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EPIDEMIOLOGY

P53 codon 72 polymorphism contributes to breast cancer risk: a meta-analysis based on 39 case–control studies

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Abstract *P53* is a tumor suppressor gene and plays important roles in the etiology of breast cancer. Studies revealing conflicting results on the role of *p53* codon 72 polymorphism (G>C) on breast cancer risk led us to perform a meta-analysis to investigate this relationship. Thirty-nine published studies, including 26,041 breast cancer cases and 29,679 controls were identified. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of the associations. The overall results suggested that the variant genotypes were associated with a significantly reduced breast cancer risk (GC vs. GG: OR = 0.91, 95% CI: 0.83–1.00; CC/GC vs. GG: OR = 0.90, 95% CI: 0.82–0.99). In the stratified analyses, significantly decreased risks were also found among European populations (GC vs. GG: OR = 0.89, 95% CI: 0.80–0.99; CC/GC vs. GG: OR = 0.88, 95% CI: 0.80–0.98) and studies with population-based controls (GC vs. GG: OR = 0.88, 95% CI: 0.78–0.98; CC/GC vs. GG: OR = 0.87, 95% CI: 0.78–0.97). The results suggested that *p53* codon 72 polymorphism may contribute to susceptibility to breast cancer, especially in Europeans. Additional well-designed large studies were required to validate this association in different populations.

Keywords *P53* · Breast cancer · Meta-analysis · Molecular epidemiology · Genetic variation

Introduction

Breast cancer is one of the major cancers affecting morbidity and mortality of females worldwide [1]. Although many risk factors for breast cancer have been identified, such as the genetic predisposition and estrogen level, the molecular mechanisms related to breast carcinogenesis remain under investigation [2, 3]. Previous studies have shown alterations in the cell cycle regulatory proteins in breast carcinoma including overexpression and amplification of the cyclin genes, inactivation and deletions of the Rb gene and alterations of the *p53* gene [4–6]. Thus, this disease seems to be the result of cumulative alterations of oncogenes and tumor suppressor genes.

The *p53* tumor suppressor gene, located on chromosome 17p13, is one of the most commonly mutated genes in all types of human cancer [7]. P53 protein is involved in many important physiological processes, such as cell cycle arrest, gene transcription, DNA repair, and apoptosis. If a mutation occurs, p53 may lose its normal functions, leading to unchecked cell proliferation and tumorigenesis. In breast cancers, it is mutated in around 30–35% of the cases and mutations often lead to poorer prognosis [8].

Besides mutations, a common single nucleotide polymorphism (SNP) in codon 72 of *p53* (*p53* codon 72, rs1042522), resulting in either an arginine (Arg) residue

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(CGC) or proline (Pro) residue (CCC), has been demonstrated to affect p53 function. The two polymorphic variants have been shown to have not only structural differences, as reflected by distinct electrophoresis patterns of migration, but also different biological properties [9, 10].

Over the last two decades, a number of case–control studies were conducted to investigate the association between the *p53* codon 72 polymorphism and breast cancer risk in humans. But these studies reported conflicting results. In consideration of the extensive role of *p53* in the carcinogenesis of breast cancer, we carried out a meta-analysis on all eligible case–control studies to estimate the overall breast cancer risk of *p53* codon 72 polymorphism as well as to quantify the between-study heterogeneity and potential bias.

Materials and methods

Identification and eligibility of relevant studies

We searched the electronic literature MEDLINE for all relevant reports (the last search update was March 1, 2009, using the search terms "p53", "polymorphism," and "breast cancer"). The search was limited to English-language papers. Additional studies were identified by a hand search of the references of original studies. We also used the PubMed option "Related Articles" in each research article to search potentially relevant articles. Of the studies with the same or overlapping data published by the same investigators, we selected the most recent ones with the largest number of subjects. Studies included in our meta-analysis have to meet the following criteria: (1) use a case–control design and (2) contain available genotype frequency. Major reasons for exclusion of studies were (1) no control population and (2) duplicate of previous publication.

Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. For each study, the following information was sought: the first author's last name, year of publication, country of origin, ethnicity, matching conditions, numbers of genotyped cases and controls, source of control groups (population- or hospital-based controls), genotyping methods, and quality control. Different ethnic descents were categorized as European, Asian, African, or Mixed that included more than one ethnic descent. For studies including subjects of different ethnic groups, data were extracted separately for each ethnic group whenever possible.

Statistical analysis

For control group of each study, the allelic frequency was calculated and the observed genotype frequencies of the *p53* codon 72 polymorphism were assessed for Hardy–Weinberg equilibrium using the χ^2 test. The strength of the association between the *p53* codon 72 polymorphism and breast cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). We first estimated the risks of the GC and CC genotypes on breast cancer, compared with the wild-type GG homozygote, and then evaluated the risks of (GC/CC) versus GG and CC versus (GC/GG) on breast cancer, assuming dominant and recessive effects of the variant C allele, respectively. Stratified analyses were also performed by ethnicity, source of controls, and clinicopathologic characteristics. In consideration of the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the *Q*-test. If the *P* value is greater than 0.05 of the *Q*-test, which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method) [11]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [12]. Sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias [13]. All analyses were done Stata software (version 8.2; StataCorp LP, College Station, TX), using two-sided *P* values.

Results

Characteristics of studies

Through literature search and selection based on the inclusion criteria, 62 studies were found. During the extraction of data, 23 articles were excluded, because they did not provide allele frequencies needed for OR calculation, leaving 39 eligible studies [14–52] that had assessed the association between the *p53* codon 72 polymorphism and breast cancer risk. Study characteristics are summarized in Supplementary Table 1. Among the 39 eligible case–control studies, there were 26,041 breast cancer cases and 29,679 controls. Besides, there were 29 studies of European descendents, 9 studies of Asian descendents, 1 of African descendents. Breast cancers were confirmed histologically or pathologically in most studies. Of the 39 studies, 34 studies used frequency-matched controls to the cases by the age or ethnicity. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was

Table 1 Meta-analysis of the *P53* codon 72 polymorphism on breast cancer risk

Variables	n^a	GC vs. GG		CC vs. GG		CC/GC vs. GG (dominant)		CC vs. GC/GG (recessive)	
		OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*
Total	39	0.91 (0.83–1.00)†	<0.001	0.92 (0.82–1.04)†	<0.001	0.90 (0.82–0.99)†	<0.001	0.95 (0.87–1.04)†	0.032
Ethnicities									
Asian	9	1.04 (0.86–1.25)	0.216	0.92 (0.65–1.31)†	0.013	1.01 (0.82–1.25)	0.065	0.93 (0.70–1.23)	0.059
European	29	0.89 (0.80–0.99)†	<0.001	0.92 (0.81–1.05)†	<0.001	0.88 (0.80–0.98)†	<0.001	0.96 (0.87–1.06)†	0.028
African	1	0.36 (0.13–0.99)	–	0.79 (0.16–4.04)	–	0.42 (0.17–1.07)	–	1.25 (0.26–6.02)	–
Source of controls									
Population-based	30	0.88 (0.78–0.98)†	<0.001	0.88 (0.77–1.00)†	0.001	0.87 (0.78–0.97)†	<0.001	0.94 (0.87–1.02)	0.100
Hospital-based	7	0.95 (0.66–1.37)†	<0.001	1.08 (0.66–1.78)†	0.003	0.97 (0.66–1.42)†	<0.001	1.12 (0.78–1.62)	0.058
Premenopause	2	0.63 (0.36–1.12)	0.362	1.05 (0.48–2.29)	0.705	0.73 (0.43–1.23)	0.338	1.30 (0.62–2.73)	0.977
Postmenopause	2	0.65 (0.10–4.16)†	0.004	1.21 (0.17–8.80)†	0.021	0.77 (0.10–5.71)†	0.001	1.85 (0.85–4.04)	0.260

* *P* value of *Q*-test for heterogeneity test

† Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used

[a] Number of comparisons

adopted in 21 of the 39 studies; however, only 54% of the included studies mentioned quality control on genotyping, such as blindness to the case–control status, randomly repeated assays, or validation using a different genotyping method. The distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium in all studies except for three studies ($P < 0.01$) [19, 27, 52].

Quantitative synthesis

There was a wide variation in the C allele frequency of the *p53* codon 72 polymorphism among the controls across different ethnicities, ranging from 0.23 to 0.74. For Asian controls, the C allele frequency was 0.40 (95% CI: 0.35–0.46), which was higher than that in European controls (0.34; 95% CI: 0.29–0.39).

Overall, there was evidence of an association between the reduced risk of breast cancer and the variant genotypes in different genetic models when all the eligible studies were pooled into the meta-analysis. As shown in Table 1, the variant heterozygote genotype GC, was associated with a significantly decreased risk of breast cancer (OR = 0.91, 95% CI: 0.83–1.00), compared with the wild-type homozygote GG. In addition, significant main effects were also observed in dominant model (OR = 0.90, 95% CI: 0.82–0.99).

In the stratified analysis by ethnicity, significantly decreased risks were also found among European populations (heterozygote comparison: OR = 0.89, 95% CI: 0.80–0.99; dominant model: OR = 0.88, 95% CI: 0.80–0.98) and African populations (heterozygote comparison: OR = 0.36, 95% CI: 0.13–0.99). However, these similar signifi cant associations were not observed for Asian populations (Table 1; Fig. 1).

Then, we divided these studies into two subgroups according to their sources of controls. For the studies with population-based controls, we found that the variant genotypes were associated with a significantly decreased breast cancer risk in all genetic models except for recessive model (homozygote comparison: OR = 0.88, 95% CI: 0.77–1.00; heterozygote comparison: OR = 0.88, 95% CI: 0.78–0.98; dominant model: OR = 0.87, 95% CI: 0.78–0.97; Fig. 2). However, among studies with hospital-based controls, no significant association was observed in any genetic model (Table 1).

One of the problems with these included studies is their small sample size, because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate. Then, we repeated our analyses with studies containing more than 500 subjects and stratified the analyses by ethnicity and source of control. As a result, no significant association was detected in any comparison (Table 2).

The data on genotypes of the *p53* codon 72 among cases and controls stratified by menopause status were available in two studies [27, 52]. Our results showed that there was no association between the variant genotypes and breast cancer risk regardless of the menopause status (Table 1).

Furthermore, we stratified the included studies by clinicopathologic characteristics of breast cancer such as tumor grade and lymph node metastasis status. Similarly, no statistically significant result was observed for any analysis (Table 3).

Test of heterogeneity

Significant heterogeneity between studies was observed in overall comparisons. Then, we assessed the source of

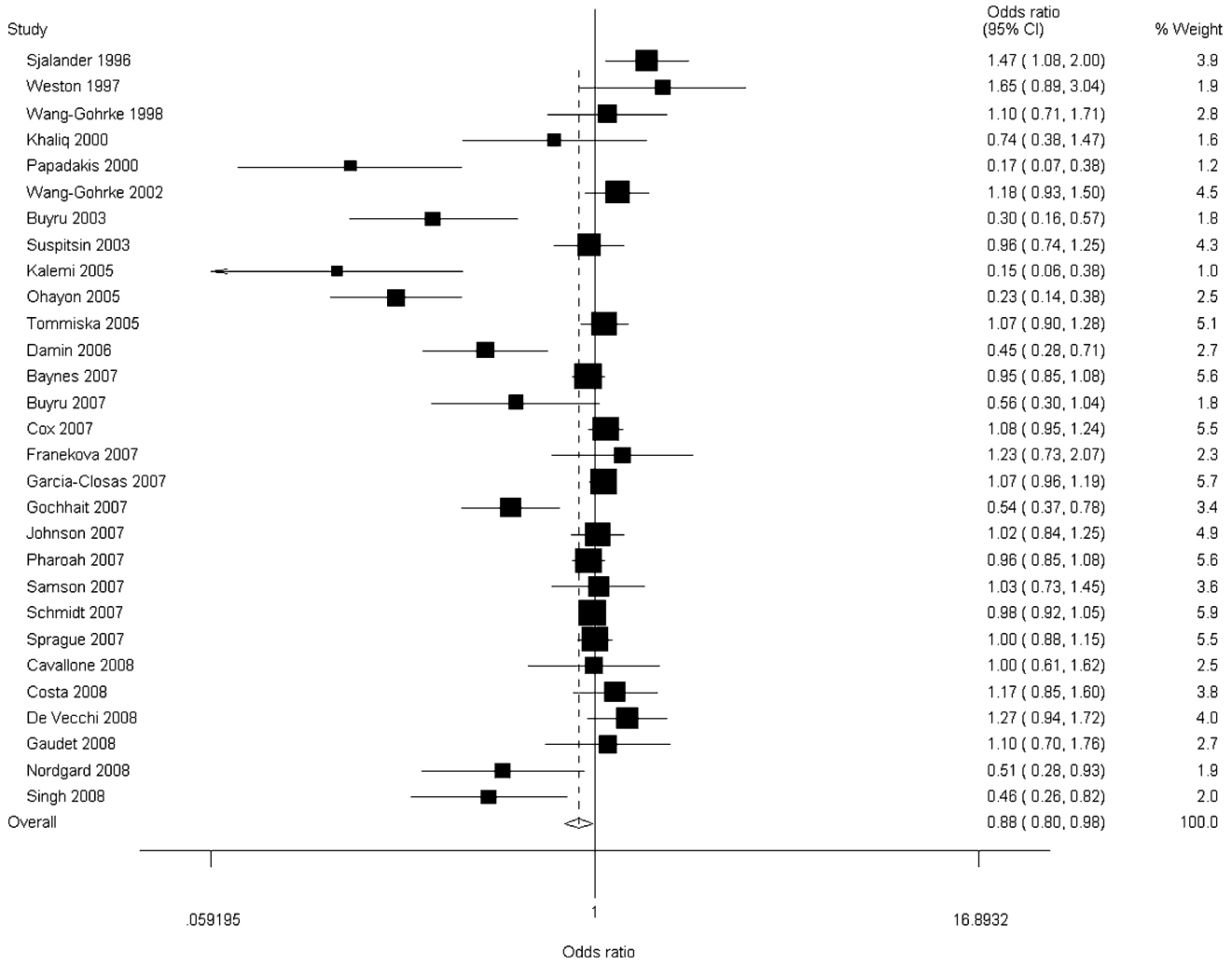

Fig. 1 Forest plot of breast cancer risk associated with the *p53* codon 72 polymorphism (CC/GC vs. GG) among Europeans. The *squares* and *horizontal lines* correspond to the study-specific OR and 95% CI. The area of the *squares* reflects the study-specific weight (inverse of the variance). The *diamond* represents the pooled OR and 95% CI

heterogeneity for heterozygote comparison (GC vs. GG) and dominant model comparison (GC/CC vs. GG) by ethnicity, source of controls, and sample size (more than 500 subjects). As a result, sample size (GC vs. GG: $\chi^2 = 9.26$, $df = 1$, $P = 0.002$; GC/CC vs. GG: $\chi^2 = 6.16$, $df = 1$, $P = 0.013$) and ethnicity (GC vs. GG: $\chi^2 = 6.32$, $df = 2$, $P = 0.042$; GC/CC vs. GG: $\chi^2 = 6.29$, $df = 2$, $P = 0.043$) but not the source of controls (GC vs. GG: $\chi^2 = 0.34$, $df = 1$, $P = 0.559$; GC/CC vs. GG: $\chi^2 = 0.16$, $df = 1$, $P = 0.687$) were found to contribute to substantial heterogeneity. The heterogeneity was effectively decreased or removed after exclusion of those studies with small sample size (less than 500 subjects), suggesting that sample size is very important in the study design.

Sensitivity analyses

Sensitivity analyses indicated that two independent studies by Huang et al. [23] and Lum et al. [50] were the main origin of heterogeneity in Asians. The heterogeneity was effectively decreased or removed after exclusion of these two studies (CC vs. GG: $P_{\text{heterogeneity}} = 0.616$). In addition, no other single study influenced the pooled OR qualitatively, as indicated by sensitivity analyses, suggesting that the results of this meta-analysis are stable.

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of literatures. As shown in

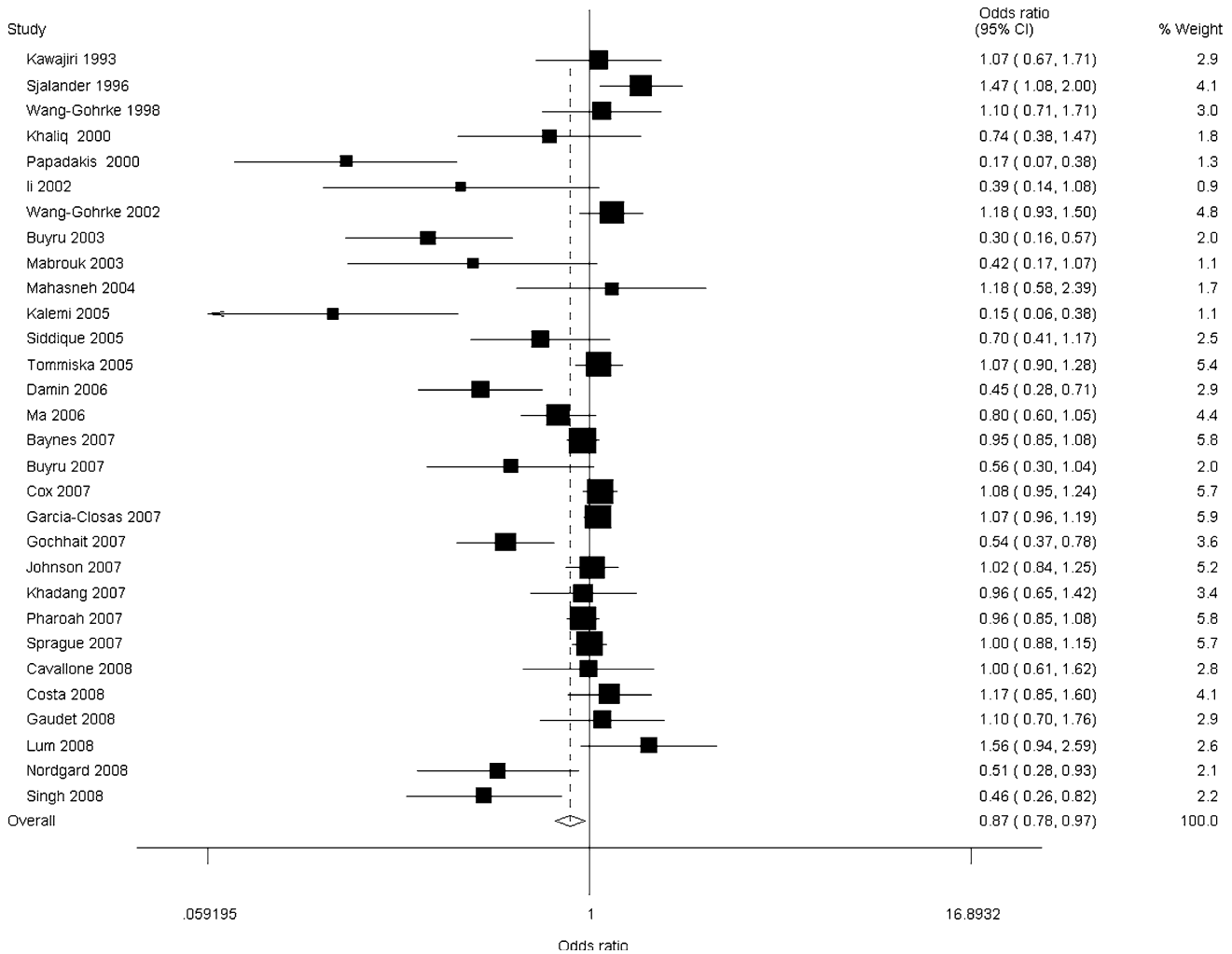

Fig. 2 Forest plot of breast cancers risk associated with the *p53* codon 72 polymorphism (CC/GC vs. GG) among studies with population-based controls. The *squares* and *horizontal lines* correspond to the study-specific OR and 95% CI. The area of the *squares* reflects the study-specific weight (inverse of the variance). The *diamond* represents the pooled OR and 95% CI

Table 2 Stratified analyses of the *P53* codon 72 polymorphism on breast cancer risk with studies containing more than 500 subjects

Variables	n^a	GC vs. GG		CC vs. GG		CC/GC vs. GG (dominant)		CC vs. GC/GG (recessive)	
		OR (95% CI)	*P**	OR (95% CI)	*P**	OR (95% CI)	*P**	OR (95% CI)	*P**
Total	18	1.01 (0.97–1.05)	0.123	0.99 (0.92–1.06)	0.078	1.02 (0.96–1.08)†	0.023	0.97 (0.91–1.03)	0.302
Ethnicities									
Asian	1	0.81 (0.60–1.09)	–	0.78 (0.53–1.13)	–	0.80 (0.60–1.06)	–	0.88 (0.63–1.22)	–
European	17	1.02 (0.98–1.06)	0.155	1.00 (0.93–1.07)	0.086	1.02 (0.97–1.09)†	0.033	0.97 (0.91–1.04)	0.263
Source of controls									
Hospital-based	2	1.07 (0.87–1.32)	0.128	1.15 (0.75–1.77)	0.905	1.08 (0.89–1.32)	0.163	1.14 (0.75–1.73)	0.864
Population-based	14	1.02 (0.97–1.07)	0.099	0.98 (0.86–1.11)†	0.024	1.02 (0.94–1.10)†	0.012	0.96 (0.89–1.04)	0.184
Asian	1	0.81 (0.60–1.09)	–	0.78 (0.53–1.13)	–	0.80 (0.60–1.06)	–	0.88 (0.63–1.22)	–
European	13	1.03 (0.98–1.08)	0.135	0.99 (0.87–1.14)†	0.027	1.03 (0.95–1.11)†	0.019	0.97 (0.89–1.05)	0.150

* *P* value of *Q*-test for heterogeneity test

† Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fix-effects model was used

[a] Number of comparisons

Table 3 Stratified analyses of the *P53* codon 72 polymorphism by clinicopathologic characteristics on breast cancer risk

Stratification of breast cancer	n^a	GC vs. GG		CC vs. GG		CC/GC vs. GG (dominant)		CC vs. GC/GG (recessive)	
		OR (95% CI)	*P**	OR (95% CI)	*P**	OR (95% CI)	*P**	OR (95% CI)	*P**
Grade 3 vs. Grade (1/2)	5	0.90 (0.52–1.54)†	0.048	0.79 (0.46–1.35)	0.353	0.88 (0.63–1.23)	0.278	0.77 (0.49–1.21)	0.146
Asian	1	0.92 (0.38–2.20)	–	0.37 (0.08–1.75)	–	0.74 (0.32–1.68)	–	0.39 (0.09–1.74)	–
European	4	0.92 (0.45–1.85)†	0.023	0.88 (0.48–1.62)	0.321	0.90 (0.58–1.39)	0.185	0.84 (0.52–1.36)	0.123
Lymph node: positive vs. negative	3	0.99 (0.77–1.27)	0.283	0.82 (0.53–1.28)	0.571	0.96 (0.76–1.21)	0.219	0.83 (0.54–1.27)	0.754
Asian	1	1.03 (0.51–2.08)	–	0.86 (0.34–2.20)	–	0.98 (0.52–1.85)	–	0.85 (0.35–1.07)	–
European	2	0.98 (0.76–1.28)	0.113	0.81 (0.49–1.33)	0.293	0.95 (0.74–1.23)	0.082	0.82 (0.50–1.34)	0.455

* *P* value of *Q*-test for heterogeneity test

† Random-effects model was used when *P* value for heterogeneity test <0.05; otherwise, fixed-effects model was used

[a] Number of comparisons

Fig. 3, the shape of the funnel plots seemed asymmetrical in both heterozygote comparison and dominant model comparison, suggesting the presence of publication bias. Then, the Egger's test was adopted to provide statistical evidence of funnel plot asymmetry. As expected, the results have shown an obvious evidence of publication bias ($t = -2.45$, $P = 0.019$ for GC vs. GG; $t = -2.54$, $P = 0.015$ for CC/GC vs. GG).

Discussion

This meta-analysis examined the association between a commonly studied *p53* polymorphism (codon 72 G>C, Arg72Pro) and breast cancer risk. A total of 26,041 breast cases and 29,679 controls from 39 studies were included in the final analysis. We found that the variant genotypes of the Arg72Pro polymorphism were associated with significant decrease in overall breast cancer risk. Given the important roles of p53 in multiple cellular functions, such as gene transcription, DNA repair, and apoptosis, it is biologically plausible that *p53* polymorphisms may modulate the risk of breast cancer.

The *p53* Arg72Pro polymorphism was well characterized in both functional analyses and association studies. Many studies have shown significant difference in the biochemical properties of the p53 protein depending on the particular polymorphic form. Storey et al. [53] reported that patients with human papilloma virus (HPV)-associated tumors revealed a striking overexpression of homozygous Arg-72 p53 compared with the normal population. Moreover, the Arg allele is more susceptible to degradation by the HPV E6 protein, with individuals homozygous for Arg being about seven times more susceptible to HPV-associated tumorigenesis than heterozygotes. Recent studies demonstrated that HPV DNA had been detected in breast carcinoma by different laboratorial techniques, suggesting the virus could play an important role in the pathogenesis of breast tumor [54, 55]. Therefore, the Arg-encoding allele (G allele) represents a significant risk factor in the development of HPV-associated breast cancer. The results of our meta-analysis were consistent with these experimental findings.

We found an evidence for the association between the Arg72Pro and breast cancer risk among Europeans and Africans, but not among Asians, a possible reflection of differences in genetic background and gene–environment interactions in the etiology. For example, the C allele frequency among controls was 0.40 in Asian populations and 0.34 in European populations, suggesting a possible ethnic difference. Other factors such as selection bias, different matching criteria may also play a role. The above-mentioned differences may account for the inconsistent results. In addition, there is only one reported study using African population. So, it is also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this functional polymorphism on breast cancer risk, especially in Africans.

Significant association was also observed among studies using the population-based controls, but not the hospital-based controls. This may be because the hospital-based studies have inherent selection biases due to the fact that such controls may not be representative of the study population or the general population, particularly when the genotypes under investigation were associated with the disease-related conditions that hospital-based controls may have. Thus, the use of proper and representative population-based control participants is of great importance in reducing biases in such genotype association studies.

No significant association between variant genotypes and breast cancer risk was observed when the included

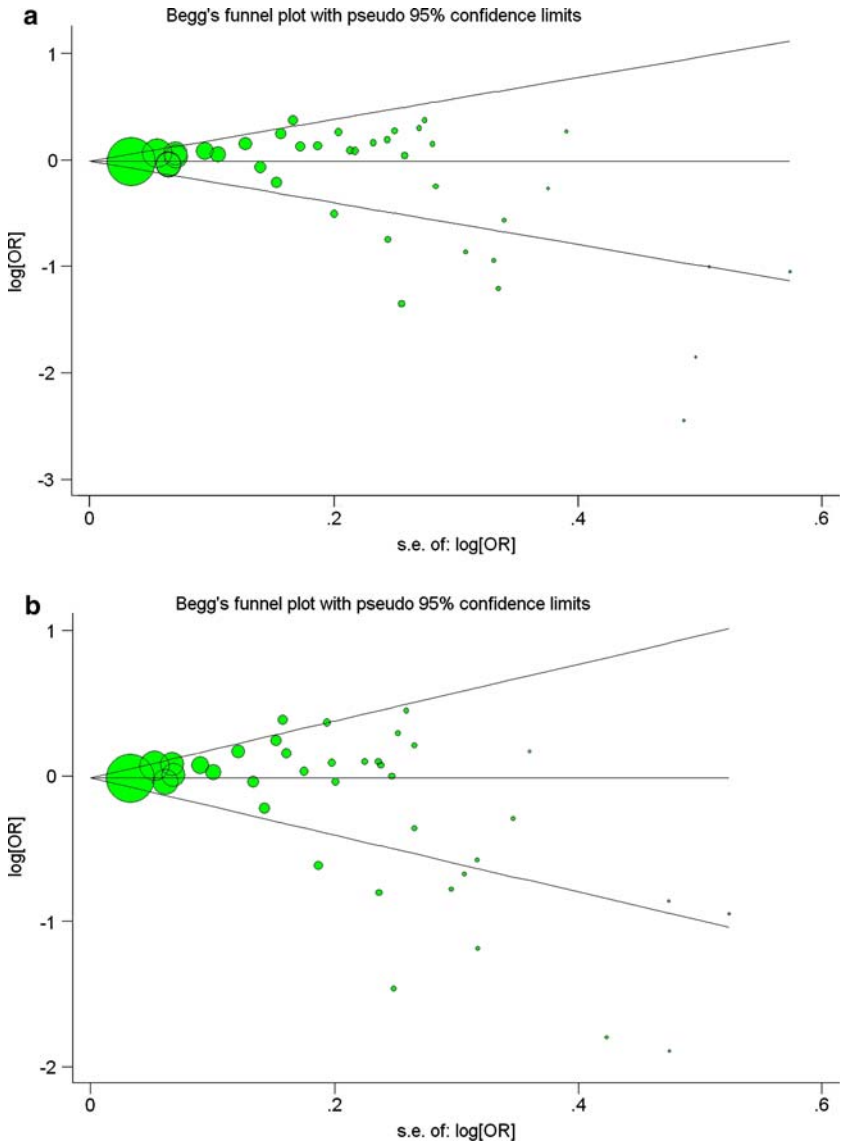

Fig. 3 Begg's funnel plot for publication bias test. **a** GC vs. GG. **b** CC/GC vs. GG. Each *point* represents a separate study for the indicated association. Log[OR], natural logarithm of odds ratio. *Horizontal line*, mean effect size

studies were stratified by menopause status, pathological grade, or lymph node metastasis status. The null result may be due to limited number of studies with available data on these characteristics, which had insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.

Some limitations of this meta-analysis should be addressed. First, most of the studies had a very small sample size and did not have adequate power to detect the possible risk for *p53* codon 72 polymorphism, and the observed significant ORs in some studies of small sample size may be false association. Therefore, more large and well-designed studies should be performed to further confirm all these results. Second, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between gene–gene, gene–environment, and even different polymorphic loci of the same gene may modulate breast cancer risk. Third, misclassifications on disease status and genotypes may also influence the results, because cases in several studies were not confirmed by pathology or other gold standard method, and the quality control of genotyping was also not well documented in some studies. In spite of these, our present meta-analysis also had some advantages. First, substantial number of cases and controls were pooled from different studies, which greatly increased statistical power of the analysis. Second, the quality of case–control studies included in this meta-analysis was satisfactory according to our selection criteria.

In conclusion, this meta-analysis showed some evidence that the *p53* codon 72 polymorphism was associated with a decreased risk of breast cancer. As studies among the Asians and Africans are currently limited, further studies including a wider spectrum of subjects should be carried

out to investigate the role of this functional variant in other populations, which should lead to better, comprehensive understanding of the association between the *p53* codon 72 polymorphism and breast cancer risk.

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