

RESEARCH ARTICLE

Common Variants in the *PALB2* Gene Confer Susceptibility to Breast Cancer: a Meta-analysis

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Abstract

Objective: Increasing scientific evidence suggests that common variants in the *PALB2* gene may confer susceptibility to breast cancer, but many studies have yielded inconclusive results. This meta-analysis aimed to derive a more precise estimation of the relationship between *PALB2* genetic variants and breast cancer risk. **Methods:** An extensive literary search for relevant studies was conducted in PubMed, Embase, Web of Science, Cochrane Library, CISCOR, CINAHL, Google Scholar, CNKI and CBM databases from their inception through September 1st, 2013. A meta-analysis was performed using the STATA 12.0 software and crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. **Results:** Six case-control studies were included with a total of 4,499 breast cancer cases and 6,369 healthy controls. Our meta-analysis reveals that *PALB2* genetic variants may increase the risk of breast cancer (allele model: OR>1.36, 95% CI: 1.20~1.52, $P < 0.001$; dominant model: OR>1.64, 95% CI: 1.42~1.91, $P < 0.001$; respectively). Subgroup analyses by ethnicity indicated *PALB2* genetic variants were associated with an increased risk of breast cancer among both Caucasian and Asian populations (all $P < 0.05$). No publication bias was detected in this meta-analysis (all $P > 0.05$). **Conclusion:** The current meta-analysis indicates that *PALB2* genetic variants may increase the risk of breast cancer. Thus, detection of *PALB2* genetic variants may be a promising biomarker approach.

Keywords: Breast cancer - *PALB2* - genetic variants - meta-analysis

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Introduction

Breast cancer, as a substantial global public health concern, is one of the most common cancers in women worldwide (Benson and Jatoti, 2012). It is estimated that over one million women are diagnosed with breast cancer every year, and more than 410,000 will die from the disease (Bray et al., 2012). However, the exact mechanisms of breast cancer are still poorly understood. Generally, breast cancer is a multifactorial disease resulting from the interaction between genetic and environmental factors (Pern et al., 2012). Previous studies showed that family history, reproductive status, endocrine disorders and body mass index may play important roles in the development of breast cancer (Colditz et al., 2012; Llanos et al., 2012). Furthermore, genetic factors are also involved in the initiation and maintenance of breast cancer (Stephens et al., 2012).

The Partner and Localizer of BRCA2 (*PALB2*) protein, identified as a nuclear partner of BRCA2, promoting its localization and stability in key nuclear structures, which in turn facilitates BRCA2 functions in DNA repair and cell cycle regulation and thereby maintaining genome stability (Xia et al., 2006; Erkkö et al., 2007). Human *PALB2* gene is located on chromosome 16p12.2, spanning approximately 38kb, containing 13 exons and 12 introns, and encodes for a

protein involved in BRCA2-related pathways (Chen et al., 2008). In general, *PALB2* indirectly affect the expression of BRCA2, and the loss-of-function mutations in *BRCA2* usually cause genetic instability, avoiding the defense system, resulting in non-controlling cell proliferation and thereby inevitably leading to tumorigenesis (Xia et al., 2006; Frankenberg-Schwager and Gregus, 2012). Therefore, it was hypothesized that *PALB2* genetic variants might be significantly associated with the development and progression of breast carcinogenesis (Casadei et al., 2011). Previous studies have demonstrated that loss-of-function mutations in *PALB2* are contributes to breast cancer initiation and progression (Erkkö et al., 2007; Chen et al., 2008; Cao et al., 2010). Bogdanova et al showed that *PALB2* germline mutations accounted for a small, but not negligible, proportion of bilateral breast carcinomas in German and Russian populations (Bogdanova et al., 2011). Furthermore, mutational and functional analysis of common single nucleotide polymorphism (SNP) in exons of *PALB2*, including rs249954, rs447529 and rs16940342, that were highly associated with the susceptibility of breast cancer, but they did not provide evidence on whether other polymorphism correlate with breast cancer susceptibility (Chen et al., 2008; Cao et al., 2009). However, the geographical spread of *PALB2* mutations has not been comprehensively analyzed yet, and several recent studies

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have failed to identify any *PALB2* mutations in breast cancer series from their population (Heikkinen et al., 2009; Guenard et al., 2010). Therefore, we attempt to perform a meta-analysis of all eligible case-control studies to evaluate the relationships between common variants in the *PALB2* gene and the risk of breast cancer, and to understand the biological processes associated with breast cancer formation and progression, which subsequently may be further utilized as a diagnostic tool for accurate determination of endocrine therapeutic strategies in breast cancer.

Materials and Methods

Literature Search

A comprehensive search for relevant studies published before August 1st, 2013 was conducted on PubMed, Embase, Web of Science, Cochrane Library, CISCOR, CINAHL, Google Scholar, China BioMedicine (CBM) and China National Knowledge Infrastructure (CNKI) databases. We used the following keywords and MeSH terms: (“genetic polymorphism” or “single nucleotide polymorphism” or “polymorphism” or “SNP” or “mutation” or “variation” or “variant”) and (“breast neoplasms” OR “breast cancer” or “breast tumor” or “breast carcinoma”) and (“*PALB2* protein, human” or “*PALB2*” or “*FANCN*”). There were no language restrictions. The references used in eligible articles or textbooks were also reviewed to find other potential studies.

Selection Criteria

Studies included in our meta-analysis have to meet the following criteria: (1) case-control studies focused on the associations between *PALB2* genetic variants and breast cancer risk; (2) all patients should meet the diagnostic criteria for breast cancer confirmed by histological examinations; (3) the minimum number of cases in included studies should be greater than 30; (4) published data about the allele and genotype frequencies of SNPs must be sufficient. Studies were excluded if they did not meet all of these inclusion criteria. If more than one study by the same author using the same case series was published, either the study with the largest sample size or the most recent publication was included.

Data Extraction

Data from the published studies were extracted independently by two authors into a standardized form. For each study, the following characteristics and numbers were collected: the first author, year of publication, country, language, ethnicity of subjects, study design, number of subjects, detecting sample, genotype method, allele and genotype frequencies, etc. In cases of conflicting evaluations, disagreements among inconsistent data from the eligible studies were resolved through discussions and careful reexaminations of the full text by the authors.

Quality Assessment

The quality of the included studies was assessed independently by two authors based on the Newcastle-

Ottawa Scale (NOS) (Stang, 2010). The NOS criteria use a “star” rating system to judge the methodological quality, which was based on three perspectives of the study: selection, comparability, and exposure. Scores ranged from 0 stars (worst) to 9 stars (best); a score equal to or greater than 7 indicates a generally good methodological quality. Disagreements on NOS scores of the included studies were resolved through a comprehensive reassessment by the authors

Statistical Analysis

The crude odds ratio (OR) with 95% confidence interval (CI) were calculated under five genetic models: the allele model (mutant [M] allele vs. wild [W] allele), the dominant model (WM+MM vs. WW), the recessive model (MM vs. WW+WM), the homozygous model (MM vs. WW), and the heterozygous model (MM vs. WM). The statistical significance of the pooled OR was examined by Z test. Genotype frequencies of controls were tested for Hardy-Weinberg equilibrium (HWE) using the χ^2 test for each study included in the meta-analysis. The statistical significance of the pooled OR was examined using the Z test. Power calculations were done by PS Power and Sample Size Calculations (Dupont and Plummer, 1990). Between-study heterogeneity was estimated using Cochran’s Q-statistic, whereas a $P < 0.05$ was set to identify heterogeneity in the associations (Jackson et al., 2012). We also quantified the effects of heterogeneity by using the I^2 test (ranges from 0 to 100%), which represents the proportion of inter-study variability that can be contributed to heterogeneity rather than to chance (Zintzaras and Ioannidis, 2005). When a significant Q-test with $P < 0.05$ or $I^2 > 50\%$ indicated existence of heterogeneity among studies existed, the random effects model (DerSimonian Laird method) was conducted for the meta-analysis; otherwise, the fixed effects model (Mantel-Haenszel method) was used. To explore potential sources of heterogeneity, subgroup analysis was performed by clinical subtype, ethnicity, and genotype method. Sensitivity analysis was performed by omitting each study in turn to assess the quality and consistency of the results. Begger’s funnel plots and Egger’s linear regression test were used to evaluate the publication bias (Peters et al., 2006). Two-sided $P < 0.05$ was considered to be statistically significant. All calculations were performed using the STATA version 12.0 software (STATA Corporation, College Station, Texas, USA).

Results

Characteristics of Included Studies

A total of 127 articles relevant to the searched keywords were initially identified. Of these articles, 69 were excluded after a review of their titles and abstracts; then, full texts and data integrity were reviewed, and another 52 papers were excluded. Six case-control studies met our inclusion criteria for this meta-analysis (Erkko et al., 2007; Chen et al., 2008; Cao et al., 2009; Heikkinen et al., 2009; Cao et al., 2010; Guenard et al., 2010). The publication year of involved studies ranged from 2007 to 2010. The flow chart of the study selection process

Table 1. Main Characteristics and Methodological Quality of All Eligible Studies

| First author | Year | Country | Ethnicity | Number | | | Source of controls | Genotype method | Gene | SNP | NOS score |
|-----------------|------|---------|-----------|--------|---------|------------|--------------------|-----------------|--------------|--|-----------|
| | | | | Case | Control | Power size | | | | | |
| Erkko et al | 2007 | Finland | Caucasian | 113 | 2501 | 0.924 | Population-based | DNA Sequencing | <i>PALB2</i> | rs45494092 (T/C) 1592delT (ins/del) rs152451 (A/G) rs45624036 (G/A) rs8053188 (T/G) G3433C (G/C) IVS1-46 (G/A) IVS4-70 (T/G) IVS4-58 (A/C) | 7 |
| Chen et al | 2008 | China | Asian | 1049 | 1073 | 0.903 | Population-based | MicroArray | <i>PALB2</i> | rs249954 (C/T) rs120963 (T/C) rs16940342 (A/G) rs249935 (A/G) | 8 |
| Cao et al | 2009 | China | Asian | 360 | 864 | | Population-based | DHPLC | <i>PALB2</i> | rs8053188 (C/T) | 7 |
| Heikkinen et al | 2009 | Finland | Caucasian | 2221 | 1079 | 0.978 | Population-based | DNA Sequencing | <i>PALB2</i> | 1592delT (ins/del) | 7 |
| Cao et al | 2010 | China | Asian | 660 | 756 | 0.881 | Hospital-based | MicroArray | <i>PALB2</i> | rs8053188 (C/T) rs16940342 (A/G) rs249954 (C/T) rs447529 (C/G) rs249935 (A/G) | 7 |
| Guénard et al | 2010 | Canada | Caucasian | 96 | 96 | 0.725 | Hospital-based | DNA Sequencing | <i>PALB2</i> | rs8053188 (C/T) rs152451 (G/A) rs249954 (C/T) rs45551636 (A/G) | 6 |

Ref, reference; SNP, single nucleotide polymorphism; NOS, the Newcastle-Ottawa Scale

Table 2. Meta-analysis of the Association Between *PALB2* Genetic Variants and Breast Cancer Risk

| Subgroups | M allele vs. W allele (allele model) | | | WM + MM vs. WW (dominant model) | | | MM vs. WW + WM (recessive model) | | | MM vs. WW (homozygous model) | | | MM vs. WM (heterozygous model) | | |
|-------------------|--------------------------------------|-----------|--------|---------------------------------|-----------|--------|----------------------------------|-----------|--------|------------------------------|-----------|--------|--------------------------------|-----------|--------|
| | OR | 95%CI | P | OR | 95%CI | P | OR | 95%CI | P | OR | 95%CI | P | OR | 95%CI | P |
| Overall | 1.36 | 1.20~1.52 | <0.001 | 1.64 | 1.42~1.91 | <0.001 | 0.92 | 0.82~1.04 | 0.179 | 1.08 | 1.06~1.21 | 0.028 | 1.67 | 1.60~2.75 | <0.001 |
| Ethnicity | | | | | | | | | | | | | | | |
| Caucasians | 1.45 | 1.03~2.03 | 0.032 | 1.92 | 1.24~2.96 | 0.004 | 1.41 | 0.40~4.96 | 0.592 | 1.47 | 1.42~5.17 | 0.026 | 1.76 | 1.32~3.55 | 0.023 |
| Asians | 1.28 | 1.23~1.34 | <0.001 | 1.58 | 1.35~1.83 | <0.001 | 0.92 | 0.81~1.03 | 0.159 | 1.17 | 1.05~1.21 | 0.025 | 1.67 | 1.60~2.75 | <0.001 |
| Country | | | | | | | | | | | | | | | |
| Finland | 3.79 | 1.85~6.94 | 0.018 | 2.34 | 1.69~3.25 | <0.001 | 1.25 | 0.96~2.10 | 0.171 | 1.55 | 1.13~2.57 | 0.002 | 1.63 | 1.09~1.97 | 0.033 |
| China | 1.28 | 1.23~1.34 | <0.001 | 1.58 | 1.35~1.83 | <0.001 | 0.92 | 0.81~1.03 | 0.159 | 1.07 | 0.95~1.21 | 0.251 | 0.67 | 0.60~0.75 | <0.001 |
| Canada | 1.33 | 0.94~1.89 | 0.103 | 1.4 | 0.93~2.10 | 0.11 | 1.41 | 0.40~4.96 | 0.592 | 1.47 | 0.42~5.17 | 0.546 | 1.06 | 0.32~3.55 | 0.923 |
| Source of control | | | | | | | | | | | | | | | |
| Population-based | 1.32 | 1.25~1.39 | <0.001 | 1.39 | 1.32~1.46 | <0.001 | 1.09 | 0.94~1.26 | 0.25 | 1.33 | 1.15~1.53 | <0.001 | 0.8 | 0.70~0.92 | 0.002 |
| Hospital-based | 1.23 | 1.14~1.33 | <0.001 | 1.37 | 1.27~1.49 | <0.001 | 1.67 | 1.54~2.83 | <0.001 | 1.72 | 1.59~1.89 | 0.003 | 1.49 | 1.40~2.59 | <0.001 |
| Genotype method | | | | | | | | | | | | | | | |
| DNA sequencing | 1.45 | 1.03~2.03 | 0.032 | 1.78 | 1.41~2.25 | <0.001 | 1.41 | 0.40~4.96 | 0.592 | 1.47 | 0.42~5.17 | 0.546 | 1.06 | 0.32~3.55 | 0.923 |
| MicroArray | 1.29 | 1.23~1.34 | <0.001 | 1.37 | 1.31~1.43 | <0.001 | 0.92 | 0.81~1.03 | 0.159 | 1.07 | 0.95~1.21 | 0.251 | 0.67 | 0.60~0.75 | <0.001 |
| DHPLC | 1.05 | 0.49~2.26 | 0.895 | 1.05 | 0.49~2.24 | 0.894 | 0.88 | 0.39~1.27 | 0.652 | 0.79 | 0.26~1.19 | 0.747 | 0.59 | 0.27~1.52 | 0.283 |

OR, odds ratios; 95%CI, 95% confidence interval; PCR-RFLP, polymerase chain reaction~restriction fragment length polymorphism

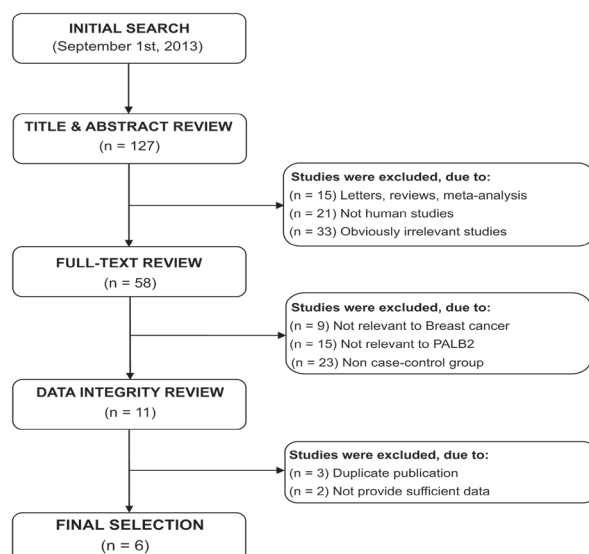


Figure 1. Flow Chart Shows Study Selection Procedure. Six case-control studies were included in this meta-analysis

is shown in Figure 1. A total of 10, 868 subjects were involved in this meta-analysis, including 4, 499 breast cancer cases and 6, 369 healthy controls. All the power for the sample size of included studies were higher than 0.70. Overall, three studies were conducted in Caucasian populations and the other three in Asian populations. The classical direct DNA sequencing method was performed in three studies, two studies used MicroArray method the other one used DHPLC method. The HWE test was conducted to evaluate the genotype distribution of the controls in all included studies. Each study did not deviate from the HWE (all $P > 0.05$). NOS scores of all included studies were higher than 6 (moderate-high quality). Characteristics and methodological quality of the included studies are summarized in Table 1.

Quantitative Data Synthesis

A summary of the meta-analysis findings on the associations between *PALB2* genetic variants and susceptibility to breast cancer is provided in Table 2.

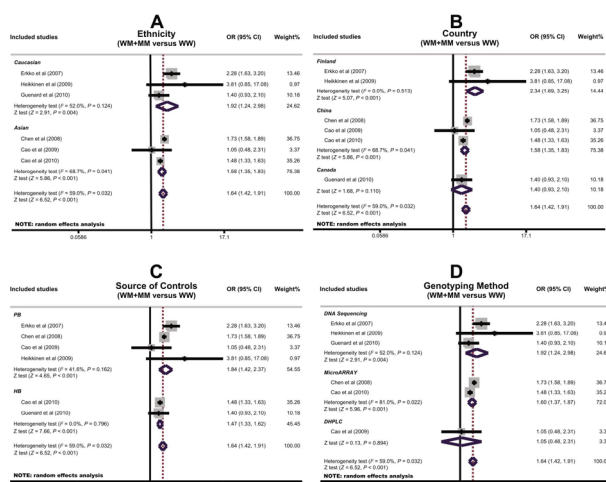


Figure 2. Subgroup Analyses for the Associations between *PALB2* Genetic Variants And Breast Cancer Risk Under The Dominant Models. (A) Subgroup analysis by ethnicity; (B) Subgroup analysis by country; (C) Subgroup analysis by source of controls; (D) Subgroup analysis by genotyping method

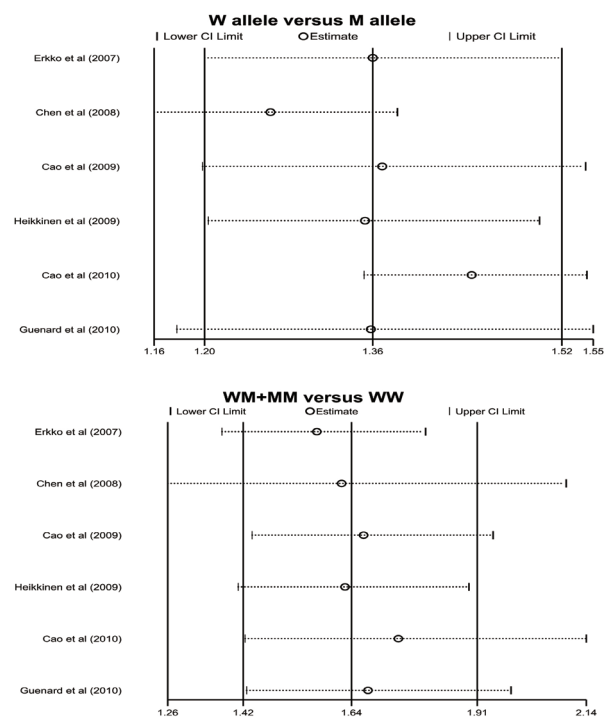


Figure 3. Sensitivity Analysis of the Associations Between *PALB2* Genetic Variants and Breast Cancer Risk under the Allele and Dominant Models. Results were computed by omitting each study in turn. Meta-analysis random-effects estimates (exponential form) were used. The two ends of the dotted lines represent the 95% CI

Subgroup analyses by ethnicity indicated *PALB2* genetic variants were associated with an increased risk of breast cancer among both Caucasian and Asian populations (Figure 2A). In the stratified subgroup based on country, the results suggested that *PALB2* genetic variants might increase the risk of breast cancer in the populations of Finland and China (Figure 2B). Further subgroup analysis by source of controls and genotyping method also showed significant associations between *PALB2* genetic variants

Table 3. Univariate and Multivariate Meta-regression Analyses of Potential Source of Heterogeneity

| Heterogeneity factors | Coefficient | SE | z | P | 95%CI | |
|---------------------------|-------------|-------|-------|-------|--------|--------|
| | | | | | LL | UL |
| Publication year | | | | | | |
| Univariate | 0.929 | 0.317 | 2.93 | 0.093 | -0.155 | 1.031 |
| Multivariate | 0.077 | 0.034 | 2.24 | 0.052 | -0.144 | 1.009 |
| Ethnicity | | | | | | |
| Univariate | -0.189 | 0.169 | -1.12 | 0.264 | -0.52 | 0.142 |
| Multivariate | -0.092 | 0.138 | -0.67 | 0.505 | -0.363 | 0.179 |
| Country | | | | | | |
| Univariate | -0.282 | 0.142 | -1.09 | 0.31 | -0.156 | 1.044 |
| Multivariate | -0.147 | 0.142 | -1.03 | 0.302 | -0.427 | 0.132 |
| Source of controls | | | | | | |
| Univariate | -0.175 | 0.066 | 2.64 | 0.108 | -0.234 | 1.045 |
| Multivariate | -0.176 | 0.062 | 2.65 | 0.098 | -0.306 | 1.0461 |
| Genotyping method | | | | | | |
| Univariate | -0.212 | 0.15 | -1.41 | 0.159 | -0.506 | 0.083 |
| Multivariate | -0.198 | 0.127 | -1.56 | 0.118 | -0.447 | 0.051 |

SE, standard error; 95%CI, 95% confidence interval; LL, lower limit; UL, upper limit

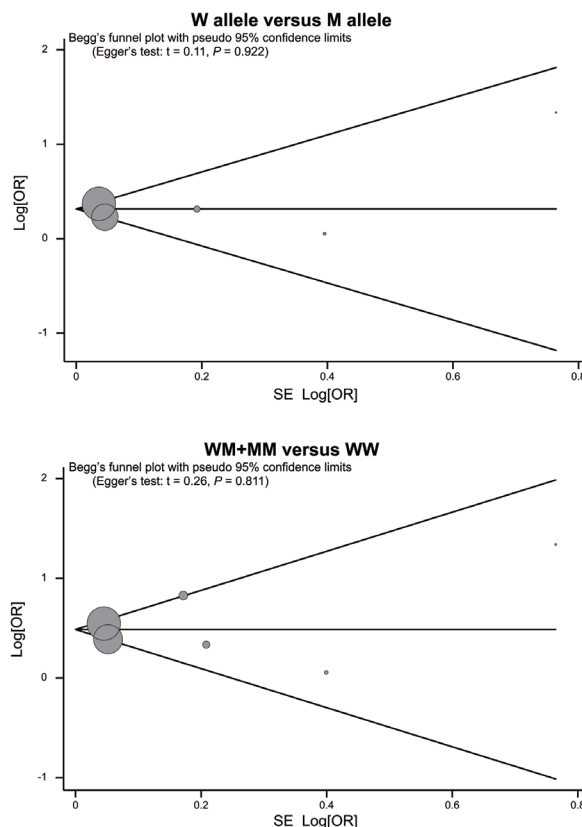


Figure 4. Begger's Funnel Plots of The Associations Between *PALB2* Genetic Variants and Breast Cancer Risk under the Allele and Dominant Models. Each point represents a separate study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line, mean magnitude of the effect

and increased risk of breast cancer in both population-based, hospital-based, DNA sequencing and MicroArray subgroups (Figure 2C-D). Although no association was found between *PALB2* genetic variants and breast cancer risk in the population of Canada and the DHPLC subgroup (all $P > 0.05$), but these results lacked statistical reliability due to the small sample size.

Meta-Regression and Sensitivity Analyses

Univariate and multivariate meta-regression analyses were conducted for the associations between *PALB2* genetic variants and breast cancer risk. The results showed that none of factors may be the main sources of heterogeneity (Table 3). Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by omitting each individual studies. The analysis results suggested that no individual studies significantly affected the pooled OR (Figure 3), indicating a statistically robust result.

Publication Bias Evaluation

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry under the allele and dominant models (Figure 4). Egger's test also displayed no significant statistical evidence of publication bias (allele model: $t = 0.11$, $P = 0.922$; dominant model: $t = 0.26$, $P = 0.811$; respectively), suggesting that no publication bias exists.

Discussion

PALB2, a recently discovered protein that interacts with BRCA2, is implicated in its nuclear localization and stability and is required for some functions of BRCA2 in homologous recombination and double-strand break repair (Rahman et al., 2007; Hellebrand et al., 2011). Generally, *BRCA1* and *BRCA2* are tumor suppressor genes, both of which are involved in maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control and even the regulation of key mitotic or cell division steps (Cao et al., 2009). Like *BRCA1* mutations, which almost exclusively result in female breast and ovarian cancers, BRCA2 families also show a marked increase in breast and ovarian cancer (O'Donovan and Livingston, 2010). Recent studies have demonstrated that mutations of *PALB2* had a significant impact on susceptibility to breast cancer (Cao et al., 2010; Kuusisto et al., 2011). It is well established that tumorigenesis is a multi-step process of genetic alterations that transform a normal human cell into a malignant derivative (Bogdanova et al., 2011). Consequently, DNA repair genes, which have the ability of maintaining genomic stability through DNA repair mechanisms, are essential to prevent human cancer initiation and development (Guenard et al., 2010). The functional interaction between the DNA helicase *PALB2* and *BRCA2* genes makes common variants in *PALB2* good candidates for low- to moderate-penetrance susceptibility to breast cancer (Casadei et al., 2011). Several studies have shown that mutations of *PALB2* may play an extremely important role in the development and progression of breast cancer. However, there are also some contradictory conclusions in the documents with regard to the exact role of *PALB2* mutations in breast cancer risk (Cao et al., 2009; Heikkinen et al., 2009; Guenard et al., 2010). The controversial findings are probably a result of several reasons, such as the differences in study designs, sample size, ethnicity, source of controls, genotype methods, etc.

Given controversial results in those previous studies, we conducted a meta-analysis to explore the associations

between *PALB2* genetic variants and breast cancer risk. In this meta-analysis, 6 independent case-control studies were included with a total of 4,499 breast cancer cases and 6,369 healthy controls. When all the eligible studies were pooled into the meta-analysis, the results showed that *PALB2* genetic variants were associated with an increased risk of breast cancer, suggesting that *PALB2* genetic variants may be causative factors for breast cancer. Although the exact function of *PALB2* in the development of breast cancer is not clear yet, a potential explanation might be that *PALB2* gene mutations decreased its functions as an important cofactor of breast cancer susceptibility proteins BRCA2 in promoting DNA repair function and regulating cell cycle, and thereby maintaining genome stability (Teo et al., 2013). Consistent with our work, several other studies were also find evidence to support a significant contribution to breast cancer susceptibility by the *PALB2* genetic variants. Cao et al suggested that *PALB2* mutations were responsible for approximately 1% of Chinese women with early-onset breast cancer and affected relatives (Cao et al., 2009). Since obvious heterogeneity obviously existed, we performed stratified analyses based on ethnicity, country, source of controls and genotyping method. In the stratification analysis by ethnicity, the results indicated that *PALB2* mutations were associated with the susceptibility of breast cancer among Caucasian and Asian populations, suggesting that there was no ethnicity difference for the influences of *PALB2* mutations on susceptibility to breast cancer. Further subgroup analyses suggested that *PALB2* genetic variants might increase the risk of breast cancer in the populations of Finland and China, as well as in the population-based, hospital-based, DNA sequencing and MicroArray subgroups, but no similar association was found in the population of Canada and the DHPLC subgroup, which may be associated with the small sample size. These findings are consistent with the previous hypothesis that variability in the *PALB2* genetic variants may alter the risk of developing breast cancer, suggesting that they may be useful as biomarkers in predicting an individual's genetic susceptibility to breast cancer.

In interpreting our results of the current meta-analysis, some limitations need to be addressed. Firstly, the sample size is still relatively small and may not provide sufficient power to estimate the association between *PALB2* genetic variants and breast cancer risk. Therefore, more researches with larger sample size are needed to accurately provide a more representative statistical analysis. Secondly, a meta-analysis may encounter recall or selection bias, possibly influencing the reliability of our study results (Eeles et al., 2013). Thirdly, our lack of access to the original data from the studies limited further evaluation of potential interactions between other factors and breast cancer risks (Siaud et al., 2011). Finally, although all cases and controls of each study were well defined with similar inclusion criteria, there may be other potential factors that were not taken into account that may have influenced our results.

In conclusion, our meta-analysis suggests that *PALB2* genetic variants may increase the risk of breast cancer. Thus, detection of *PALB2* genetic variants may be a promising biomarker for the early detection of MI. Based

on the limitations mentioned before, detailed studies are needed to confirm our findings.

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