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ORIGINAL ARTICLE

MDM2 Gene *rs2279744* Polymorphism and Breast Cancer Risk: Evidence from Meta-Analysis and Meta-Regression Analysis

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Abstract

Background Several case–control studies have previously assessed the association of mouse double minute 2 homolog (MDM2) gene *rs2279744* polymorphisms, and the risk of breast cancer (BC) that has resulted in incongruous conclusions. In order to clarify the conflicting outcomes obtained from different individual association studies, here we performed the most updated meta-analysis of *rs2279744* polymorphism and risk of BC.

Methods A comprehensive systematic search of literature, including ISI Web of Science, Scopus, and PubMed/MEDLINE, was carried out prior to March 2023, and the pooled odds ratio (OR) and their corresponding 95% confidence interval (CI) were calculated to determine the overall association power in the pooled population.

Results Literature search led to retrieving of 39 studies, containing 22,764 cases and 22,444 healthy controls. The pooled analysis indicated that the dominant model (OR = 1.04, 95% CI = 1–1.09, $P = 0.03$), recessive model (OR = 1.13, 95% CI = 1.01–1.26, $P = 0.2$), allelic model (OR = 1.07, 95% CI = 1.02–1.12, $P = 0.009$), and GG genotype (OR = 1.18, 95% CI = 1.04–1.34, $P = 0.008$) were significantly associated with increased risk of BC. This polymorphism was also associated with increased risk of BC in Asians (dominant, allelic, and heterozygote models) but not Caucasians.

Conclusions The current meta-analysis suggests that MDM2 gene *rs2279744* polymorphism is a predisposing genetic factor in BC, particularly in Asians.

Keywords Breast cancer · Genetic susceptibility MDM2 · Polymorphism · Meta-analysis · Genetic factor · Asians

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Introduction

Breast cancer (BC) is widely recognized as the predominant malignancy affecting women, with the highest incidence rate among all cancers diagnosed. Additionally, it stands as the second primary contributor to cancer-related deaths in women, after lung cancer.[1, 2]. With regard to statistical findings, BC has a high incidence rate worldwide, and 2 million new cases are recognized yearly, accounting for 23% of all cancer cases.

The past three decades witnessed a 128% increase in the total number of incident cases worldwide [3]. In 2020, female breast cancer became the most commonly diagnosed cancer globally for the first time, with an estimated 2.26 million new cases reported [4]. The most recent prediction suggests that by 2040, the global burden of breast cancer is expected to increase to over 3 million new cases annually [5, 6]. From epidemiological perspective, BC is growing strongly in South America, Africa, and Asia.

Investigation highlight that early detection of BC has an indispensable role in diminishing the mortality rate and ameliorating its prognosis [7]. BC is a heterogeneous disease influenced by both genetic and environmental factors, including hormonal alteration, unhealthy life style, and a family history of BC [8, 9]. In addition to the mentioned factors, genetic polymorphisms have become a remarkable factor in recent years. Polymorphisms occurred in the oncogenes, tumor suppressors, and the controlling elements may even modulate the BC onset and outcome. Accordingly, p53 as a tumor suppressor gene and MDM2 as an oncogene play a pivotal role in the pathophysiology of BC [10–12].

MDM2 gene is located on chromosome 12 ql3-14 and encodes a negative regulator of p53 facilitating its degradation through proteasomal pathways. Furthermore, MDM2 functions as a nuclear phosphoprotein and can directly inhibit the transcriptional activity of p53 by forming a direct interaction with it [13–15]. Any genetic polymorphism in sensitive sites can alter the expression of MDM2 and may lead to inactivation of p53, allowing damaged cells to evade cell-cycle checkpoints and progress toward a cancerous state [16–18].

A functional single-nucleotide polymorphism (SNP) known as MDM2 SNP309 (*rs2279744*) occurs in the promoter region of the human MDM2 gene. As the result of this trans version, *G* nucleotide is substituted by *T* (*T* > *G*). Subsequently, the affinity of the MDM2 promoter is augmented for transcription factor SP1, leading to upregulation of MDM2 expression. Since overexpression of MDM2 gene attenuates the function of p53, which is involved in the etiopathogenesis of various cancers, therefore MDM2 gene *rs2279744* SNP can be a predisposing factor in different malignancies, such as cervical, prostate, lung, and oral carcinomas [19–24].

A growing body of studies has evaluated the potential association between the MDM2 gene polymorphism and susceptibility to BC, but the results have been contradictory. Two potential reasons can be considered for such findings; first, each published study has had small sample size, resulting in relatively weak statistical power to find the overall effects. Second, it is suggested that the allele frequency of MDM2 gene *rs2279744* polymorphism is altered by ethnicity, raising the hypothesis that ethnic differences may influence the impact of this polymorphism. Considering the mentioned points, we performed a thorough and most update meta-analysis to examine the correlation between the *rs2279744* polymorphism of the MDM2 gene and the risk of breast cancer. Our analysis encompassed a total of 39 studies, comprising 22,764 cases of breast cancer and 22,444 healthy controls. The aim was to establish a more accurate and dependable conclusion regarding this association.

Methods

This project was carried out in accordance with the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [25]. Furthermore, it should be noted that the present research project does not involve any studies involving human participants or animals conducted by any of the authors.

Search Strategy

The major databases (PubMed/MEDLINE, ISI Web of Science, and Scopus) were systematically searched up to March 2023 to identify potential publications considering the association between MDM2 gene polymorphism (*rs2279744* or SNP309) and susceptibility to BC. The main key words were: ("murine double minute 2" OR "mouse double minute 2" OR "MDM2") AND ("breast cancer" OR "breast tumor" OR "breast carcinoma" OR "breast neoplasm*") AND ("polymorphism*" OR "variant*" OR "mutation" OR "genotype" OR "SNP" OR "allele" OR "single nucleotide polymorphism" OR "SNP309" OR "*rs2279744*"). Additionally, comprehensive cross-referencing was conducted within both eligible and reviewed articles to identify any potential additional publications. Original studies conducted in the English language were gathered with a focus on human populations.

Study Selection

The initial search strategy resulted in a total of 1191 publications, which were subsequently imported into the Endnote X9 software. Duplicate entries were eliminated. Two investigators then proceeded to review the titles and abstracts of the remaining studies, excluding those that were deemed irrelevant. A thorough assessment of the full text was conducted if we could not stratify studies based on the title & abstract. Any discrepancies or disagreements between the investigators were thoroughly discussed and resolved through consensus.

Eligibility Criteria

Studies considered eligible if they met the following criteria: (i) all case–control or cohort studies considering MDM2 gene polymorphism and BC as the major outcome; (ii) studies containing allele frequency and genotype distribution for case and control groups; (iii) studies including sufficient data to extract or calculate odds ratios (ORs) and 95% confidence intervals (CIs). Only studies with female BC cases were included in the final meta-analysis. Duplicates, animal study,

book chapters, review articles, letters to editor, case reports, and studies with repetitive subjects all were excluded. The application of these criteria identified 39 eligible studies for quantitative analysis.

Data Extraction and Quality Assessment

Two investigators independently collected the required information by following a standardized extraction checklist. The data included the name of the first author, age, country of origin, ethnicity, and journal and publication year, number of subjects in the case and control groups, genotyping method, and genotype, and allele counts in the case and control groups. Methodological quality of qualified publication was scored by Newcastle–Ottawa scale (NOS), a validated scale for non-randomized studies in meta-analysis [26]. Based on the NOS score, studies were stratified to high-quality (7–9), intermediate-quality (4–6), and low-quality (1–3).

Statistical Analysis

Deviation from Hardy–Weinberg equilibrium (HWE) for genotype frequency was evaluated by Pearson's chi-square test in the control group ($P < 0.05$ was considered as significant). The five comparison models were as follow: dominant model (GG + GT *vs*. TT), recessive model (GG *vs*. GT + TT), allelic model (*G vs*. *T*), homozygote (GG *vs*. TT), and heterozygote (GT *vs*. TT). The strength of association between *rs2279744* polymorphism and BC risk was evaluated via pooled ORs and their 95% CIs. Cochrane's *Q* test and the I^2 test were explored to measure potential between study heterogeneity. In this regard, the fixed-effected model (FEM) was used if $P_{Q\text{-statistic}} > 0.10$ or I^2 was < 50%; otherwise, the random-effected model (REM) was applied [27, 28]. In order to assess sources of heterogeneity among included studies, subgroup analysis, and meta-regression analysis based on year of population, the continent of the study population, and the genotyping method were performed. The influence of individual study on the overall effect size was estimated by sensitivity analysis. Begg's test, Egger's regression test, and visual examination of the funnel plot were applied to measure publication bias [29, 30]. All statistical analyses were conducted using Stata statistical software (version 14.0; Stata Corporation, College Station, TX, USA) and SPSS (version 23.0; SPSS, Inc. Chicago, IL, USA).

Trial Sequential Analysis

The poor effect of systematic or random errors may stem from sparse data and mislead results in meta-analyses. To attenuated their effects and get more reliable results, the trial sequential analysis (TSA) was used (Copenhagen Trial Unit, Denmark, 2011; https://ctu.dk/tsa/). In this study, we set up TSA with type-I error of 5%, a statistical test power of 80%, and a − 50% relative risk reduction.

Results

Study Characteristics

The study selection process, in accordance with the PRISMA statement, is depicted in Fig. 1, illustrating four distinct phases. Initially, after eliminating duplicate publications (331 in total), 860 publications remained. Subsequently, 631 publications were excluded based on title and abstract screening, followed by the exclusion of 190 publications through full-text evaluation. Ultimately, a total of 39 eligible studies were included for the final analysis. All references from these selected publications were cross-checked, and no additional relevant studies were identified. These studies were published between 2006 and 2022 and were deemed to possess good methodological quality overall, as determined by NOS scores ranging from five to eight. The majority of the included studies employed polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) or PCR methods for genotyping. The sample size in case and control groups varied, ranging from. 39 to 2811 and 45 to 3749 individuals, respectively. The mean ages of participants in both the case and control groups ranged from 23 to 82, indicating that the studies were conducted among adult populations. Detailed characteristics and genotype frequencies of the included studies can be found in Tables 1 and 2.

Quantitative Synthesis

In the current meta-analysis, the major TT genotype of the MDM2 gene *rs2279744* SNP was used as the reference category for the statistical comparisons.

Meta-Analysis of MDM2 Gene rs2279744 Polymorphism and BC Risk

Overall Analysis

In this study, a comprehensive search yielded 42 studies (derived from 39 publications) that presented relevant data on the association between the MDM2 gene *rs2279744* polymorphism and breast cancer (BC) risk. The quantitative analysis encompassed a total of 22,764 BC cases and 22,444 controls. Of them, 17 studies were performed among countries with Caucasian ethnicity [31–44], 16 studies were in Asians [2, 45–53], 5 studies were in countries with mix ethnicity (American, African-America, Latin) [54–58], and one study in Oceania [8]. The pooled OR divulged a positive association between *rs2279744* and risk of BC

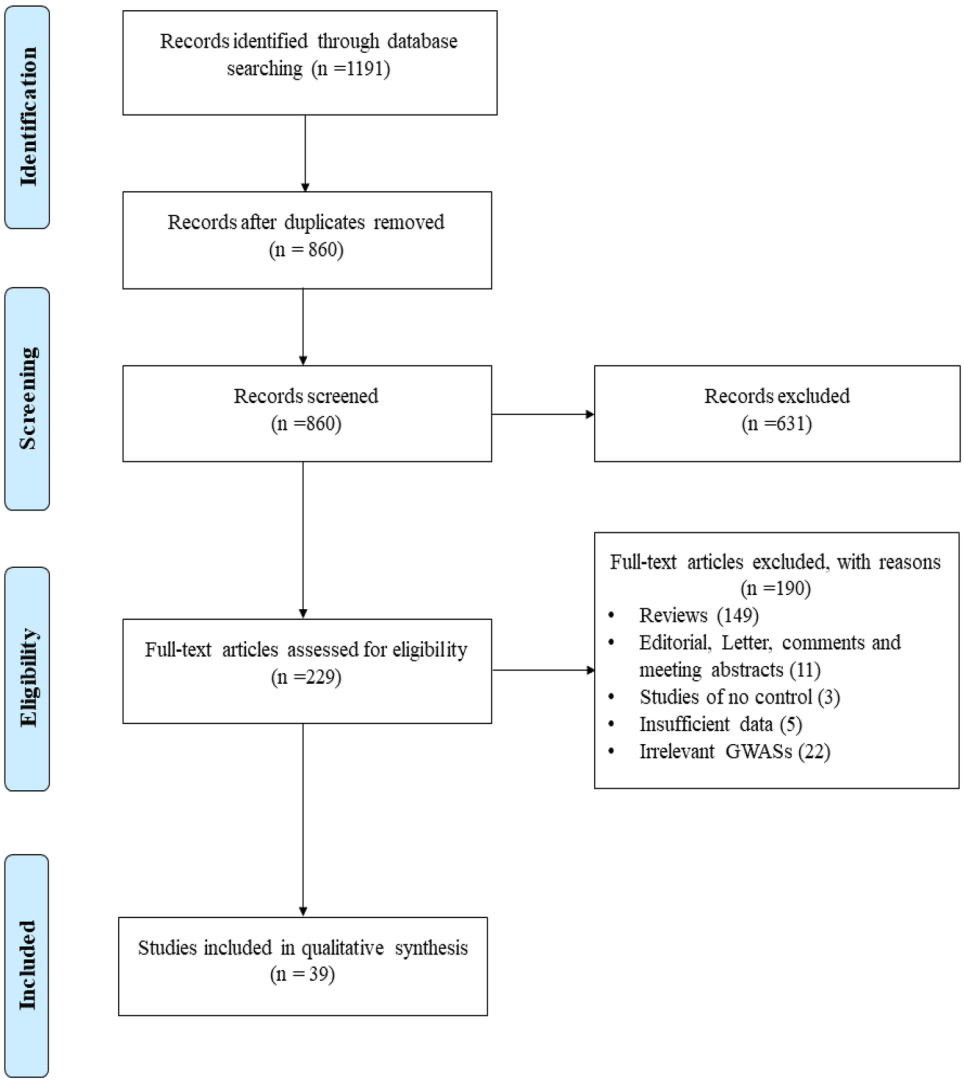

Fig. 1 Flow diagram of study selection process

and demonstrated this SNP as a predisposing factor for BC, according to dominant model (odds ratio = 1.04, 95% CI = 1–1.09, $P = 0.03$), recessive model (odds ratio = 1.13, 95% CI = from 1.01 to 1.26, $P = 0.02$), allelic model (odds ratio = 1.07, 95% CI = from 1.02 to 1.12, $P = 0.009$), and GG *versus*. TT model (odds ratio = 1.18, 95% CI = from 1.04 to 1.34, P 0.008) (Fig. 2). REM was employed to assess recessive, allelic, and GG versus TT models, whereas FEM was utilized to analyze dominant and GT versus TT models. Table 3 displays the outcomes of heterogeneity tests, pooled odds ratios (ORs), and publication bias assessments across various analytic models.

Subgroup Analysis by Ethnicity

We stratified eligible articles into three groups, including Caucasians (17 articles), Asians (16 articles), and mixed population (five articles). The results of quantitative analysis demonstrated *rs2279744* as a potential risk factor for Asians under some genotype models. In details, dominant model (odds ratio = 1.13, 95% CI = from 1.01 to 1.27, $P = 0.02$), allelic model (odds ratio = 1.13, 95% CI = from 1 to 1.28, $P = 0.05$), and GT *versus* TT model (odds ratio = 1.17, 95% CI = from 1.04 to 1.32, $P = 0.01$) for Asian indicated significant association with increased risk of BC (Fig. 3). No significant association was detected for population with Caucasians and mixed ethnicity (Table 3).

Meta-Regression Analyses

To explore the potential factors contributing to the observed heterogeneity among the included studies, logistic meta-regression analyses were conducted (Table 4). The results revealed that none of the examined parameters, including publication year, continent, and genotyping method were the source of heterogeneity (Fig. 4).

Table 1 Characteristics of studies included in meta-analysis

Study author	Year	Country	Study design	Ethnicity	Total cases/controls	Age case/control (Mean)	Genotyping method	Quality score
Boersma et al	2006	United States	Case–control	Mixed	290/314	54 ± 14.4/52.9 ± 13.3	PCR	7
Campbell et al	2006	UK	Case–control	Caucasian	351/258	40/39	PCR	7
Copson et al	2006	UK	Cohort	Caucasian	59/102	41.2/NR	PCR	5
Ma et al	2006	China	Case–control	Asian	366/605	52.41/47.34	PCR	7
Millikan et al	2006	United States	Case–control	Mixed	2037/1813	48.5/NR	PCR–RFLP	6
petenkaya et al	2006	Turkey	Case–control	Caucasian	223/149	51/47	PCR–RFLP	6
Wilkening et al	2006	Germany	Case–control	Caucasian	549/1065	46.5/42	TaqMan	8
Cox et al	2007	United States	Case–control	Mixed	1519/2271	NR/NR	PCR–RFLP	8
Wasielewski et al	2007	Netherlands	Cohort	Caucasian	343/126	44/43.5	PCR	6
Schmidt et al.(i)	2007	Finland	Cohort	Caucasian	580/549	NR/NR	Genotyping assay	7
Schmidt et al.(ii)	2007	Germany	Cohort	Caucasian	1043/784	NR/NR	Genotyping assay	7
Schmidt et al. (iii)	2007	Netherlands	Cohort	Caucasian	1402/258	NR/NR	Genotyping assay	7
Schmidt et al. (iv)	2007	UK	Cohort	Caucasian	2811/1092	NR/NR	Genotyping assay	7
Krekac et al	2008	Czech Republic	Case–control	Caucasian	158/149	56/58	PCR–RFLP	6
Lum et al	2008	China	Case–control	Asian	402/128	43/44	PCR	6
Paulin et al	2008	UK	Cohort	Caucasian	299/275	53/53	qPCR	6
Singh et al	2008	India	Case–control	Asian	104/105	47/42	ARMS-PCR	6
Yarden et al	2008	Israel	Case–control	Caucasian	187/138	57.5/37.2	qPCR	6
lang et al	2009	Sweden	Case–control	Caucasian	123/146	34/30	PCR	6
Sun et al	2009	Taiwan	Case–control	Asian	124/97	54/38	PCR–RFLP	6
Sinilnikova et al	2009	mixed	Case–control	Caucasian	1333/889	42/41.5	PCR–RFLP	8
Knappskog et al	2011	Norway, Netherlands	Cohort	Caucasian	1973/2518	NR/NR	PCR	8
Akisik et al	2010	Turkey	Case–control	Caucasian	147\120	42.9 ± 12.4/41.1 ± 11.3	PCR–RFLP	6
Wu et al	2010	China	Case–control	Asian	698/525	49/47	PCR–RFLP	7
Koh et al	2011	Singapore	Case–control	Asian	385/614	61.5/61.3	qPCR	7
Leu et al	2011	Taiwan	Case–control	Asian	255/324	55.2/62.1	PCR–RFLP	7
Alshatwi et al	2011	Saudi Arabia	Case–control	Asian	100\100	50 ± 5/50 ± 5	qPCR	5
Piotrowski et al	2012	Poland	Case–control	Caucasian	468\550	59.4 ± 10.2/58.7 ± 10.5	PCR–RFLP	8
Wang et al	2013	China	Case–control	Asian	600/600	NR/NR	PCR–RFLP	7
Gansmo et al	2014	Norway	Case–control	Caucasian	1717/3749	NR/NR	Light SNiP assays	8
Guan et al	2014	China	Case–control	Asian	305/345	50.1/48.7	TaqMan	6
Yadav et al	2015	India	Case–control	Asian	100\100	NR/NR	ARMS-PCR	5
Márquez-Rosales et al	2016	Mexico	Case–control	Mixed	529/408	54.36/46.14	PCR	7
Afshari et al	2017	Iran	Case–control	Asian	128/126	46.1 ± 10.2/43.8 ± 11.8	ARMS-PCR	5
Isakova et al	2017	Kyrgyzstan	Case–control	Asian	117/102	52.2 ± 10.8/52.2 ± 10.8	PCR–RFLP	5
Macedo et al	2017	Brazil	Case–control	Mixed	39/186	42/52	TaqMan	5
Yilmaz et al	2018	Turkey	Case–control	Caucasian	110/138	51.67 ± 14.02/54.08 ± 11.03	PCR–RFLP	5
Miedl et al	2019	Austria	Case–control	Oceania	406/254	58.6 ± 13.9/57.6	qPCR	6
Isakova et al	2020	Kyrgyzstan	Case–control	Asian	103/102	50.3 ± 18.1/45.8 ± 8.7	PCR–RFLP	5
Jalilvand et al	2020	Iran	Case–control	Asian	100/100	47.5/47.5	PCR–RFLP	5
Shivam et al	2022	India	Case–control	Asian	45/45	NR/NR	ARMS-PCR	4
Floris et al	2022	Sardinian	Cohort	Caucasian	136/125	NR/NR	PCR	5

Evaluation of Publication Bias and Heterogeneity

For all five genetic models, the level of heterogeneity was assessed. Overall, significant heterogeneity was detected in certain models, leading to the adoption of a random effect model (Table 3). The application of Egger's regression, Begg's rank correlation analysis, and quantitative analysis-based funnel plot revealed no statistically significant findings, indicating the absence of publication bias (Table 3 and Fig. 5).

Table 2 Distribution of genotype and allele among BC patients and controls

Study author	Breast cancer cases					Healthy control					*P*-HWE	MAF
	TT	TG	GG	*T*	*G*	TT	TG	GG	*T*	*G*		
Boersma et al	185	81	24	451	129	211	87	16	509	119	0.08	0.189
Campbell et al	132	160	59	424	278	105	111	42	321	195	0.17	0.377
Copson et al	27	27	5	81	37	48	38	16	134	70	0.07	0.343
Ma et al	85	196	85	366	366	145	308	152	598	612	0.65	0.505
Millikan et al	1110	731	196	2951	1123	1016	599	198	2631	995	0.23	0.274
Petenkaya et al	42	124	57	208	238	32	79	38	143	155	0.44	0.52
Wilkening et al	218	243	88	679	419	445	585	35	1475	655	0.12	0.307
Cox et al	656	674	189	1986	1052	958	1027	286	2943	1599	0.67	0.352
Wasielewski et al	111	185	47	407	279	38	67	21	143	109	0.35	0.432
Schmidt et al.(i)	181	297	102	659	501	185	257	107	627	471	0.29	0.428
Schmidt et al.(ii)	433	477	133	1343	743	301	366	117	968	600	0.73	0.382
Schmidt et al.(iii)	581	635	186	1797	1007	103	122	33	328	188	0.73	0.364
Schmidt et al.(iv)	1130	1320	361	3580	2042	1266	1373	443	3905	2259	0.24	0.366
Krekac et al	62	80	16	204	112	61	71	17	193	105	0.59	0.352
Lum et al	75	204	123	354	450	37	58	33	132	124	0.29	0.484
Paulin et al	118	141	40	377	221	123	116	36	362	188	0.29	0.341
Singh et al	25	48	31	98	110	25	47	33	97	113	0.3	0.538
Yarden et al	49	77	61	175	199	30	68	40	128	148	0.91	0.536
Lang et al	52	57	14	161	85	68	60	18	196	96	0.4	0.328
Sun et al	18	80	26	116	132	25	56	16	106	88	0.1	0.453
Sinilnikova et al	530	615	188	1675	991	358	405	126	1121	657	0.5	0.369
Knappskog et al	805	910	258	2520	1426	1090	1124	304	3304	1732	0.58	0.343
Akisik et al	26	88	33	140	154	24	93	3	141	99	0.47	0.343
Wu et al	142	372	184	656	740	122	266	137	510	540	0.74	0.343
Koh et al	77	212	96	366	404	140	300	174	580	648	0.62	0.527
Leu et al	47	150	58	244	266	90	172	62	352	296	0.2	0.456
Alshatwi et al	21	47	32	89	111	33	49	18	115	85	0.97	b0.425
Piotrowski et al	183	207	78	573	363	233	241	76	707	393	0.28	0.357
Wang et al	138	273	189	549	651	191	295	114	677	523	0.99	0.435
Gansmo et al	672	794	251	2138	1296	1464	1783	502	4711	2787	0.26	0.371
Guan et al	76	132	97	284	326	53	168	124	274	416	0.75	0.602
Yadav et al	35	46	19	116	84	33	53	14	119	81	0.31	0.405
Márquez-Rosales et al	124	263	142	511	547	101	205	102	407	409	0.92	0.501
Afshari et al	19	33	76	71	185	19	47	60	85	167	0.06	0.662
Isakova et al	26	62	29	114	120	19	55	28	93	111	0.38	0.544
Macedo et al	15	18	6	48	30	79	83	24	241	131	0.76	0.352
Yilmaz et al	19	69	22	107	113	46	70	22	162	114	0.58	0.413
Isakova et al	22	55	26	99	107	19	55	28	93	111	0.38	0.544
Miedl et al	169	178	59	516	296	105	122	27	332	176	0.33	0.346
Jalilvand et al	23	52	25	98	102	22	40	38	84	116	0.13	0.648
Shivam et al	10	22	13	42	48	20	19	6	59	31	0.66	0.344
Floris et al	61	54	21	176	96	50	57	18	157	93	0.78	0.372

P-HWE, *p*-value for Hardy–Weinberg equilibrium; MAF, minor allele frequency of control group

Sensitivity Analysis

The influence of each study on the combined odds ratio (OR) was assessed through a systematic removal of each study in a sequential manner. The results confirmed that none of the individual studies had a substantial impact on the combined ORs across all genotype models of the MDM2 gene *rs2279744* polymorphism (Fig. 6).

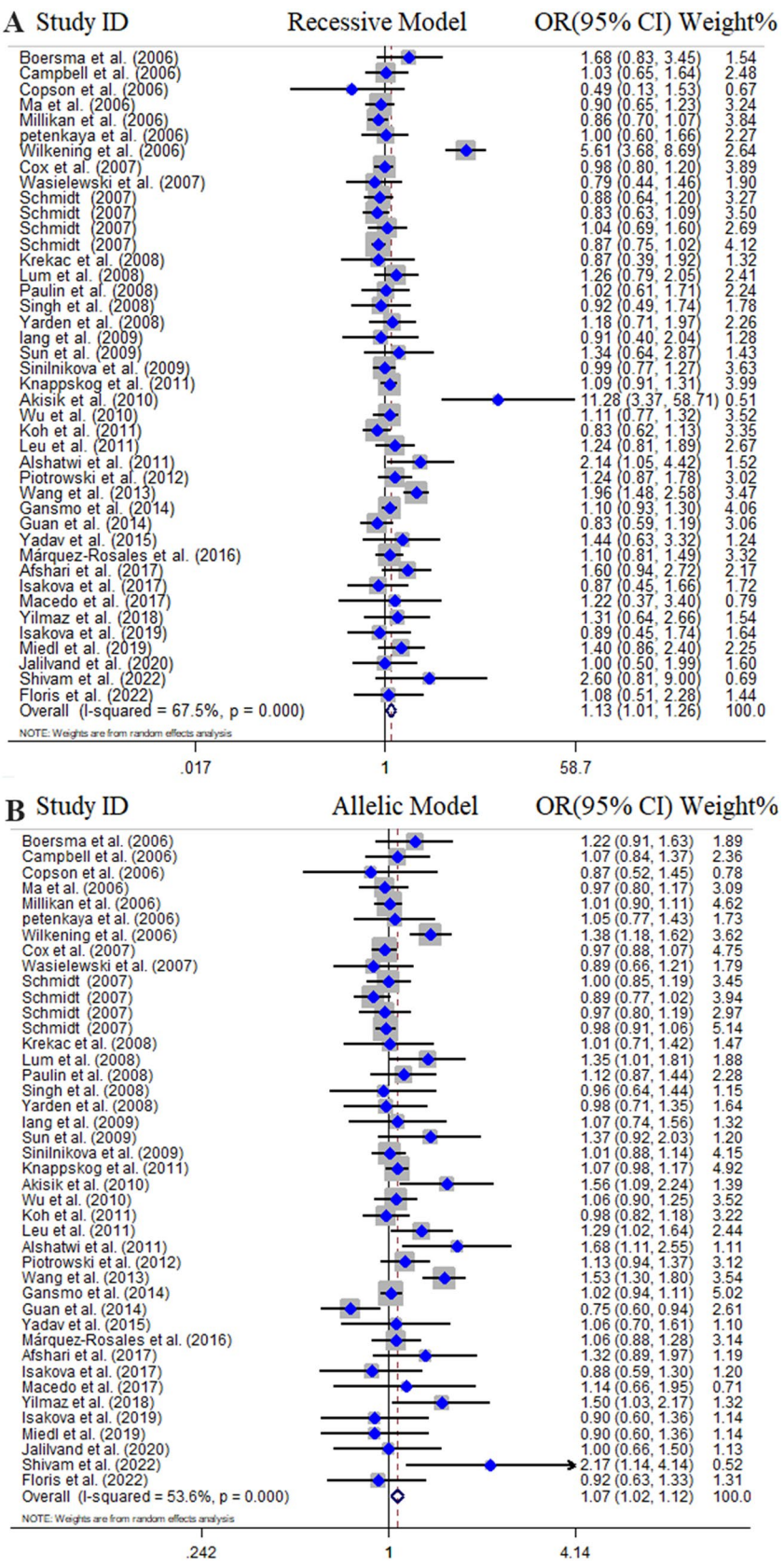

Fig. 2 Pooled OR and 95% CI of individual studies and pooled data for the association between MDM2 gene *rs2279744* and BC risk in: **A**; recessive model and **B**; allelic model

Table 3 Main results of pooled ORs in meta-analysis of MDM2 gene polymorphism

Subgroup		Sample size	Test of association		Test of heterogeneity			Test of publication bias (Begg's test)		Test of publication bias (Egger's test)
	Genetic model	Case/Control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
Overall	Dominant	22,764/22444	1.04	1–1.09 (0.03)	35.2	0.01	1.49	0.13	1.64	0.11
	Recessive	22,764/22444	1.13	1.01–1.26 (0.02)	67.5	≤ 0.001	1.33	0.17	1.45	0.14
	Allelic	22,764/22444	1.07	1.02–1.12 (0.009)	53.6	< 0.001	1.45	0.16	1.59	0.13
	GG versus TT	22,764/22444	1.18	1.04–1.34 (0.008)	67	< 0.001	1.50	0.62	0.68	0.50
	GT *versus* TT	22,764/22444	1.04	0.99–1.08 (0.11)	21.3	0.11	1.07	0.16	1.89	0.07
Subgroup (Ethnicity)										
Caucasian	Dominant	14,012/13180	1.04	0.99–1.09 (0.15)	0	0.69	− 0.80	0.42	− 0.44	0.64
	Recessive	14,012/13180	1.12	0.94–1.34 (0.19)	77.3	< 0.001	0.45	0.65	0.54	0.61
	Allelic	14,012/13180	1.05	0.99–1.11 (0.10)	41.5	0.02	− 1.43	0.15	− 0.98	0.34
	GG versus TT	14,012/13180	1.15	0.96–1.38 (0.11)	73.2	< 0.001	− 0.45	0.64	0.39	0.7
	GT *versus* TT	14,012/13180	1.01	0.96–1.07 (0.59)	1	0.45	− 1.10	0.27	− 0.35	0.73
Asian	Dominant	3932/4018	1.13	1–1.27 (0.02)	64.4	< 0.001	3.06	0.02	3.79	0.01
	Recessive	3932/4018	1.16	0.97- 1.39 (0.09)	54.6	< 0.001	1.24	0.21	0.74	0.48
	Allelic	3932/4018	1.13	1–1.28 (0.05)	68	< 0.001	2.99	0.003	3.65	0.001
	GG versus TT	3932/4018	1.27	0.98–1.64 (0.06)	64.8	< 0.001	1.37	0.16	1.58	0.13
	GT *versus*. TT	3932/4018	1.17	1.04–1.32 (0.01)	41.4	0.04	2.96	0.003	3.65	0.001

Table 3 (continued)

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity			Test of publication bias (Begg's test)		Test of publication bias (Egger's test)
		Case/Control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
Mixed	Dominant	4414/4992	1.02	0.94–1.11 (0.63)	0	0.71	0.19	0.85	−0.53	0.62
	Recessive	4414/4992	0.98	0.85–1.13 (0.76)	8	0.36	0.19	0.85	−0.53	0.62
	Allelic	4414/4992	1.01	0.85–1.13 (0.76)	0	0.60	1.01	0.31	1.44	0.18
	GG versus TT	4414/4992	0.98	0.85–1.13 (0.80)	0	0.45	−0.19	0.85	−0.47	0.66
	GT *versus* TT	4414/4992	1.03	0.94–1.13 (0.49)	0	0.65	0.19	0.85	−0.53	0.62

Trial Sequential Analysis

The results of TSA analysis for dominant model revealed that *Z* curve crosse both conventional statistical significance boundary corresponding to two-sided *P*-value of 0.05 (− 2, 2) and TSA monitoring boundary. These evidences indicated that the current meta-analysis is conclusive at this level and further relevant studies are unnecessary (Fig. 7).

Discussion

Up to now, a bulk of individual case–control replication studies have tried to decipher the correlation between MDM2 gene *rs2279744* polymorphism and risk of BC. However, these replication investigations have produced conflicting results due to certain disparities. Factors such as differences in the racial composition of the study population, differences in the diagnostic criteria used for identifying cases, and low sample sizes may underlie these discrepancies [59]. Nevertheless, meta-analysis studies offer an approach to address this issue by mitigating the limitations inherent in individual replication studies, including inadequate statistical power. Consequently, in order to overcome the above-mentioned limiting factors with respect to the association of MDM2 gene *rs2279744* polymorphism and risk of BC, here we performed the most update and comprehensive systematic review and meta-analysis through including 39 studies (containing 22,764 cases and 22,444 healthy controls).

From genetic and functional perspective, *T* to *G* substitution in *rs2279744* SNP at nucleotide 309 in the first intron of MDM2 gene causes a promoted affinity of the promoter to the transcription activator SP1, resulting in upregulation of mRNA and protein expression of MDM2. This issue, in turn, interferes with the function of tumor suppressing p53 pathway [24]. Several studies have revealed that MDM2 gene *rs2279744* polymorphism could increase the susceptibility of individuals to develop several types of cancers, such as breast, gastric, bladder, endometrial, ovary.

Zhang et al. [60] performed a systematic review and meta-analysis of MDM2 gene *rs2279744* and rs117039649 polymorphisms and risk of gynecological cancers, encompassing cervical, breast, ovarian, and endometrial cancer. They included 24 articles for *rs2279744* polymorphism, involving 6808 controls and 6094 cases. This meta-analysis revealed that the TT and *T* (compared to those with GG, *G*) genotype exhibited a reduced risk of gynecological cancer. Conversely, the GG genotype, (in comparison to the combined TG + TT genotype) was associated with an increased risk of gynecological cancer. This meta-analysis indicated no significant association of MDM2 gene

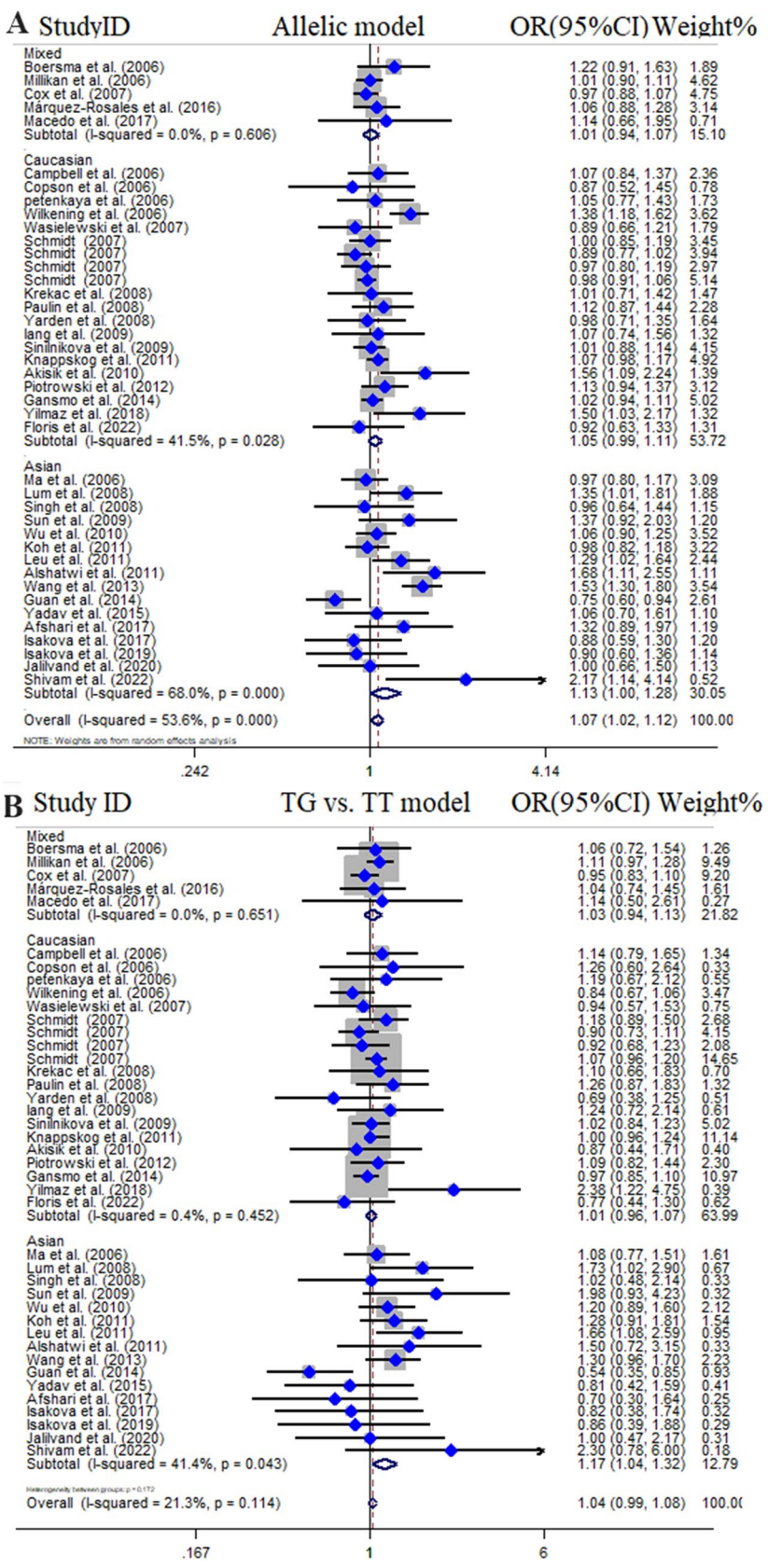

Fig. 3 Pooled OR and 95% CI of individual studies and pooled data for the association between MDM2 gene *rs2279744* and BC risk in different ethnicity subgroups for: **A**; allelic model and **B**; TG versus TT model

Table 4 Meta-regression analyses of potential source of heterogeneity

Heterogeneity factor		Coefficient	SE	*T*-test	*P*-value	95% CI	
						UL	LL
Publication year	Dominant	0.008	0.011	0.76	0.45	− 0.015	0.033
	Recessive	− 0.027	0.083	− 0.32	0.74	− 0.197	0.143
	Allelic	0.003	0.008	0.39	0.69	− 0.014	0.021
	GG versus TT	− 0.020	0.074	− 0.27	0.78	− 0.171	0.131
	GT *versus* TT	0.006	0.013	0.48	0.63	− 0.021	0.033
Continent	Dominant	− 0.055	0.055	− 1.01	0.32	− 0.168	0.057
	Recessive	0.137	0.493	0.28	0.78	− 0.872	1.146
	Allelic	− 0.038	0.045	− 0.85	0.40	− 0.132	0.054
	GG versus TT	0.048	0.437	0.11	0.91	− 0.846	0.943
	GT *versus* TT	− 0.089	0.064	− 1.38	0.17	− 0.221	0.043
Genotyping methods	Dominant	− 0.012	0.023	− 0.50	0.62	− 0.060	0.036
	Recessive	− 0.072	0.230	− 0.31	0.75	− 0.542	0.398
	Allelic	− 0.003	0.021	− 0.17	0.86	− 0.047	0.039
	GG versus TT	− 0.114	0.203	− 0.56	0.57	− 0.529	0.300
	GT *versus* TT	− 0.037	0.29	− 1.28	0.21	− 0.097	0.022

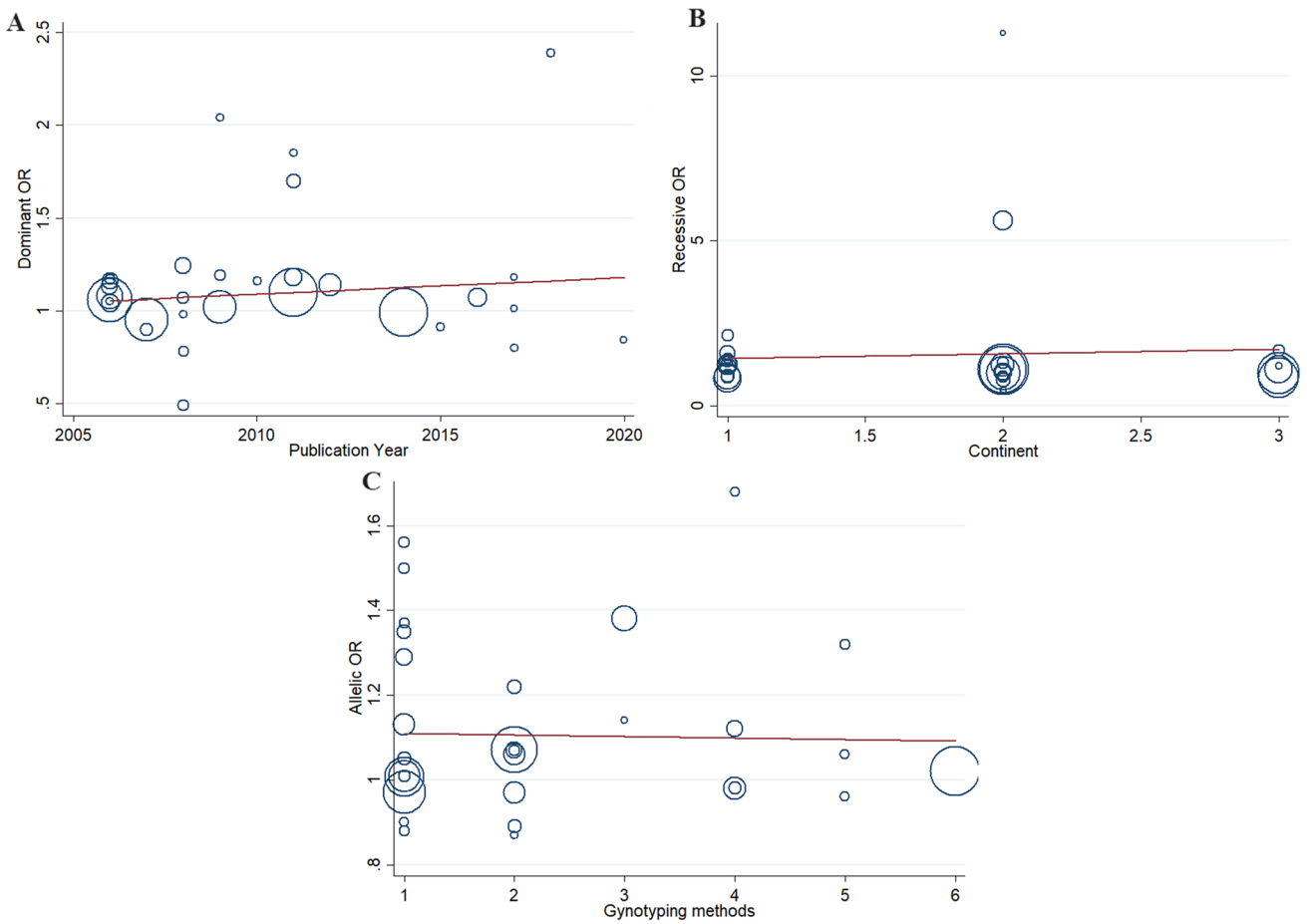

Fig. 4 Meta-regression plots for the meta-analysis of the association between MDM2 gene *rs2279744* and risk of BC based on; **A**: Publication year, **B**: continent (Asian = 1, Europa = 2, America = 3), **C**: genotyping methods (RFLP-PCR = 1, PCR = 2, Taqman-PCR = 3, RT-PCR = 4, ARMS-PCR = 5, others = 6)

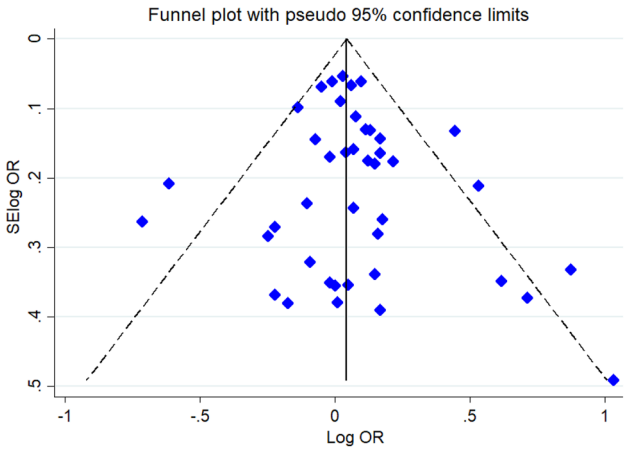

Fig. 5 Begg's funnel plot for publication bias test. Each point represents a separate study for the association between MDM2 gene *rs2279744* and risk of BC (dominant model)

rs2279744 and risk of BC. Additionally, Gao et al. [61] in 2014 performed a meta-analysis of association between MDM2 gene *rs2279744* SNP and risk of BC by including 19 studies, involving 7815 BC cases and 8677 controls. The overall analysis revealed that GT (OR = 1.10) and GG (OR = 1.09) genotypes were associated with increased risk of BC. Our meta-analysis, on the other hand, specifically considered the BC patients in the meta-analysis and included a large number of subjects in the analysis (39 studies containing 22,764 cases and 22,444 healthy controls), which is considered a remarkable improvement with respect to sample size, conferring robust statistical power and reliable results. Based on the analysis performed in the current meta-analysis, the dominant model (OR = 1.04), recessive model (OR = 1.13), allelic model (OR = 1.07), GG genotype (OR = 1.18) indicated a statistically significant increased risk of BC.

We conducted a subgroup analysis by categorizing the patients according to their ethnic backgrounds. The populations were stratified into three groups, including Caucasians, Asians, and mixed populations. The results indicated that the dominant model (OR = 1.13), allelic model (OR = 1.13), and GT genotype (OR = 1.17), of the MDM2 gene *rs2279744* SNP was associated with increased risk of BC in Asians. The previous meta-analysis by Zhang et al. [60], on the other hand, revealed that TT or *T* allele was associated with a lower risk of gynecological cancer in the dominant, heterozygote, and allele models in Caucasian. However, the GG genotype exhibited a significantly elevated susceptibility to gynecological cancer among individuals of Asian descent. Furthermore, their subgroup analysis, according to the type of cancer, did not indicate significant association of MDM2 gene *rs2279744* SNP with risk of BC. Furthermore, Gao et al. [61] meta-analysis indicated significant association of GT in Caucasians, GT in Africans, and allelic, GG genotype, GT genotype, and dominant models in Asians.

In our meta-analysis, meta-regression analyses were conducted to look for potential sources of heterogeneity, suggesting that none of the potential heterogeneity sources, including publication year, continent, and genotyping method were conferring heterogeneity to the results. Interestingly, the TSA analysis revealed that the present meta-analysis provided sufficient evidence to draw a conclusive understanding of the association between *rs2279744* polymorphism of the MDM2 gene and risk of BC.

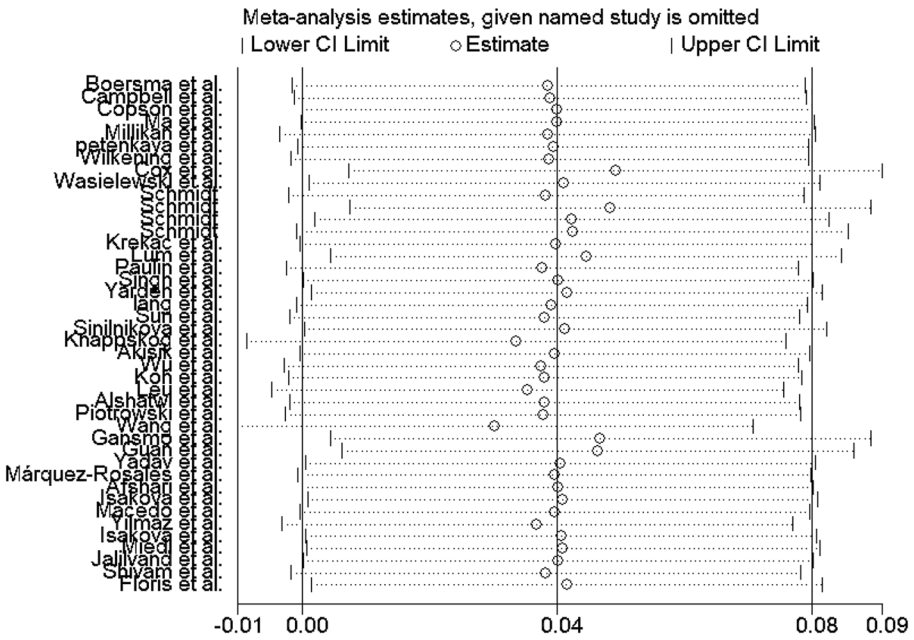

Fig. 6 Sensitivity analysis for the meta-analysis of MDM2 gene *rs2279744* in association with the risk of BC (dominant model)

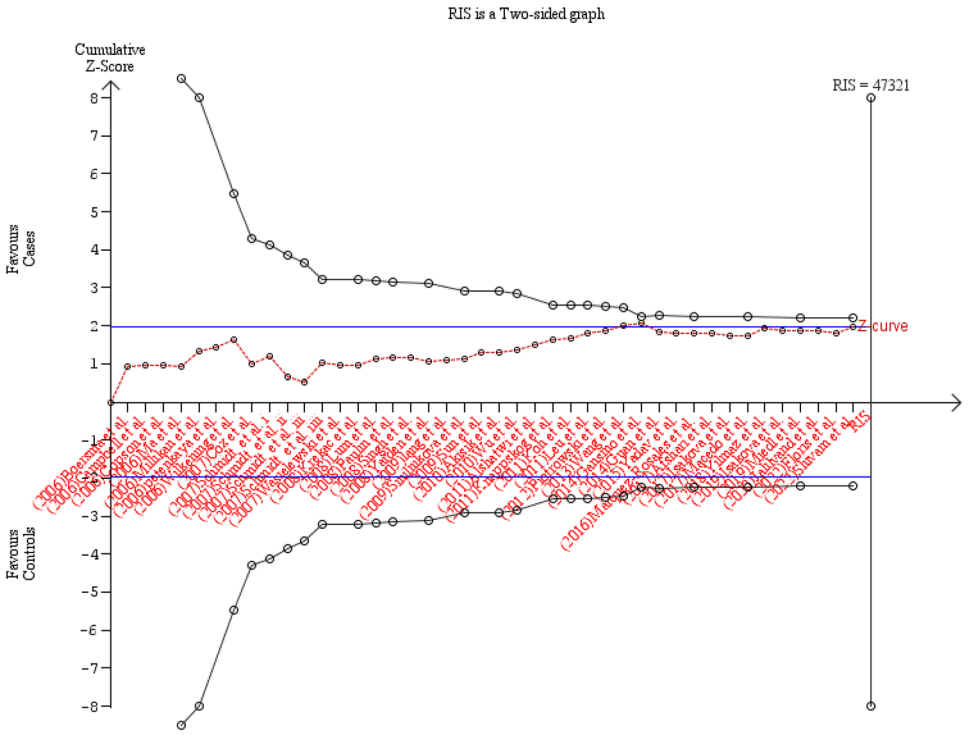

Fig. 7 TSA of the association between MDM2 gene *rs2279744* (dominant model) and risk of BC

This meta-analysis holds a number of caveats and limitations. Initially, the analysis was bases on the crude estimation of MDM2 gene *rs2279744* polymorphism association with risk of BC. This assessment did not take into account the influence of confounding factors or the involvement of other genes linked to the MDM2 gene. Second, potential bias raised through population stratification and false positive, which are very common in candidate approach studies, could be a source of heterogeneity that was unable to be abrogated in the analysis. Third, our analysis did not encompass an examination of additional genes that may play a role in elucidating the relationship between tumor suppressor genes/oncogenes in the susceptibility to BC.

Conclusion

Taking into account all the relevant information, this study represents the most recent and comprehensive systematic review and meta-analysis examining the correlation between the MDM2 gene *rs2279744* polymorphism and risk of BC. The analysis consisted of a comprehensive evaluation of 39 studies comprising a total of 22,764 BC cases and 22,444 healthy controls. Our analysis indicated increased risk of BC in the overall pooled analysis. Furthermore, this polymorphism was a genetic risk variation in the Asians. This study suggests that further studies should consider other genetic variations of the MDM2 gene in an interaction with *rs2279744* polymorphism as well as other tumor suppressor genes/oncogenes in BC patients.

Declarations

Conflict of interest The authors have no competing interests to disclose.

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