Assessing Interactions between the Association of Common Genetic Variant at 1p11 (rs11249433) and Hormone Receptor Status with Breast Cancer Risk

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Abstract

Background: The association between rs11249433 polymorphism on 1p11 and breast cancer (BC) has been widely evaluated since it was first identified through genome-wide association approach. However, the results have been inconclusive. To investigate this inconsistency, we performed a meta-analysis of all available studies dealing with the relationship between the 1p11-rs11249433 polymorphism and BC.

Methods: Databases including Pubmed, SCOPUS, ISI web of knowledge, Embase and Cochrane databases were searched to find relevant studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. The random-effects model was applied, addressing heterogeneity and publication bias.

Results: A total of 15 articles involving 90,291 cases and 137,525 controls were included. In a combined analysis, the summary per-allele odds ratio (OR) for BC of 1p11-rs11249433 polymorphism was 1.09 (95% CI: 1.06–1.12; P < 10^-5). Significant associations were also observed under dominant and recessive genetic models. In the subgroup analysis by ethnicity, significantly increased risks were found in Caucasians; whereas no significant associations were found among Asians and Africans. In addition, our data indicate that 1p11-rs11249433 polymorphism is involved in BC susceptibility and confer its effect primarily in estrogen receptor-positive and progesterone receptor-positive tumors.

Conclusions: In conclusion, this meta-analysis demonstrated that the G allele of 1p11-rs11249433 is a risk factor associated with increased breast cancer susceptibility, but these associations vary in different ethnic populations.

Introduction

Breast cancer (BC), as a substantial global public health concern, is one of the most common cancers diagnosed in women and is the primary cause of death among women in both the developing and developed world [1]. Despite much investigation, the mechanism of breast carcinogenesis is still not fully understood. Although life/environment related factors, such as age at menarche, menopause, first birth age and exogenous hormone use are implicated in breast carcinogenesis [2,3], accumulated evidence suggests that it is a complex polygenic disorder for which genetic factors play an important role in disease etiology [4,5]. Genetic determinants including several high and moderate penetrance genes (BRCA1, BRCA2, BRIP1, CHEK2, PALB2, PTEN, and TP53) have been identified as BC susceptibility gene through the candidate gene approach in the past decade [6]. After accounting for all the known BC loci, more than 75% of the familial risk of the disease remains unexplained [7].

Recently, spectacular advance was made in identifying susceptible genes involved in breast cancer through genome-wide association strategy (GWAS) [8–10]. So far, genome-wide association studies (GWASs) have reported over 40 common low-penetrance variants in 25 loci that are associated with the BC risk reported in the National Human Genome Research Institute catalog [11]. More recently, a genome-wide association (GWA) study conducted in European ancestry population by Thomas et al. identified a new genetic susceptibility locus, rs11249433, at chromosome 1p11.2 was associated with BC risk [12]. Associations between the 1p11-rs11249433 polymorphism and BC have been independently replicated by subsequent studies; however, a proportion of them have produced inconsistent results. These disparate findings may be due partly to insufficient power, phenotypic heterogeneity, population stratification, small effect of the polymorphism on BC risk, and even publication biases. With the increased studies in recent years among East Asians, Africans and some other ethnic populations, there is a need to reconcile this inconsistency and to clarify the problems in previous studies. We therefore performed a meta-analysis of the published studies to clarify this inconsistency and to establish a comprehensive picture of the relationship between 1p11-rs11249433 polymorphism and BC susceptibility.
Materials and Methods

Literature search strategy and inclusion criteria

Epidemiological genetic association studies published before the end of Feb 2013 on breast cancer and polymorphism in the chromosome 1p11 were sought by computer-based searches from databases including PubMed, SCOPUS, ISI Web of knowledge, Embase and Cochrane databases without language restriction. Search term combinations were keywords relating to the chromosome 1p11 (e.g., “1p11,” “rs11249433”) in combination with words related to breast cancer (e.g., breast cancer or ‘malignant breast neoplasm’). We replaced one of those search terms each time until all possible combination mode were searched to avoid any missing literature. The titles and abstracts of potential primary studies and review articles were also reviewed by a manual search to identify additional relevant publications (Checklist S1).

Eligible studies and data extraction

Eligible studies had to meet all of the following criteria: (1) original papers containing independent data which have been published in peer-reviewed journal, (2) case-control or cohort studies, (3) genotype distribution information or odds ratio (OR) with its 95% confidence interval (CI) and *P*-value, (4) genotype distribution of control group must be consistent with Hardy–Weinberg equilibrium (HWE). The major reasons for exclusion of studies were (1) overlapping data, (2) case-only studies, (3) family-based studies and review articles.

Data extraction was performed independently by two reviewers and differences were resolved by further discussion among all authors. For each included study, the following information was extracted from each report according to a fixed protocol: first author, publication year, definition and numbers of cases and controls, frequency of genotypes, age, cigarette smoking, alcohol drinking, ethnicity, Hardy–Weinberg equilibrium (HWE) status, source of control, estrogen receptor (ER) status, progesterone receptor (PR) status, BRCA1 status, BRCA2 status and genotyping method. Studies with different ethnic groups were considered as individual studies for our analyses.

### Table 1. Characteristics of studies included in a meta-analysis of the association between 1p11-rs11249433 and breast cancer.

| Reference | Year | Country         | Ethnicity | Cases/controls | Matching criteria | Genotyping method |
|-----------|------|-----------------|-----------|----------------|-------------------|-------------------|
| He [20]   | 2012 | Europe, USA     | Caucasian | 3683/34174     | Ethnicity and age | TaqMan            |
| Sueta [21]| 2012 | Japan           | Asian     | 697/1394       | Menopausal status and age | TaqMan |
| Kim [22]  | 2012 | Korea           | Asian     | 2257/2052      | Age and region    | SNP Array, TaqMan |
| Huo [23]  | 2012 | Nigeria         | African   | 1509/1383      | Age               | GoldenGate        |
| Antoniou [24]| 2011| Europe, Australia, USA, Canada | Caucasian | 9006/8155 | Ethnicity and age | TaqMan, iPLEX |
| Figueroa [25]| 2011| Europe, Australia, USA, China | Caucasian, Asian | 46036/46930 | Ethnicity and age | TaqMan, iPLEX |
| Campa [26]| 2011 | USA, Europe     | Caucasian, Hispanic white, Asian, African | 8360/11513 | Ethnicity and age | TaqMan |
| Jiang [27]| 2011 | China           | Asian     | 1766/1853      | Age and region    | TaqMan            |
| Chen [28] | 2011 | USA             | African   | 3016/2745      | Ethnicity and age | SNP Array          |
| Stevens [29]| 2011| Europe, Australia, USA | Caucasian | 2976/4968 | Ethnicity and age | iPLEX |
| Hutter [30]| 2011| USA             | African   | 316/7484       | NA                | SNP Array          |
| Li [31]   | 2011 | Sweden, Finland | Caucasian | 1557/4584      | Ethnicity, age and region | SNP Array |
| Bhatti [32]| 2010| USA             | Caucasian | 774/989        | Ethnicity and age | TaqMan            |
| Long [33] | 2010 | China           | Asian     | 2044/2054      | Age and region    | SNP Array, iPLEX |
| Thomas [12]| 2009| USA, Poland     | Caucasian | 6294/7247      | Ethnicity and age | SNP Array, TaqMan |

NA: not applicable.
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Statistical methods

Crude ORs with 95% CIs were used to assess the strength of association between the 1p11-rs11249433 polymorphism and BC risk. The meta-analysis examined the association between the 1p11-rs11249433 polymorphism and the risk of breast cancer, for the: (i) allele contrast, (ii) recessive, and (iii) dominant models [13]. Heterogeneity across individual studies was calculated using the Q-statistic test followed by subsidiary analysis or by random-effects regression models with restricted maximum likelihood estimation [14]. Both fixed-effects (Mantel–Haenszel method) [15] and random-effects (DerSimonian–Laird method) [16] models were performed to calculate the pooled ORs. Owing to a priori assumptions about the likelihood of heterogeneity between primary studies, the random-effects model, which usually is more conservative, was reported in the text. Subgroup analyses were performed by ethnicity (Asian, Caucasian, African and others) and sample size (No. of cases ≤1000 and >1000). The Z test was used to determine the significance of the pooled OR. One-way sensitivity analyses were performed to access the stability of the meta-analysis’ results [17]. The potential publication bias was estimated using Egger’s linear regression test by visual inspection of the funnel plot [18]. If publication bias existed, the Duval and Tweedie nonparametric “trim and fill” method was used to adjust for it [19]. All *P* values are two-sided at the *P* = 0.05 level. All of the statistical tests used in this meta-analysis were performed by STATA version 10.0 (Stata Corporation, College Station, TX).
Results

Characteristics of included studies

The combined search yielded 97 references. 82 articles were excluded because they clearly did not meet the criteria or overlapping references (Figure S1). Finally, a total of 15 eligible association studies were included involving 90,291 breast cancer cases and 137,525 controls [9,15,16,21–41]. Of the cases, 82% were Caucasian, 12% were Asian, 5% were African descent, and 1% were of other ethnic origins. The main study characteristics were summarized in Table 1.
Significant heterogeneity was present among the included studies of the 1p11-rs11249433 polymorphism ($P < 0.05$). In meta-regression analysis, genotyping method ($P = 0.18$), sample size ($P = 0.09$), mean age of cases ($P = 0.25$) and controls ($P = 0.36$) did not significantly explained such heterogeneity. By contrast, ethnicity ($P = 0.002$) was significantly correlated with the magnitude of the genetic effect, explaining 23% of the heterogeneity. Using random effect model, the per-allele overall OR of the G variant for breast cancer was $1.09$ (95% CI: 1.06–1.12, $P = 10^{-5}$; Figure 1), with corresponding results under dominant and recessive genetic models of $1.11$ (95% CI: 1.07–1.15, $P < 10^{-5}$) and $1.11$ (95% CI: 1.06–1.17, $P < 10^{-5}$), respectively. When stratifying for ethnicity, significantly increased risks were found among Caucasian populations (G allele: OR = 1.10, 95% CI: 1.06–1.13, $P = 10^{-5}$; dominant model: OR = 1.12, 95% CI: 1.07–1.17, $P = 10^{-5}$; recessive model: OR = 1.12, 95% CI: 1.06–1.19, $P = 10^{-5}$). However, no significant association was found for Asian and African populations with a per-allele OR of 1.11 (95% CI: 0.99–1.24, $P = 0.06$) and of 1.03 (95% CI: 0.94–1.12, $P = 0.38$), respectively. Among other ethnic populations, still no significant results were detected. Similar results were also observed for under dominant and recessive genetic models (Table 2). Subsidiary analyses of sample size yielded a per-allele OR for larger studies of $1.08$ (95% CI: 1.03–1.12, $P = 10^{-5}$) and for small studies of $1.13$ (95% CI: 1.08–1.18, $P = 10^{-5}$); Significant associations were also observed for both large and small studies under dominant and recessive models (Table 2).

Interactions between rs11249433 and hormone receptor status with BC risk

Since ER and PR status is one of the major markers of BC subtypes, we further performed analyses to test for differences in the associations of the polymorphism with BC risk with respect to different ER and PR status (Table 3). The minor allele of SNP 1p11-rs11249433 was associated with a significantly higher risk for ER-positive breast cancer with a per-allele OR of $1.13$ (95% CI: 1.08–1.18, $P = 10^{-5}$); whereas no significant association was detected for ER-negative tumors (per-allele OR = 1.01, 95% CI: 0.98–1.04, $P = 0.49$; Figure 2). Similarly, a stronger association was also observed for the polymorphism with PR-positive tumors (per-allele OR = 1.13, 95% CI: 1.10–1.16, $P = 10^{-5}$) compared with PR-negative tumors (per-allele OR = 1.04, 95% CI: 0.97–1.12, $P = 0.30$; Figure 3).

Sensitivity analyses and publication bias

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled

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**Quantitative synthesis**

**Figure 2. Per-allele odds ratios and 95% confidence intervals for the association between 1p11-rs11249433 and BC risk by ER status.**

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Table 2. Results of meta-analysis for 1p11-rs11249433 polymorphism and BC risk.

| Sub-group analysis | No. of data sets | No. of case/ control | G vs. A allele | Dominant model | Recessive model |
|--------------------|------------------|----------------------|----------------|---------------|----------------|
|                    |                  |                      | OR (95%CI)     | P(Z)          | P(Q)*          | OR (95%CI)     | P(Z)          | P(Q)*          | OR (95%CI)     | P(Z)          | P(Q)*          |
| Total              | 32               | 90291/137525         | 1.09 (1.06–1.12) | <10^-5        | 0.001          | 1.11 (1.07–1.15) | <10^-5        | 0.02          | 1.11 (1.06–1.17) | <10^-4        | <10^-4        |
| Ethnicity          |                  |                      |                |               |                |                |               |               |                |               |               |
| Caucasian          | 19               | 73771/114428         | 1.10 (1.06–1.13) | <10^-5        | <10^-4        | 1.12 (1.07–1.17) | <10^-5        | 0.001         | 1.12 (1.06–1.19) | <10^-4        | <10^-4        |
| Asian              | 7                | 10767/10366          | 1.11 (0.99–1.24) | 0.06          | 0.62          | 1.09 (0.97–1.19) | 0.15          | 0.83          | 1.18 (0.93–1.49) | 0.17          | 0.29          |
| African            | 4                | 5242/12044           | 1.03 (0.94–1.12) | 0.58          | 0.87          | 1.02 (0.93–1.12) | 0.63          | 0.98          | 1.03 (0.88–1.12) | 0.72          | 0.31          |
| Other              | 2                | 511/687              | 1.11 (0.92–1.35) | 0.28          | 0.32          | 1.11 (0.91–1.46) | 0.23          | 0.52          | 1.20 (0.55–2.61) | 0.64          | 0.19          |
| Sample size        |                  |                      |                |               |                |                |               |               |                |               |               |
| <1000              | 17               | 10336/22564          | 1.13 (1.08–1.18) | <10^-4        | 0.93          | 1.15 (1.09–1.21) | <10^-5        | 0.98          | 1.15 (1.07–1.25) | <10^-4        | 0.28          |
| ≥1000              | 15               | 79955/114961         | 1.08 (1.03–1.12) | <10^-5        | 0.001         | 1.09 (1.04–1.15) | <10^-4        | 0.007         | 1.10 (1.03–1.17) | <10^-4        | <10^-4        |

*Cochran's chi-square Q statistic test used to assess the heterogeneity in subgroups.

*Coehran's chi-square Q statistic test used to assess the heterogeneity between subgroups.

Figure 3. Per-allele odds ratios and 95% confidence intervals for the association between 1p11-rs11249433 and BC risk by PR status.

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that variation at this locus has modest effects on breast cancer, but or some environmental factors may affect the results. It is possible these populations. Furthermore, study design or small sample size by the relatively lower prevalence of G allele of 1p11-rs11249433. tions could be due to substantially lower statistical power caused still did not show publication bias (Begg test, P = 0.63; Egger test, P = 0.89, Figure S3).

**Discussion**

Multiple lines of evidence support an important role for genetics in determining risk for breast cancer, and association studies are appropriate for searching susceptibility genes involved in breast cancer [34]. Nevertheless, small sample sized association studies lack statistical power and have resulted in apparently contradicting findings [35]. Meta-analysis is a means of increasing the effective sample size under investigation through the pooling of data from individual association studies, thus enhancing the statistical power of the analysis for the estimation of genetic effects [36]. In the current meta-analysis, on the basis of 15 case-control studies providing data on the 1p11-rs11249433 polymorphism and breast cancer involving 90,291 cases and 137,525 controls, we find significant association between the 1p11-rs11249433 polymorphism and breast cancer among overall and Caucasian populations. Meta-analysis is often dominated by a few large studies, which markedly reduces the evidence from smaller studies. However, in the stratified analysis according to sample size, significantly increased BC risk was found in both large and small studies.

Since ethnic group was identified as the main source of between-study heterogeneity, subgroup meta-analyses based on ethnicity was performed. Significant associations were found in Caucasians and but not for Asians and Africans, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in [37]. In fact, the distribution of the less common G allele varies extensively between different races, with a 42% among Caucasians, 2% among Asians and 12% among African population [26–30]. Thus, failing to identify any significant association in Asian and African populations could be due to substantially lower statistical power caused by the relatively lower prevalence of G allele of 1p11-rs11249433. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this functional polymorphism on breast cancer risk. Such result could also be due to the limited number of studies among Asian and African populations, which had insufficient statistical power to detect a slight effect or different linkage disequilibrium (LD) pattern of the polymorphism among these populations. Furthermore, study design or small sample size or some environmental factors may affect the results. It is possible that variation at this locus has modest effects on breast cancer, but environmental factors may predominate in the progress of breast cancer, and mask the effects of this variation.

Our data indicate that the association among population-based breast cancer cases is the strongest in ER-positive breast tumors. In addition, we also found that the association appeared to be much stronger for PR-positive than the PR-negative breast cancer. It is unclear whether PR status has an effect on breast carcinogenesis independent of ER status. About 65% of ER-positive breast cancers are also PR-positive, and there is a high correlation between ER and PR expression [38,39]. Besides, the per-allele odds ratio estimates were very similar for ER+ and PR+ tumors. These findings provide further support for the notion that ER-negative and ER-positive tumors result from different etiologic pathways, rather than different stages of tumor evolution within a common carcinogenic pathway [40].

A number of factors predict breast cancer, however, detailed pathogenesis mechanisms of breast cancer remain a matter of speculation. A recent study found some evidence of increased NOTCH2 expression in breast tumors in carriers of the G allele of rs11249433 [41]. In addition, the association between rs11249433 and NOTCH2 expression was dependent on the mutational status of the tumor suppressor gene TP53 and ER status of the tumors. This suggests that either the estrogen receptor or the TP53 may have a function in the regulation of NOTCH2 expression, as the restoration of p53 expression has been shown to affect NOTCH1 expression [42,43]. An active NOTCH pathway is important for the induction of breast stem cells to differentiate into luminal cells of breast ducts [44]. Thus, increased or persistent activation of NOTCH2 expression may favor development of ER+ breast tumors.

The strengths of this study include the very large sample size, no deviation from Hardy-Weinberg equilibrium, and the high quality of the qualified studies. However, our current study should be interpreted with several technical limitations in mind. Firstly, the vast majority of white subjects in the study are of European descent, and statistical power for analyses in other ethnicities is limited. Because the sample size was considerably smaller for African studies, the main conclusions from this manuscript are based on analyses among white European and Asian women. Future studies including larger numbers of Africans are necessary to clarify the consistency of findings across ethnic groups. Secondly, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, menopausal status, family history, environmental factors and lifestyle. Thirdly, the subgroup meta-analyses considering interactions between rs11249433 polymorphism and hormone receptor status were performed on the basis of a fraction of all the possible data to be pooled, so selection bias may have occurred and our results may be overinflated.
Nevertheless, the total number of subjects included in this part of the analysis comprises the largest sample size so far.

In summary, findings from this meta-analysis indicate that 1p11.2-rs11249433 polymorphism is significantly associated with an increased risk of breast cancer, particularly in Caucasians. More work is needed to further investigate the association of this polymorphism across different ethnic populations. Besides, future studies are recommended to identify the possible gene–gene and gene–environmental interactions in this association.

**Supporting Information**

**Figure S1** Flow chart of literature search for studies examining 1p11.2-rs11249433 polymorphism and risk of BC. (TIF)

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