0.034	65.50%
	Overall	11	1.076	1.004-1.153	0.04	REM	0.002	64.50%
AA versus TT	Caucasian	7	1.151	0.853-1.551	0.357	REM	0.001	72.80%
	Asian	4	1.229	1.038-1.455	0.016	REM	0.266	24.30%
	Overall	11	1.186	0.990-1.423	0.065	REM	0.002	64.50%
AT versus TT	Caucasian	7	1.016	0.951-1.086	0.639	REM	0.667	0.00%
	Asian	4	1.015	0.902-1.141	0.81	REM	0.492	0.00%
	Overall	11	1.016	0.959-1.076	0.599	REM	0.774	0.00%
AA versus AT+TT	Caucasian	7	1.091	0.878-1.354	0.433	REM	0.002	71.30%
	Asian	4	1.227	1.001-1.504	0.049	REM	0.006	75.90%
	Overall	11	1.147	0.992-1.325	0.064	REM	0	72.00%
AA+AT versus TT	Caucasian	7	1.036	0.947-1.132	0.443	REM	0.19	31.10%
	Asian	4	1.073	0.960-1.200	0.213	REM	0.482	0.00%
	Overall	11	1.042	0.976-1.113	0.217	REM	0.294	15.80%

OR odds ratio; CI confidence interval; REM: random effects model

significance was set at the $p<0.05$ level. The funnel plot was used to estimate the potential publication bias (Stuck et al., 1998). Egger's linear regression test on the natural logarithm scale of the OR was used to assess the funnel plot asymmetry with significance set at the $p<0.05$ level (Egger et al., 1997). STATA 12.0 software was utilized for performing the statistical analyses (Stata Corp, College Station, TX, USA).

Results

Characteristics of eligible studies

Of the 96 articles that were initially identified in the search strategy, 80 studies were removed, including 3 duplicates, 77 studies during the title/abstract review, and 5 studies during the full-text review (Ewart-Toland et al., 2005; Couch et al., 2007; Qin et al., 2013; Tang et al., 2013; Xu et al., 2013) (Figure 1). Eleven studies satisfied all of the criteria and were included in this report (Dai et al., 2004; Egan et al., 2004; Sun et al., 2004; Lo et al., 2005; Cox et al., 2006; Fletcher et al., 2006; Tchatchou et al., 2007; Vidarsdottir et al., 2007; 2010; Ruan et al., 2011; Shi et al., 2011). There were seven studies of Caucasians, and four Asians. The distribution of genotypes in the controls of all studies was in accord with HWE. The data

were collected from 11676 breast cancer cases and 17113 controls in this meta-analysis (Table 1, Figure 1).

Pooled analysis

A significant relationship between the rs2273535 polymorphism in the AURKA gene and breast tumor was found in an allelic genetic model (OR: 1.076, 95% CI: 1.004-1.153, $p=0.040$, $P_{heterogeneity}=0.002$) as shown in Table 2.

No significant association was detected in a homozygote model (OR: 1.186, 95% CI: 0.990-1.423, $p=0.065$, $P_{heterogeneity}=0.002$), a heterozygote model (OR: 1.016, 95% CI: 0.959-1.076, $p=0.064$, $P_{heterogeneity}=0.000$), a dominant genetic model (OR: 1.147, 95% CI: 0.992-1.325, $p=0.217$, $P_{heterogeneity}=0.294$) and a recessive genetic model (OR: 1.093, 95% CI: 0.878-1.361, $p=0.425$, $P_{heterogeneity}=0.707$) as shown in Table 2.

In the Caucasian subgroup analysis, no significant association was detected in an allelic genetic model (OR: 1.047, 95% CI: 0.959-1.145, $p=0.305$, $P_{heterogeneity}=0.013$), homozygote model (OR: 1.151, 95% CI: 0.853-1.551, $p=0.357$, $P_{heterogeneity}=0.001$), a heterozygote model (OR: 1.016, 95% CI: 0.951-1.086, $p=0.639$, $P_{heterogeneity}=0.667$), a dominant genetic model (OR: 1.036, 95% CI: 0.947-1.132, $p=0.443$, $P_{heterogeneity}=0.190$) and a recessive genetic
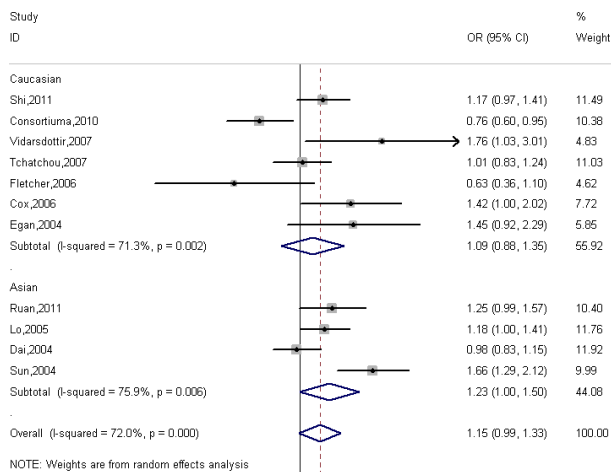
Figure 2. Forest Plot of Breast Cancer Associated with The rs2273535 Polymorphism in The AURKA Gene under A Recessive Genetic Model
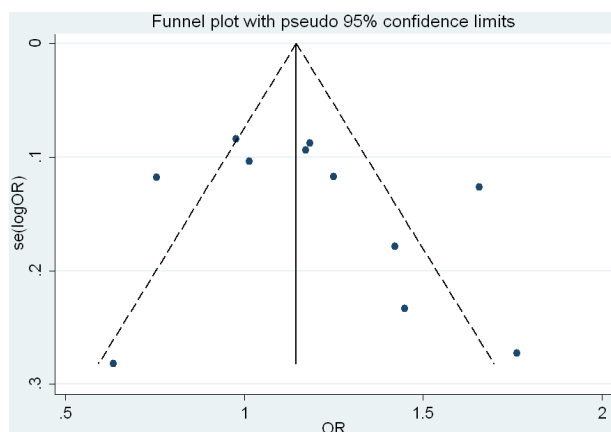

Figure 3. Funnel Plot for Studies of The Association of Breast Cancer and The rs2273535 Polymorphism in The AURKA Gene

model (OR: 1.091, 95% CI: 0.878-1.354, p=0.433, $P_{heterogeneity}$=0.002) as shown in Table 2.

A significant relationship between the rs2273535 polymorphism in the AURKA gene and breast tumor in Asian group was found in an allelic genetic model (OR: 1.124, 95% CI: 1.003-1.29, p=0.044, $P_{heterogeneity}$=0.034), a homozygote model (OR: 1.229, 95% CI: 1.038-1.455, p=0.016, $P_{heterogeneity}$=0.266) and a recessive genetic model (OR: 1.227, 95% CI: 1.001-1.504, p=0.049, $P_{heterogeneity}$=0.006) as shown in Table 2.

No significant association was detected in Asian group in a heterozygote model (OR: 1.015, 95% CI: 0.902-1.141, p=0.810, $P_{heterogeneity}$=0.492) and a dominant genetic model (OR: 1.073, 95% CI: 0.960-1.200, p=0.213, $P_{heterogeneity}$=0.482) as shown in Table2 and Figure 2 .

Bias diagnosis

The publication bias of the studies was evaluated using the funnel plot and Egger's test. Publication bias was not seen in the funnel plot (Figure 3). No statistically significant difference was discovered in the Egger's test (p=0.164), indicating low publication bias in the current meta-analysis (Figure 4).
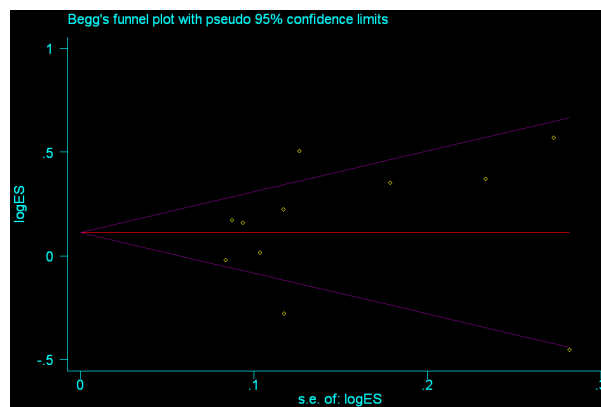

Figure 4. Begger's Funnel Plot about Studies of The Association of Breast Cancer a The rs2273535 Polymorphism in The AURKA Gene

Discussion

A significant relationship between the rs2273535 polymorphism in the AURKA gene and breast tumor was found in an allelic genetic model (OR: 1.076, 95% CI: 1.004-1.153, p=0.040, $P_{heterogeneity}$=0.002). A significant relationship between the rs2273535 polymorphism in the AURKA gene and breast tumor in Asian group was found in an allelic genetic model (OR: 1.124, 95% CI: 1.003-1.29, p=0.044, $P_{heterogeneity}$=0.034), a homozygote model (OR: 1.229, 95% CI: 1.038-1.455, P=0.016, $P_{heterogeneity}$=0.266) and a recessive genetic model (OR: 1.227, 95% CI: 1.001-1.504, p=0.049, $P_{heterogeneity}$=0.006) as shown in Table 2.

The present study suggested a significant association was observed between the rs2273535 polymorphism in the AURKA gene and breast cancer risk. Individuals with the rs2273535 polymorphism in the AURKA gene have a higher risk of breast cancer in Asian populations, but not in Caucasians. This result was the strength of this meta-analysis.

Cancer is a disease in which abnormal cells grow in an uncontrolled way. Breast cancer is a cancerous growth that begins in the tissues of the breast. Breast cancer is the most common cancer in women, but it can also appear in men. In the US, it affects one in eight women.

There is information about factors that we know increase the risk, including cancer genes, as well as information about the factors that possibly increase the risk (Guo and Xia, 2013). Like most cancers, the risk of developing breast cancer increases as women get older. Having a mother or sister diagnosed with breast cancer approximately doubles the risk of breast cancer. But more than 8 out of 10 women who have a close relative with breast cancer will never develop it. If you have a very strong family history, there may be a faulty gene in your family that increases your risk of breast cancer. There are probably several gene faults that can increase breast cancer risk. We can test for them. The female sex hormone, oestrogen, and the male hormone, testosterone, can affect the development of breast cancer. In 2003, researchers from Cancer Research UK looked at hormone replacement therapy (HRT) and the risk of breast cancer in more than a million women. They showed clearly that HRT increases

the risk of breast cancer while women take it and for up to 5 years afterwards. Other studies have also confirmed this. The million women study also showed that combined HRT (oestrogen and progesterone) is more likely to cause breast cancer than oestrogen only HRT. Other risk factor including the contraceptive pill, having children or having them early in life, When you start and stop having periods, Ethnic group, A previous breast cancer, ductal carcinoma in situ or lobular carcinoma in situ , Benign breast disease, Having dense breast tissue, Alcohol intake and smoking, Your weight and height, Chest X-rays or radiotherapy, Diabetes, Medicines, Shift work, and so on.

Commonly occurring single nucleotide polymorphisms (SNPs) have been shown to incrementally contribute to breast cancer risk. Although the effect of an individual SNP is generally small, the genetic effect of combinations of functionally relevant SNPs may additively or synergistically contribute to increased breast cancer risk. It is reported that a centrosomal serine/threonine kinase, serine/threonine kinase 15/breast tumor amplified kinase (STK15/BTAK, approved gene symbols are aurora2, ARK1, AIK1), has been identified as an oncogene. Some studies have shown that STK15/BTAK mRNA is over-expressed in a majority of breast cancers compared with normal breast tissues, and its over-expression is significantly associated with chromosomal instability, implicating STK15/BTAK in carcinogenesis through induction of chromosomal instability, though the possibility that STK15/BTAK over-expression is a simple consequence of chromosomal instability rather than a cause cannot be excluded (Miyoshi et al., 2001). Here we will discuss the rs2273535 polymorphism in the AURKA gene and breast carcinoma risk.

Overall, a significant association exists between the rs2273535 polymorphism in the AURKA gene and breast carcinoma risk. This finding indicates that the genetic variant in AURKA gene exon3 may crucially modify the susceptibility of cancers (Yang et al., 2013).

Meta-analysis is a retrospective research that is subject to the methodological deficiencies of the included studies and several specific details merit consideration in the current meta-analysis. A first consideration is that our results are based on unadjusted estimates and a more precise analysis stratified by different lifestyle related habits and different grades of breast cancer could be performed if individual data were available. A second consideration is that large-scale studies on the relationship between the rs2273535 polymorphism in the AURKA gene and breast cancer risk are still inadequate. AURKA is affected not only by gene polymorphism, but also by environmental factors. A third consideration is that Second, all recruited case-control studies were from Asians and Caucasians; thus, our results may only be suitable for these populations. Considering the complexity of cancer etiology and the low penetrance cancer susceptibility gene effects from STK15 F31I SNP, these important environmental factors should not be ignored.

Nevertheless, the total number of subjects contained in the present part of the analysis comprises the largest sample size so far. Finally, as with any meta-analysis of published results, the quality of our meta-analysis depends on that of the individual studies. Ideally we would like to pool individual level data. However, this is not possible in the present study. These considerations may distort our results.

Statistical surveys in America and England have shown that white women have a higher risk of breast cancer than women from other ethnic groups. This is at least partly due to lifestyle factors. To our surprise, the Ile/Ile homozygote frequency (rs2273535) in the Asian group in an allelic genetic model (OR: 1.124, 95% CI: 1.003-1.29, $p=0.044$, $P_{heterogeneity}=0.034$) is much higher than in the control subjects, and also much higher than in Caucasian women in an allelic genetic model (OR: 1.047, 95% CI: 0.959-1.145, $p=0.305$, $P_{heterogeneity}=0.013$), indicating that individuals with the rs2273535 polymorphism in the AURKA gene have a higher risk of breast cancer in Asian populations, but not in Caucasians.

To conclude, our meta-analysis demonstrated an association between the rs2273535 polymorphism in the AURKA gene and breast cancer risk. Nevertheless, large-scale and well-designed studies are required to investigate gene-gene and gene-environment interactions on the rs2273535 polymorphism in the AURKA gene and breast cancer risk, which may eventually lead to better comprehensive understanding of the possible roles in tumorigenesis.

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