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RESEARCH ARTICLE

Significant association between Nijmegen breakage syndrome 1 657del5 polymorphism and breast cancer risk

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Abstract Many studies were published to evaluate the association between Nijmegen breakage syndrome 1 (NBS1) 657del5 polymorphism and breast cancer risk, but the results remained inconsistent. To derive a more precise estimation on the possible association, we performed a meta-analysis of previous published studies. Case–control studies on the association between NBS1 657del5 polymorphisms and breast cancer risk were included into this meta-analysis. We used the odds ratio (OR) with 95 % confidence interval (95 % CI) to assess the strength of the association. Ten studies with a total of 25,365 subjects were identified and included into this meta-analysis. Meta-analysis of those ten studies showed that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk (pooled OR=2.66, 95 % CI 1.82–3.90, $P<0.001$). The cumulative meta-analyses showed a trend of a more significant association between NBS1 657del5 polymorphisms and breast cancer risk as data accumulated by publication year. Thus, our meta-analysis suggests that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk, and NBS1 657del5 polymorphism results in an increased risk of breast cancer.

Keywords Nijmegen breakage syndrome 1 · Polymorphism · Breast cancer · Meta-analysis

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Introduction

Breast cancer is the most common cancer among women, which accounts more than 15 % of all female cancers [1, 2]. Currently, the mechanism of breast carcinogenesis is still unclear, but it has been widely accepted that susceptibility genes combining with environmental factors play important roles in the development of breast cancer [3, 4]. Generally, genetic factors can modify the effects of environmental exposure on the cancer development, which possibly explains the different incidence rates of breast cancer throughout the world [4]. Previous studies suggest that individuals with mutations of the Nijmegen breakage syndrome 1 (NBS1) suffer from obvious immunodeficiency and an increased susceptibility to cancers [5, 6]. NBS1 657del5 polymorphism is a major mutation in NBS1 gene, and it is a 5-bp deletion of the NBS1 gene [6, 7]. Many studies were published to evaluate the association between NBS1 657del5 polymorphism and breast cancer risk, but the results remained inconsistent [8–14]. To derive a more precise estimation on the possible association, we performed a meta-analysis of previous published studies.

Methods

Identification and eligibility of studies

Two main medical databases including PubMed (1980 to January 2013) and Embase (1980 to January 2013) were searched using the following keywords: "Nijmegen breakage syndrome or NBS1 or 657del5" and "breast cancer." Additional relevant studies were identified by a hand search of the references of original studies. Studies included in this meta-analysis should meet the following criteria: (1) evaluation of the association between NBS1 657del5 polymorphism and

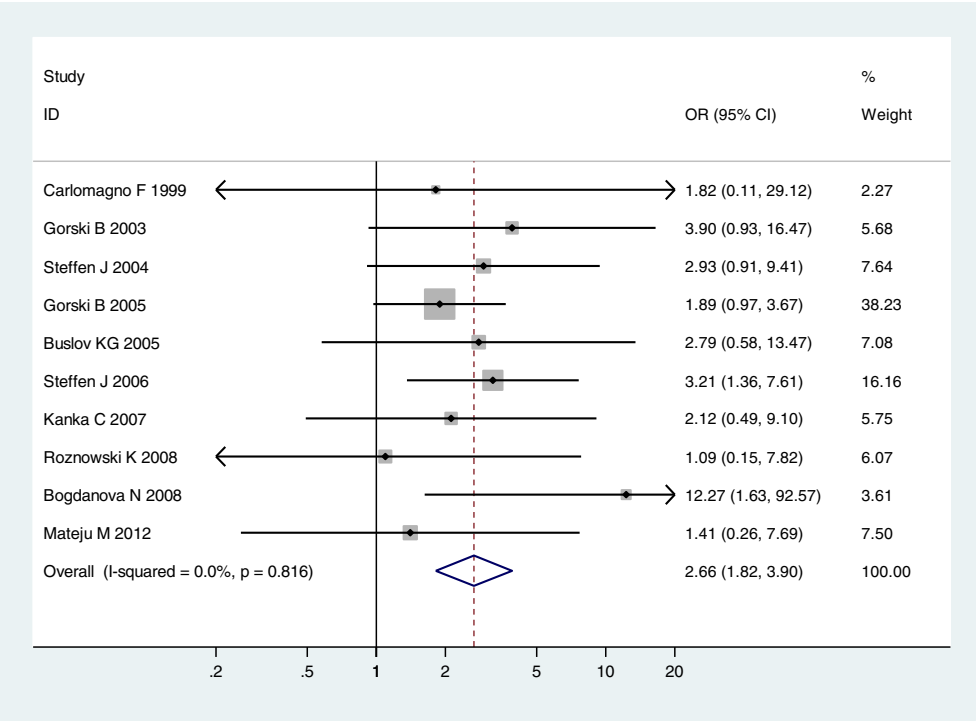

Fig. 1 Forest plot showed a significant association between NBS1 657del5 polymorphism and breast cancer risk

breast cancer risk, (2) data were published in English language, and (3) containing sufficient data for estimation of odds ratio (OR) with 95 % confidence interval (95 % CI). Of these studies with the same or overlapping data, we selected the most recent ones with the largest number of subjects. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from this review.

Data extraction

Two investigators independently extracted data, and disagreements were resolved through consensus. For each study, the following information was collected: first author, publication year, ethnicity of subjects, source of controls, number of cases and controls, and genotyping method. Different ethnic descents were categorized as Caucasians, Asians, and others. The frequencies of NBS1 657del5 polymorphism were extracted or calculated for cases and controls. All data were extracted from published articles, and we did not contact individual authors for further information.

Statistical analysis

The strength of the association between NBS1 657del5 polymorphism and breast cancer risk was measured by ORs with 95 % CIs. The statistical significance of the summary of OR was determined by the Z test. Heterogeneity was evaluated by χ^2-based Q test. A P value of greater than 0.10 indicates a lack of heterogeneity among studies, and the fixed effects model was used to estimate the pooled OR of each study (the Mantel–Haenszel method) [15]. Otherwise, the random effects model (the DerSimonian and Laird method) was used [16]. Sensitivity analysis was performed to assess the stability of results. We also performed a cumulative meta-analysis to provide a framework for updating a genetic effect from all studies and to measure how much the genetic effect changes as evidence accumulates and to find the trend in estimated risk effect [17, 18]. In cumulative meta-analysis, studies were chronologically ordered by publication year, and then, the pooled ORs were obtained at the end of each year (i.e., at each information step). Begg's funnel plot was performed to assess the publication bias of literatures. In addition, funnel-plot asymmetry was assessed by the method of Egger's linear regression test, and $P<0.05$ was considered statistically significant [19]. All statistical tests for this meta-analysis were performed with Stata (version 11.0; Stata Corporation, College Station, TX).

Results

Characteristics of included studies

With our search criterion, 36 articles were retrieved. However, 26 articles were excluded because these did not meet the inclusion criteria. Finally, ten studies with a total of 25,365 subjects were identified and included into this meta-analysis [8–14, 20–22]. All ten studies were from Caucasians, and there was no study from other populations. All studies were published in English. The controls from

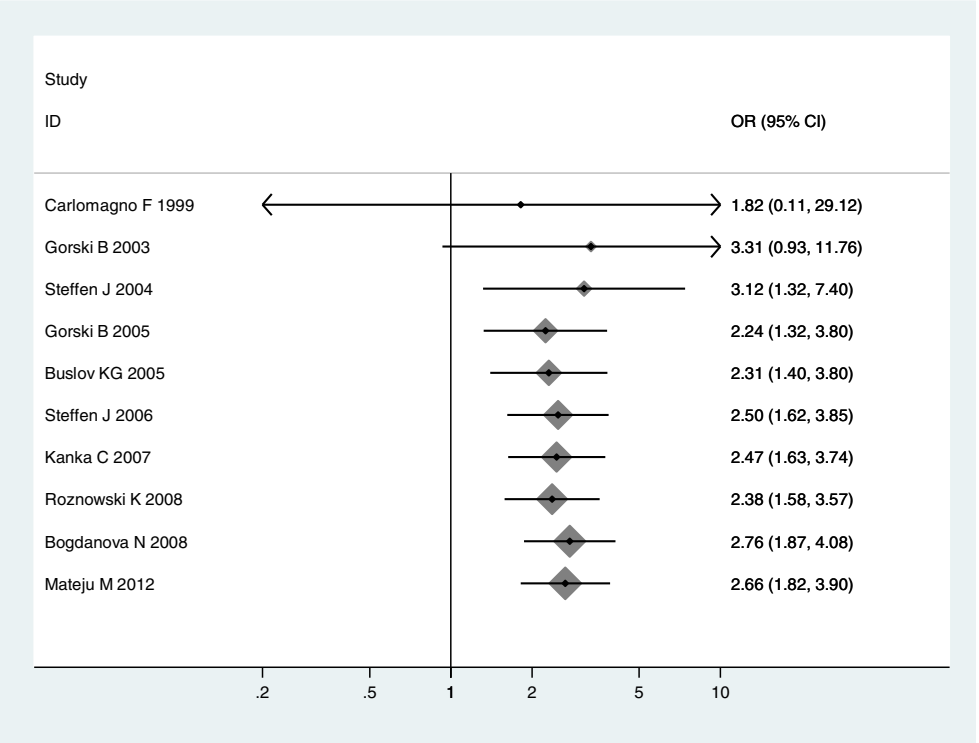

Fig. 2 Forest plots showed the results of cumulative meta-analysis. The fixed effects pooled odds ratio with the corresponding 95 % confidence interval at the end of each information step was shown

most studies were age-matched controls. The number of cases varied from 181 to 2,664, with a mean of 879, and the numbers of controls varied from 295 to 4,000, with a mean of 1,657.

Meta-analysis results

There was no obvious between-study heterogeneity among those ten studies included (P=0.816); thus, the fixed effects model was used to calculate the pooled OR. Meta-analysis of those ten studies showed that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk (pooled OR=2.66, 95 % CI 1.82–3.90, P<0.001) (Fig. 1). Sensitivity analyses by omitting those studies also did not materially alter the overall pooled ORs. The cumulative meta-analyses showed a trend of a more significant association between NBS1 657del5 polymorphisms and breast cancer risk as data accumulated by publication year (Fig. 2).

Publication bias

Begg's funnel plot and Egger's test were conducted to assess the risk of publication bias in the literature. The shape of Begg's funnel plot did not reveal any evidence of asymmetry (Fig. 3). Besides, the result of Egger's test also showed no indication of publication bias (P=0.626). Thus, the results above suggested that there was no risk of publication bias in the literature.

Discussion

MRE11/RAD50/NBS1 complex plays an important role in the maintenance of chromosomal integrity, and the NBS1 protein is a critical component of the complex [23]. In addition, NBS1 also functions as a downstream target of ATM to regulate the S-phase checkpoint [24]. Nijmegen breakage syndrome is a rare autosomal recessive disease, and it is characterized by chromosome instability, immunodeficiency, radiation sensitivity, and high susceptibility to common cancers [25]. Previous studies have proven that

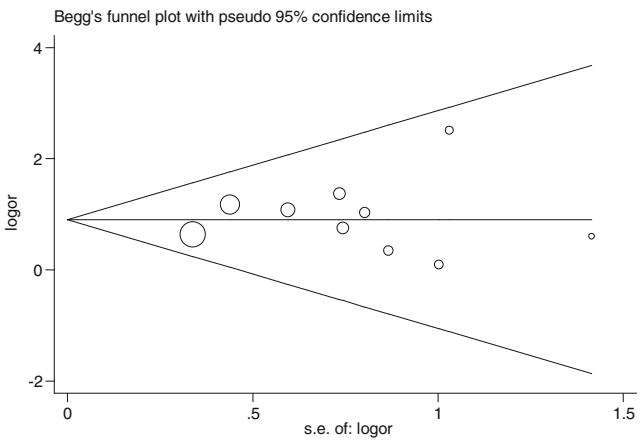

Fig. 3 Begg's funnel plot to assess the publication bias risk in the meta-analysis

mutations in the NBS1 gene are responsible for Nijmegen breakage syndrome [23, 25].

Since the NBS1 protein plays a crucial role in the repair of DNA double-strand breaks and unrepaired double-strand breaks may result in carcinogenesis, many studies have proposed that mutations in the NBS1 gene are responsible for the susceptibility to breast cancer [26]. NBS1 657del5 polymorphism may decrease the repair capacity of individuals with 657del5 mutation through a homologous recombination repair pathway and result in a higher risk of the development of breast cancer [26, 27].

Many studies were published to evaluate the association between NBS1 657del5 polymorphism and breast cancer risk, but the results remained inconsistent. To derive a more precise estimation on the possible association, we performed a meta-analysis of previous published studies. Case–control studies on the association between NBS1 657del5 polymorphisms and breast cancer risk were included into this meta-analysis. Finally, ten studies with a total of 25,365 subjects were identified and included into this meta-analysis. Meta-analysis of those ten studies showed that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk (Fig. 1). The cumulative meta-analyses showed a trend of a more significant association between NBS1 657del5 polymorphisms and breast cancer risk as data accumulated by publication year (Fig. 2). Thus, our meta-analysis suggests that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk, and NBS1 657del5 polymorphism results in an increased risk of breast cancer.

Some limitations of this meta-analysis should be addressed. Firstly, although misclassification bias was unlikely in this meta-analysis because all breast cancer cases were confirmed on the basis of histological examination in those ten studies, we could not exclude the possibility that some control subjects might suffer from latent breast cancer. Secondly, there was limited information on adjusted estimates available from those ten studies, and our meta-analysis was based on unadjusted estimates. Further studies conducted on the basis of adjustment for confounders such as age and smoking can provide a more precise assessment on the association between NBS1 657del5 polymorphisms and breast cancer risk. Finally, in the subgroup analyses by ethnicity, no study was conducted in Africans and Asians. Though we identify the significant association between NBS1 657del5 polymorphisms and breast cancer risk in Caucasians, the similar association in other populations needs further studies.

In conclusion, our meta-analysis suggests that there was a significant association between NBS1 657del5 polymorphisms and breast cancer risk, and NBS1 657del5 polymorphism results in an increased risk of breast cancer. However, the significant association is currently identified in Caucasians, and further studies from Asians and Africans are needed.

Conflicts of interest None of the authors have any conflict of interests to declare.

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