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ORIGINAL RESEARCH

Association between *MDM2* rs 2279744 polymorphism and breast cancer susceptibility: a meta-analysis based on 9,788 cases and 11,195 controls

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Purpose: Previous studies have suggested associations between *MDM2* (mouse double minute 2 homolog) polymorphisms and cancer risk. The aim of this study was to evaluate the relationship between the *MDM2* rs 2279744 polymorphism and the susceptibility of breast cancer.

Methods: We searched PubMed, Web of Knowledge, Embase, and the Chinese National Knowledge Infrastructure (CNKI) database for case–control studies published up to October 2013 that investigated *MDM2* rs 2279744 polymorphism and breast cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of these associations.

Results: A total of 19 studies were identified for the meta-analysis, including 9,788 cases and 11,195 controls. The variant heterozygote (TG) was associated with breast cancer risk in the overall population (TG vs TT: OR =1.10, 95% CI =1.04–1.17, P=0.001, P=0.23 for heterogeneity test). In the subgroup analyses by ethnicity, a significantly increased risk was observed among Asians (G vs T: OR =1.12, 95% CI =1.02–1.23, P=0.02, P_{het}=0.04; GG vs TT: OR =1.29, 95% CI =1.06–1.56, P=0.01, P_{het}=0.04; TG vs TT: OR =1.36, 95% CI =1.15–1.60, P=0.0004, P_{het}=0.45; dominant model TG+GG vs TT: OR =1.21, 95% CI =1.03–1.41, P=0.02, P_{het}=0.07). However, among Caucasians, rs 2279744 was associated with breast cancer risk in only one genotype (TG vs TT: OR =1.09, 95% CI =1.00–1.18, P=0.04, P_{het}=0.37). No publication bias was found in the present study.

Conclusion: This meta-analysis provides evidence for the association between the *MDM2* rs 2279744 polymorphism and breast cancer susceptibility. The results suggest that the *MDM2* rs 2279744 polymorphism plays an important role in breast cancer, especially in Asians.

Keywords: breast cancer, *MDM2*, single nucleotide polymorphism, susceptibility, meta-analysis

Introduction

Breast cancer is one of the major cancers affecting morbidity and mortality of women worldwide. In the US, 232,340 new breast cancer cases were estimated in 2013; breast cancer comprises 29% of all new cancers in females.[1] Breast cancer has a hereditary component and is insufficiently explained by high-penetrance genetic risk factors, such as *BRCA1* and *BRCA2* genes.[2] Allele variants in oncogenes are candidate genetic risk factors that may alter breast cancer onset and outcome. Previous research has suggested that breast cancer results from multiple environmental factors, as well as genetic alterations, such as genetic polymorphisms.[3,4] However, the exact molecular mechanisms of breast cancer still need intensive investigation.

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p53 is a critical tumor suppressor gene that is commonly mutated in human cancers.[5] *MDM2* (mouse double minute 2 homolog), which encodes the protein located on chromosome 12 ql3-14, is an important regulator of p53, and functions by suppressing p53 activity.[6] Furthermore, *MDM2* amplifications and overexpression have been considered an alternative mechanism of p53 inactivation in several human cancers.[7] *MDM2* is overexpressed in various cancers and leads to a worse prognosis in some cancers.[8]

A functional single nucleotide polymorphism (SNP) has been identified at position 309 within the first intron of the promoter region of the human *MDM2* gene, and hence has been designated SNP309 (rs 2279744).[9] Transversion of the T allele to the G allele in the region causes a higher affinity for the Sp1 transcription activator, and subsequently enhances the transcription of the *MDM2* gene. SNP309 leads to an increase in the expression of *MDM2* mRNA and protein, and thereby attenuates the p53 response.[9] In recent years, conflicting evidence has linked the SNP309G variant to enhanced risk of different cancer forms.[10] The *MDM2* rs 2279744 polymorphism has been reported to be associated with some tumors, such as colon cancer, gastric carcinoma, and hepatocellular carcinoma.[11–13] However, the association between rs 2279744 and breast cancer was inconsistent.[14]

Any single study is insufficient to confirm the association of the *MDM2* rs 2279744 polymorphism with the risk of breast cancer. This is particularly true for studies with relatively small sample sizes.[15] It is important to accumulate data from different studies to provide evidence on the association of the *MDM2* polymorphism with breast cancer risk. To clarify the effect of the *MDM2* rs 2279744 polymorphism on the risk of breast cancer, we carried out a meta-analysis on all eligible case–control studies to estimate the overall breast cancer risk of the *MDM2* rs 2279744 polymorphism. Furthermore, we conducted the subgroup analysis by stratification according to ethnicity.

Materials and methods

Publication search

Computer searches were carried out independently by two authors, in PubMed, Web of Knowledge, Embase, and the Chinese National Knowledge Infrastructure (CNKI) database (last search: October 15, 2013) to collect articles with case–control studies related to the association of the *MDM2* rs 2279744 polymorphism and breast cancer risk.

The keywords were as follows: breast cancer/breast carcinoma/breast neoplasm, murine double minute 2/*MDM2*, and polymorphism/genotype/SNP309/rs 2279744. Furthermore, reference lists of the main reports and review articles were also reviewed by manual search to identify additional relevant publications.

Selection criteria

The following criteria were used to select studies to add to the meta-analysis: 1) case–control studies; 2) the studies evaluated the associations between the *MDM2* rs 2279744 polymorphism and breast cancer risk; and 3) the studies included detailed genotyping data (total number of cases and controls, number of cases and controls with T/T, T/G, and G/G genotypes).

Accordingly, the following exclusion criteria were also used: 1) the design of the experiments was not case–control; 2) the source of cases and controls, and other essential information were not provided; 3) the genotype distribution of the control population was not in accordance with the Hardy–Weinberg equilibrium (HWE); and 4) reviews and duplicated publications.

Data extraction and synthesis

Articles were reviewed independently by two authors and data with discrepancies in identification were discussed by all authors. For each included study, the following information was collected: first author, year of publication, country of origin, ethnicity, source of control, numbers of cases and controls, genotyping methods for *MDM2* rs 2279744 T/G, and total number of cases and controls, as well as the number of cases and controls with T/T, T/G, and G/G genotypes. Different ethnic ancestries were categorized as Caucasian, Asian, African, and "mixed". The "mixed" group means mixed or unknown populations. All the case and control groups were well-controlled. The non-cancer controls had no history of gynecologic disease, and there was no present evidence of gynecologic cancer, any malignant disease, or genetic disease. There were no statistically significant differences in terms of age distribution, smoking habits, or menstrual status between case and control groups. When studies included subjects of more than one ethnicity, genotype data were extracted separately according to ethnicities for subgroup analyses.

Statistical analysis

The associations between the *MDM2* rs 2279744 polymorphism and breast cancer risk were measured by odds ratios (OR) with 95% confidence intervals (CI). The significance of the pooled OR was determined by the *Z*-test. Statistical heterogeneity among studies was assessed with the Q and I^2 statistics. The Q test and I^2 test the variation

which was due to heterogeneity or by random error. When the *P*-value of the heterogeneity tests was no more than 0.1 ($P \leq 0.1$), we used the random effects model. When the *P*-value of the heterogeneity tests was more than 0.1 ($P \geq 0.1$), we used the fixed effects model. Sensitivity analysis was also tested by removing one study at a time to calculate the overall homogeneity and effect size. Publication bias was evaluated by funnel plots and further assessed by Egger's linear regression test.

All statistical analyses were carried out with the review manager (RevMan 5.1 The Cochrane Collaboration, Oxford, UK) and Stata 10 software (Stata Corporation, College Station, TX, USA). All *P*-values in the meta-analysis were two-sided, and *P*-values less than 0.05 were considered significant.

Results

Characteristics of studies

As shown in Figure 1, a total of 31 records that fulfilled our search criteria were preliminarily identified for further detailed evaluation, which excluded 12 studies (Figure 1). Three studies were excluded because they were not case–control studies. Two studies were not focused on the association between the *MDM2* rs 2279744 polymorphism and breast cancer risk. Two studies were excluded because there was no detailed genotyping data. One was a laboratory study, and the rest of the four studies were systematic review comments. Finally, 19 studies on *MDM2* rs 2279744 genotypes and breast cancer risk were identified, including a total of 7,815 breast cancer cases and 8,677 controls.[16–34] The characteristics of the included studies are listed in Table 1.

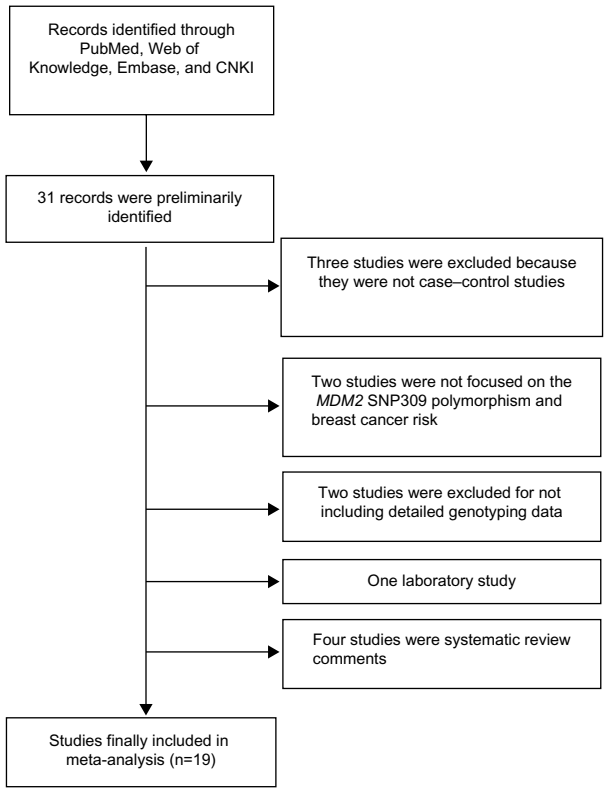

Figure 1 Flow chart of study selection.
Abbreviations: CNKI, Chinese National Knowledge Infrastructure; *MDM2*, *mouse double minute 2 homolog*.

Among the eligible studies, ten studies were based on Caucasian backgrounds which were carried out in the US, UK, Germany, the Netherlands, Finland, Sweden, Israel, and the Czech Republic. Seven were based on Asian ethnicities which were carried out in People's Republic of China, India, Singapore, and Saudi Arabia. Two included African ethnicities, while two studies included individuals with mixed ethnic descent. Breast cancers were confirmed by histology or pathology in most studies. Moreover, controls were mainly matched in age, of which twelve were population-based and seven were hospital-based.

Meta-analysis results

The main results of this meta-analysis are listed in Table 2. As shown in Figure 2, the variant heterozygote (TG) and homozygote (GG) were associated with breast cancer risk in the overall population (TG vs TT: OR =1.10, 95% CI =1.04–1.17, P=0.001, P=0.23 for the heterogeneity test; GG vs TT: OR =1.09, 95% CI =1.00–1.19, P=0.04, P_{het}=0.07). However, there were no significant associations between the *MDM2* rs 2279744 polymorphism and breast cancer risk in other genotype distributions (G allele vs T allele: OR =1.03, 95% CI =0.99–1.08, P=0.11, P_{het}=0.06; dominant model TG+GG vs TT: OR =1.06, 95% CI =1.00–1.12, P=0.05, P_{het}=0.007; recessive model GG vs TT+TG: OR =1.02, 95% CI =0.95–1.11, P=0.55, P_{het}=0.50).

Ten articles, including 5,378 cases and 5,944 controls, were used to investigate the association of the *MDM2* rs 2279744 polymorphism with breast cancer susceptibility in Caucasians. The results showed that the *MDM2* rs 2279744 polymorphism was associated with breast cancer risk in only one genotype (TG vs TT: OR =1.09, 95% CI =1.00–1.18, P=0.04, P_{het}=0.37), but no associations in other genetic models (G vs T: OR =1.03, 95% CI =0.97–1.09, P=0.30, P_{het}=0.60; GG vs TT: OR =1.10, 95% CI =0.98–1.23, P=0.11, P_{het}=0.59; TG+GG vs TT: OR =1.03, 95% CI =0.95–1.11, P=0.52, P_{het}=0.08; GG vs TT+TG: OR =1.04, 95% CI =0.93–1.16, P=0.47, P_{het}=0.48).

Seven articles, including 1,736 cases and 1,973 controls, were used to evaluate the relationship between the *MDM2* rs 2279744 polymorphism and breast cancer susceptibility in

Table 1 Characteristics of the studies included in the meta-analysis

First author	Year	Country	Ethnicity	Study design	Genotyping method	Total sample size (Case/control)
Boersma et al[16]	2006	USA	Caucasian African-American	CC	PCR	290/314
Campbell et al[17]	2006	UK	Caucasian	CC	PCR	351/258
Millikan et al[18]	2006	USA	Caucasian African-American	CC	PCR-RFLP	2,037/1,813
Petenkaya et al[19]	2006	Turkey	Mixed	CC	PCR-RFLP	223/149
Ma et al[21]	2006	People's Republic of China	Asian	CC	PCR	366/605
Wilkening et al[20]	2006	Germany	Caucasian	CC	qPCR	549/1,065
Wasielewski et al[22]	2007	The Netherlands	Caucasian	CC	PCR	343/126
Cox et al[23]	2007	America	Mixed	CC	PCR-RFLP	1,519/2,271
Lum et al[24]	2008	Singapore	Asian	CC	PCR	402/128
Singh et al[25]	2008	India	Asian	CC	qPCR	104/105
Paulin et al[26]	2008	England	Caucasian	CC	qPCR	299/275
Krekac et al[27]	2008	Czech Republic	Caucasian	CC	PCR-RFLP	158/149
Yarden et al[28]	2008	Israel	Caucasian	CC	qPCR	187/138
Lang et al[29]	2009	Sweden	Caucasian	CC	PCR-RFLP	123/146
Sun et al[30]	2009	People's Republic of China	Asian	CC	PCR-RFLP	124/97
Koh et al[31]	2011	Singapore	Asian	CC	qPCR	385/614
Leu et al[32]	2011	People's Republic of China	Asian	CC	PCR	255/324
Knappskog et al[33]	2011	WEC, Finland	Caucasian	CC	PCR-RFLP/Taqman	1,973/2,518
Alshatwi et al[34]	2012	Saudi Arabia	Asian	CC	PCR	100/100

Abbreviations: CC, case–control; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; WEC, Western European countries including the UK, the Netherlands, and Norway; qPCR, quantitative PCR.

Table 2 Meta-analysis of the association between the *MDM2* rs 2279744 polymorphism and breast cancer risk

Comparisons	OR	95% CI	*P*-value	Heterogeneity		Effects model
				I^2	*P*-value	
G vs T	1.03	0.99–1.08	0.11	36%	0.06	Random
Asian	1.12	1.02–1.23	0.02	54%	0.04	Random
Eastern Asian	1.07	0.97–1.19	0.17	65%	0.02	Random
Caucasian	1.03	0.97–1.09	0.30	0%	0.60	Fixed
African	1.15	0.94–1.42	0.17	37%	0.21	Fixed
GG vs TT	1.09	1.00–1.19	0.04	35%	0.07	Random
Asian	1.29	1.06–1.56	0.01	55%	0.04	Random
Eastern Asian	1.25	1.01–1.54	0.04	55%	0.06	Random
Caucasian	1.10	0.98–1.23	0.11	0%	0.59	Fixed
African	0.75	0.39–1.47	0.40	0%	0.57	Fixed
TG vs TT	1.10	1.04–1.17	0.001	18%	0.23	Fixed
Asian	1.36	1.15–1.60	0.0004	0%	0.45	Fixed
Eastern Asian	1.37	1.15–1.64	0.0006	20%	0.29	Fixed
Caucasian	1.09	1.00–1.18	0.04	8%	0.37	Fixed
African	1.31	1.03–1.66	0.03	60%	0.11	Fixed
TG+GG vs TT	1.06	1.00–1.12	0.05	50%	0.007	Random
Asian	1.21	1.03–1.41	0.02	49%	0.07	Random
Eastern Asian	1.19	1.00–1.41	0.05	58%	0.05	Random
Caucasian	1.03	0.95–1.11	0.52	42%	0.08	Random
African	1.24	0.99–1.56	0.07	53%	0.14	Fixed
GG vs TT+TG	1.02	0.95–1.11	0.55	0%	0.50	Fixed
Asian	1.04	0.89–1.21	0.63	38%	0.14	Fixed
Eastern Asian	1.00	0.85–1.18	0.99	16%	0.31	Fixed
Caucasian	1.04	0.93–1.16	0.47	0%	0.48	Fixed
African	0.72	0.37–1.40	0.33	0%	0.52	Fixed

Abbreviations: CI, confidence interval; OR, odds ratio; vs, versus; G, Guanine; T, Thymine; GG vs TT, homozygous genetic model; TG vs TT, allele contrast genetic model; TG+GG vs TT, dominant model; GG vs TT+TG, recessive model; *MDM2*, *mouse double minute 2 homolog*.

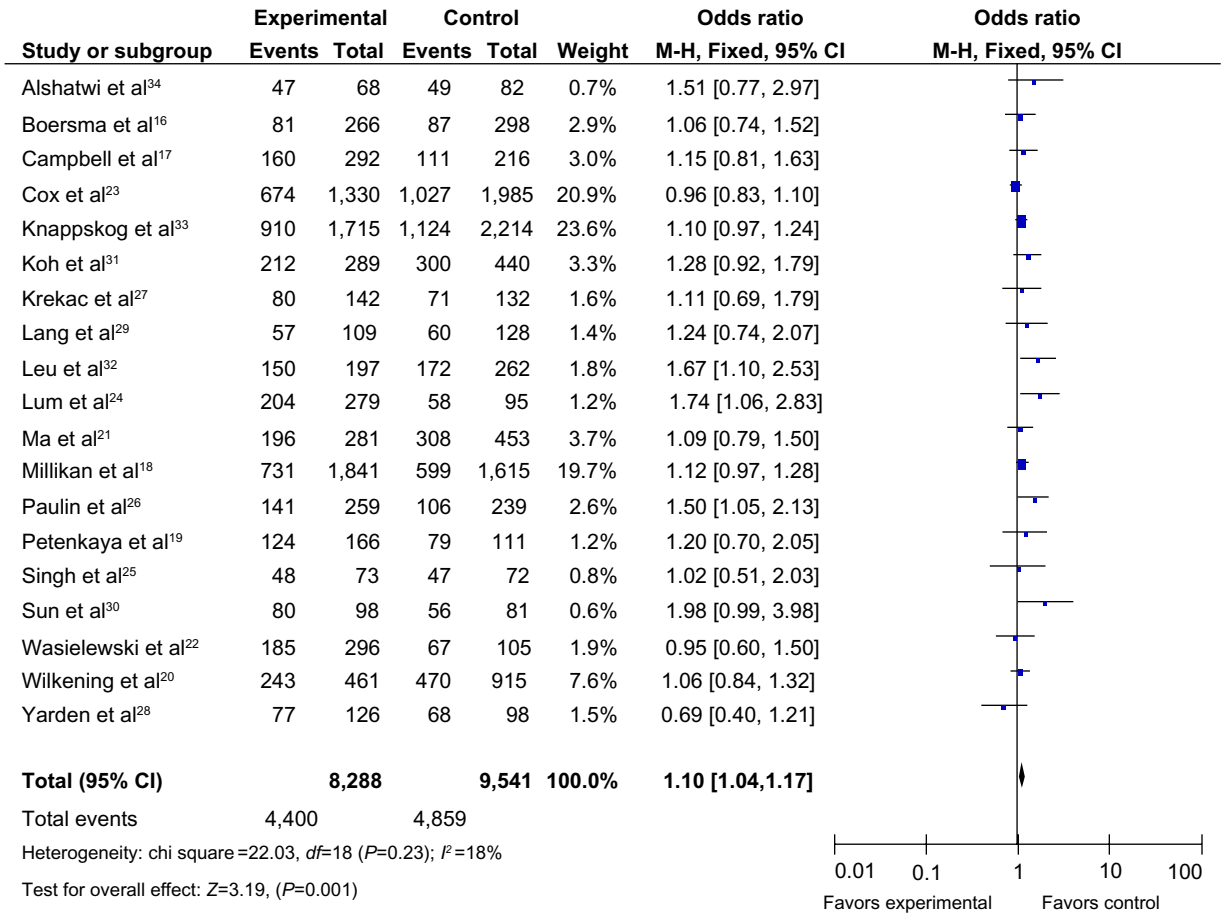

Figure 2 Forest plots of the *MDM2* rs 2279744 polymorphism and breast cancer risk in the overall population (TG vs TT).
Notes: The squares and horizontal lines correspond to the study specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
Abbreviations: CI, confidence interval; OR, odds ratio; *df*, degrees of freedom; M-H, Mantel-Haenszel; *MDM2*, *mouse double minute 2 homolog*.

Asians. In the subgroup analysis by ethnicity, in the Asian population, the results revealed significant associations between the *MDM2* rs 2279744 polymorphism and breast cancer in four genetic models (G vs T: OR =1.12, 95% CI =1.02–1.23, P=0.02, P_{het}=0.04; GG vs TT: OR =1.29, 95% CI =1.06–1.56, P=0.01, P_{het}=0.04; TG vs TT: OR =1.36, 95% CI =1.15–1.60, P=0.0004, P_{het}=0.45; TG+GG vs TT: OR =1.21, 95% CI =1.03–1.41, P=0.02, P_{het}=0.07), but not in the recessive model (GG vs TT+TG: OR =1.04, 95% CI =0.89–1.21, P=0.63, P_{het}=0.14). A forest plot of the results is shown in Figure 3.

It is somewhat strange to pool data from Chinese individuals with Arab individuals since these are two very different populations. Therefore, we pooled the data for Eastern Asians (People's Republic of China and Singapore). These results also showed association between rs 2279744 and breast cancer risk (GG vs TT: OR =1.25, 95% CI =1.01–1.54, P=0.04, P_{het}=0.06; TG vs TT: OR =1.37, 95% CI =1.15–1.64, P=0.0006, P_{het}=0.29; TG+GG vs TT: OR =1.19, 95% CI =1.00–1.41, P=0.05, P_{het}=0.05).

There were only two articles, including 932 cases and 858 controls, that were used to evaluate the relationship between the *MDM2* rs 2279744 polymorphism with breast cancer susceptibility in Africans. As shown in Figure 4, the variant heterozygote (TG) seemed to be associated with breast cancer risk in Africans (TG vs TT: OR =1.31, 95% CI =1.03–1.66, P=0.03, P=0.11 for heterogeneity test). However, there were no significant associations in the other genetic models in Africans (G vs T: OR =1.15, 95% CI =0.94–1.42, P=0.17, P_{het}=0.21; GG vs TT: OR =0.75, 95% CI =0.39–1.47, P=0.40, P_{het}=0.57; TG+GG vs TT: OR =1.24, 95% CI =0.99–1.56, P=0.07, P_{het}=0.14; GG vs TT+TG: OR =0.72, 95% CI =0.37–1.40, P=0.33, P_{het}=0.53).

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias. As shown in Figure 5, the funnel plots did not reveal any obvious asymmetry in all genotypes in the overall population, and the results of Egger's test revealed no publication bias (P>0.05).

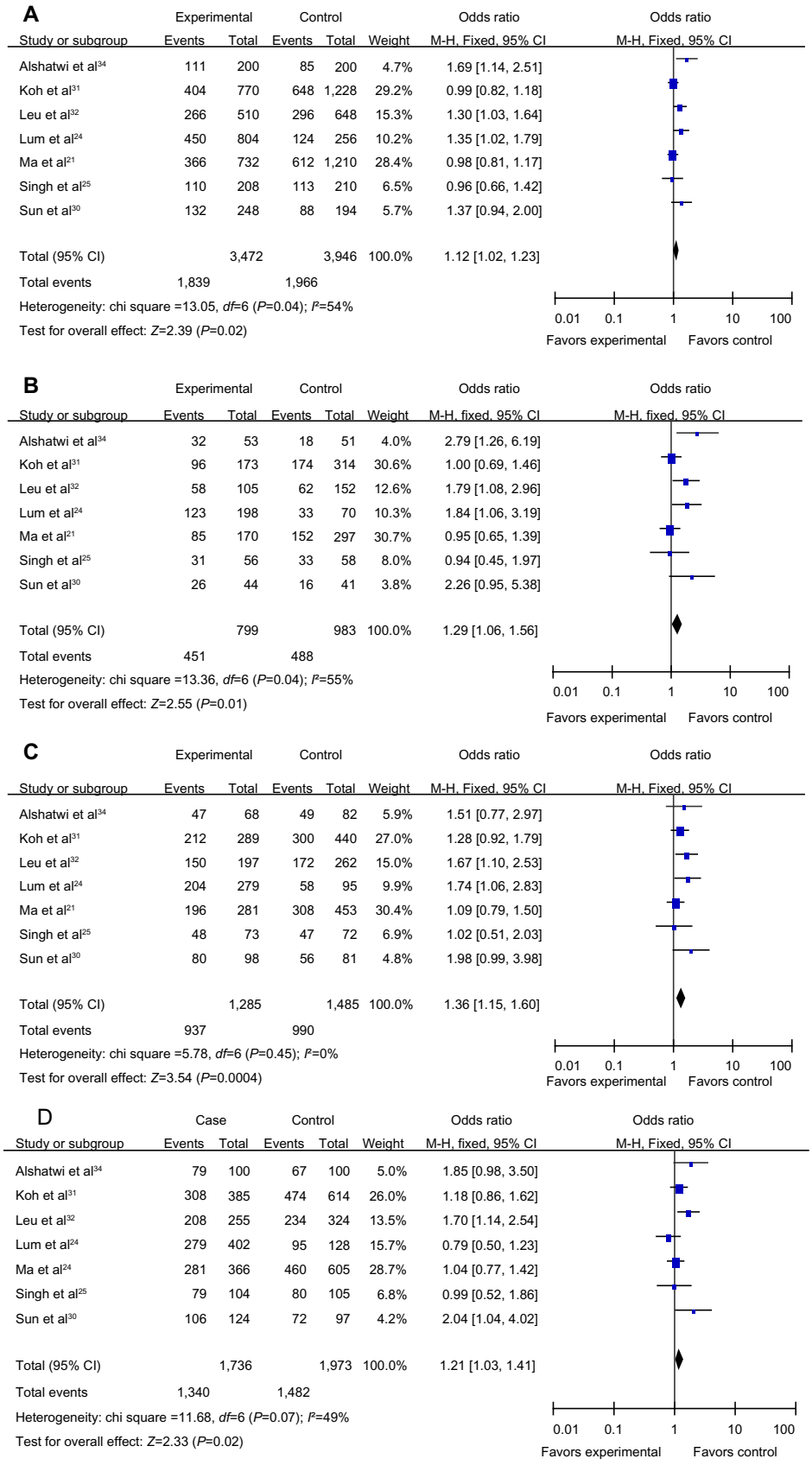

Figure 3 Forest plots showing the relationship between the *MDM2* rs 2279744 polymorphism and breast cancer risk in the Asian subgroup; (**A**) G vs T; (**B**) GG vs TT; (**C**) TG vs TT; (**D**) TG+GG vs TT.

Abbreviations: CI, confidence interval; OR, odds ratio; *df*, degrees of freedom; M-H, Mantel-Haenszel; G, Guanine; T, Thymine; GG vs TT, homozygous genetic model; TG vs TT, allele contrast genetic model; TG+GG vs TT, dominant model; GG vs TT+TG, recessive model; *MDM2*, *mouse double minute 2 homolog*.

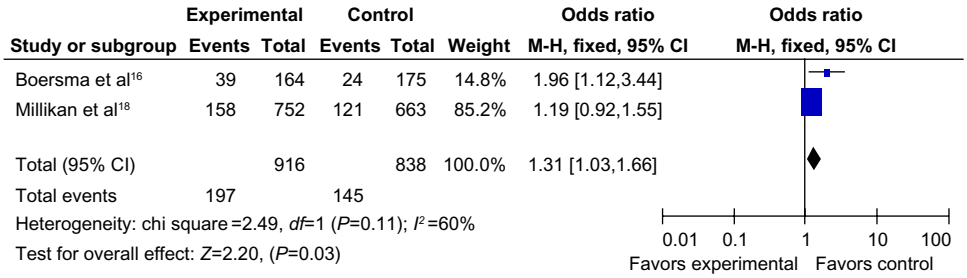

Figure 4 Forest plot showing the relationship between the *MDM2* rs 2279744 polymorphism and breast cancer risk in the African subgroup (TG vs TT).
Abbreviations: CI, confidence interval; OR, odds ratio; *df*, degrees of freedom; M-H, Mantel-Haenszel; vs, versus; *MDM2*, *mouse double minute 2 homolog*; TG vs TT, allele contrast genetic model.

Discussion

Multiple lines of evidence support an important role for genetics in determining risk for cancer, and association studies are appropriate for searching susceptibility genes involved in cancer.[35] It has been suggested that SNPs are the most common sources of human genetic variation and they may contribute to an individual's susceptibility to cancer.[36–38]

In recent years, interest in the genetic susceptibility to cancers has led to growing attention to the study of gene polymorphisms involved in tumorigenesis. Some genetic polymorphisms of genes have been implicated to alter cancer susceptibility.[36,38,39] A previous study indicates that *MDM2* SNP309 serves as a tumor susceptibility marker, and that there is an association between *MDM2* SNP309 and p53 Arg72Pro regarding tumor susceptibility.[38] In vitro analyses revealed that SNP309G enhances Sp1 promoter binding, while SNP285C strongly lessens this binding.[33] Comparing *MDM2* promoter status among different cohorts of breast cancer patients versus healthy controls, SNP285C reduced the risk of breast cancer (OR =0.79; 95% CI =0.62–1.00) among SNP309G carriers.[33]

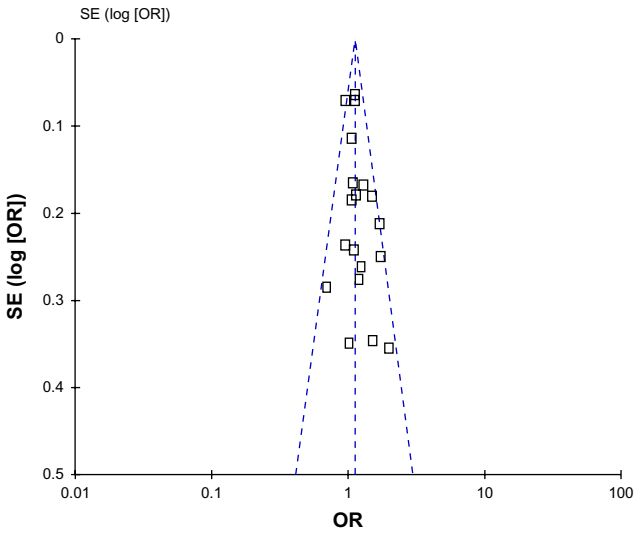

Figure 5 Funnel plot assessing evidence of publication bias from 19 studies (TG vs TT).
Abbreviations: SE, standard error; OR, odds ratio; TG vs TT, allele contrast genetic model.

In a large collaborative study by the Breast Cancer Association Consortium, there was no evidence for either an increase in risk or an earlier age at onset of breast cancer in carriers of *MDM2* rs 2279744.[14] In the previous study, G-allele of *MDM2* rs 2279744 accelerated breast cancer tumorigenesis via an estrogen-signaling pathway.[40] Meanwhile, in a Japanese study including 557 primary breast cancer patients, although the T/T genotype tended to be associated with better disease-free survival compared to other genotypes of rs 2279744, this association did not achieve significance ($P>0.05$), and no statistically significant correlation was found between prognosis and *MDM2* rs 2279744 genotype.[41] The *MDM2* promoter rs 2279744 polymorphism influences long-term survival among patients receiving paclitaxel for large primary breast cancers.[42]

The relationship between the rs 2279744 polymorphism and cancer was inconsistent. Two recent meta-analyses on colorectal and ovarian cancer showed no significant association between the *MDM2* rs 2279744 polymorphism and colorectal (or ovarian) cancer risk in total population analysis, respectively.[15,43] In the subgroup meta-analysis by ethnicity, a significantly increased risk was observed among Asians in colorectal cancer.[15] However, in ovarian cancer, a negative association was shown in the Asian subgroup.[43] Two large studies in the US[18,23] and other studies in UK,[17] Turkish,[19] and Chinese[21] breast cancer cases found no evidence for an increased risk of breast cancer. However, in the study based on the Chinese/Singapore population, the *MDM2* rs 2279744 G allele increased risk while the T allele was associated with earlier onset age of sporadic breast cancers.[24] In this meta-analysis, we found that those with the rs 2279744 TG genotype had a significantly increased risk of breast cancer (TG vs TT: OR =1.10, 95% CI =1.04–1.17, P=0.001, P_{het}=0.23).

A previous meta-analysis reported that the association between *MDM2* SNP309 and breast cancer is influenced by race. *MDM2* SNP309 represents a risk factor for breast cancer in Chinese women but not in non-Chinese women.[44]

In our subgroup meta-analysis based on ethnicity, compared with the T allele, a significantly increased risk of breast cancer is associated with the G allele in Asian. Furthermore, compared with the TT genotype, a significantly increased risk of breast cancer is associated with the TG genotype, GG genotype, and the combined TG/GG genotypes subgroup. In the Caucasian subgroup, rs 2279744 was associated with breast cancer risk in only one genotype (TG vs TT: OR =1.09, 95% CI =1.00–1.18, P=0.04, P_{het}=0.37). Our results indicate that ethnicity may be a main factor on the effects of the polymorphic alleles. It was partially in line with the results of Economopoulos and Sergentanis.[44]

In the subgroup analysis, we also found that the TG genotype was associated with a significantly increased risk of breast cancer in African individuals. Unfortunately, there were only two studies involved. In addition, as individuals in these two studies were African-American, environmental factors need to be eliminated, as previous findings have shown implications for reconciling differences in the estimates of population growth parameters made using African and African-American populations.[45] Further investigations on a large scale on African populations are needed to verify this result.

Some limitations in this meta-analysis must be addressed. First, in the subgroup analyses, the numbers of Asians and Africans were relatively low, with inadequate statistical power to explore the exact correlation. Second, only published studies in English were included in this meta-analysis; some ongoing studies and data published in other languages were not pooled, which may have skewed the results. Third, since limited studies were from Africans, large-scale multicenter epidemiological studies based on Africans with different environmental background are urgently needed. Moreover, further studies estimating the effect of gene–gene and gene–environment interactions may eventually provide a comprehensive understanding of the association between the *MDM2* rs 2279744 polymorphism and breast cancer risk.

Conclusion

In summary, the present meta-analysis provides evidence of the association between *MDM2* rs 2279744 polymorphism and breast cancer risk. The rs 2279744 polymorphism plays an important role in breast cancer, especially in Asians.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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