MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3231-3240
DOI: 10.12659/MSM.894637

Received: 2015.05.12
Accepted: 2015.06.24
Published: 2015.10.25

Association Between XRCC3 Thr241Met Polymorphism and Risk of Breast Cancer: Meta-Analysis of 23 Case-Control Studies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This work was supported by National Natural Science Foundation of China (Grant No. 30700814 and 30872517), China Scholarship Council (CSC) joint PhD Dissertation Research Program from Chinese Ministry of Education (No. 2010761014), and General Financial Grant from the China Postdoctoral Science Foundation (Grant No. 2014M552628)

Background: Studies have shown that gene and environmental factors, such as BRCA1/2 mutations, ionized radiation, and chemical carcinogens, are related with breast cancer. X-ray repair cross-complementing group 3 (XRCC3) is involved in homologous repair of double DNA breaks. It was reported that Thr241Met single-nucleotide polymorphism (SNP) in XRCC3 is associated with increased risk of breast cancer. However, the finding remains controversial. The current meta-analysis aims to determine whether XRCC3 Thr241Met polymorphism is associated with increased risk of breast cancer.

Material/Methods: We performed a meta-analysis of association between XRCC3 T241M polymorphism and the risk of breast cancer. Crude odds ratios (ORs) together with 95% confidence intervals (CIs) were used to assess the strength of association in dominant, recessive, and homozygote models.

Results: We included 23 studies consisting of 13513 cases and 14100 controls in our study. For meta-analysis on the entire database, association of the SNP and breast cancer risk was observed in recessive (OR=1.10, 95% CI: 1.03–1.18, p=0.005) and homozygote (OR=1.09, 95% CI: 1.01–1.18, p=0.023) models. For the analysis on the Asian population subgroup, association of the SNP and breast cancer risk was also observed in recessive (OR=1.615, 95% CI: 1.17–2.228, p=0.004) and homozygote (OR=1.609, 95% CI: 1.154-2.241, p=0.005) models. For the evaluation of the patients without family history of breast cancer, association of the SNP and breast cancer risk was observed in dominant (OR=1.364, 95% CI: 1.096–1.698, p=0.005), recessive (OR=1.336, 95% CI: 0.999–1.788, p=0.051) and homozygote (OR=1.492, 95% CI: 1.085–2.051, p=0.014) models.

Conclusions: We can conclude that XRCC3 Thr241Met polymorphism might be associated with breast cancer risk, especially in Asian populations and in patients without family history of breast cancer.

MeSH Keywords: Genes, Neoplasm • Polymorphism, Genetic • Polymorphism, Single Nucleotide

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894637

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Background

Breast cancer is the leading malignancy in women. Its incidence is relatively high in developed countries while it is low but increasing in developing countries. It is a disease caused by a combination of genetic and environmental factors. Although the exact mechanism of breast cancer carcinogenesis is still not fully understood, some well-established risk factors, such as early menarche, late menopause, age of first child's birth, nulliparity, and family history, have been previously described [1]. In addition, exposure to environmental factors, such as ionizing radiation and chemical carcinogens, have also been related to increased risks of breast cancer [2]. Studies have shown that DNA double-strand breaks induced by ionizing radiation are associated with statistically significantly increased risk for breast cancer [3]. Mammalian cells have evolved distinct pathways to repair different types of DNA damage in order to maintain genome stability. Some studies have demonstrated a strong association of higher levels of DNA damage and lower DNA repair capacity in breast cancer patients [4]. X-ray repair cross-complementing group 3 (XRCC3) protein is involved in single-strand DNA break rejoining and double-strand DNA break rejoining [5]. As a member of the Rad-51-related protein family, it interacts directly with RAD51 protein. RAD51 protein family has an important role in homologous recombination repair of DNA double-strand break repair. XRCC3 helps the assembly of the nucleofilament protein and its selection and interaction with appropriate recombination substrates [6]. To date, 3 different polymorphisms of XRCC3 have been found in the population: XRCC3 T241M (XRCC3-18067C>T, rs861539), A4541G (5'-UTR, rs1799794), and A17893G (IVS6-14, rs1799796) [7]. It has been reported that XRCC3 Thr241Met polymorphism, located on exon 7, affected the enzyme function and/or its interaction with other proteins involved in DNA damage and repair. More importantly, many studies indicated that XRCC3 T241M polymorphism might be associated with increased risks of a number of human cancers, such as glioma, bladder, and breast cancer [8]. For breast cancer, although a number of studies suggested that it might be related to increased risks of carcinogenesis, the results remain controversial. In this study, meta-analysis on a single-nucleotide polymorphism (SNP) Thr241Met in the XRCC3 gene (XRCC3 Thr241Met) was conducted. We pooled 23 studies involving 13 513 cases and 14 100 controls in the meta-analysis to evaluate the association of XRCC3 Thr241Met polymorphism with the risk of breast cancer. Subgroup analyses based on different ethnic populations were also conducted.

Material and Methods

Data collection

Multiple databases under the NCBI global database and Google Scholar were searched for relevant studies; 23 case-control studies focusing on XRCC3 T241M polymorphism and breast cancer risk were covered in this meta-analysis. For the first-round search, articles were searched with NCBI Global Cross-database, including PubMed, PMC, Gene, PubChem, and Google Scholar, using "XRCC3 polymorphism", "XRCC3 Thr241Met polymorphism", and "breast cancer" as key words; 271 results were retrieved. Books and other literature which were not case-control studies were excluded, along with literature published before Jan 1st, 2000, which yielded a total of 65 articles. For the second-round selection, articles which were not aimed at investigating association between XRCC3 Thr241Met polymorphism and breast cancer risk were excluded, which resulted in 20 articles, including 1 meta-analysis article published in 2010. Subsequently, articles without control group information or in which the original data could not be retrieved were excluded. For overlapping studies, we kept the ones that showed the most extensive results. Ultimately, 23 case-control studies were included in the final meta-analysis.

Statistical methods

Due to the relatively larger database of studies performed in white (13 studies), Asian (3 studies), and American (3 studies) populations, we created 3 subgroups which covered all studies of these 3 specific populations. After collecting necessary information from the studies, we divided these breast cancer patients into another 2 subgroups: patients with family history and without family history. In order to get a more reasonable result, 3 different comparison models were applied: dominant model (TM+MM *vs.* TT), recessive model (MM *vs.* TM+TT), and homozygote comparison (MM *vs.* TT). In the dominant model, we investigated the distribution of TM+MM genotype referred to TT genotype. In the recessive model, we investigated the distribution of MM genotype referred to TM+TT genotype. In the homozygote model, we used TT as reference genotype, and investigated the distribution of MM genotype. For each study, numbers of the 3 genotypes in case and control group were used as pooled data. In the analysis, the heterogeneity between studies was tested using I^2 index, and the equation is $I^2 = \frac{Q-df}{Q} \times 100\%$, where Q is statistical data and df is its freedom. The higher I^2 is, the more significant the heterogeneity is. Values of I^2=25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively. When $I^2 \leq 50\%$, there is no significant heterogeneity between pooled data. In this meta-analysis, 6 studies were included in the final analysis for XRCC3 T241M polymorphism. For each analysis, we first used the M-H fixed-effects model to test the heterogeneity and then chose different models based on the testing results. Crude odds ratios

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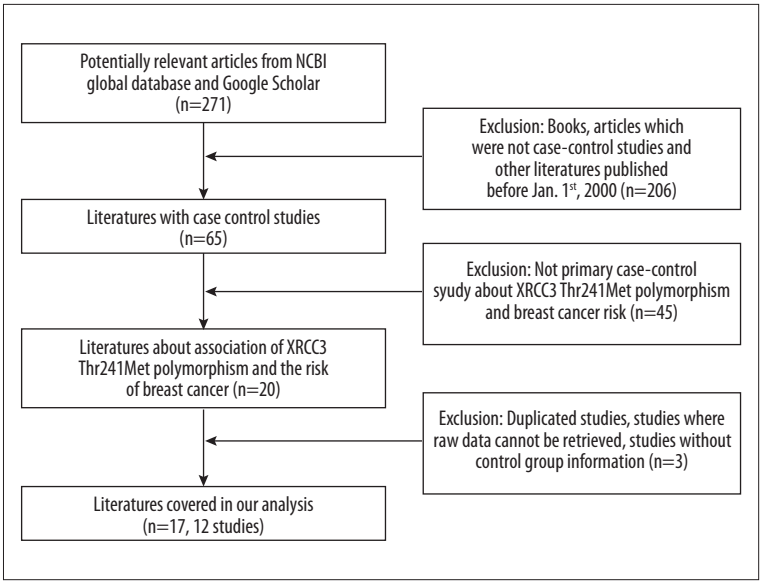

Figure 1. Study flow chart explaining the selection of the 23 eligible case-control studies.

(Ors) were calculated with each model within 95% confidence intervals (CIs). The available polymorphism data were analyzed with STATA 12 software. Forest plots were generated to summarize the results. To evaluate publication bias, Begg's funnel plots were generated based on the analysis results and database size. Egger's test was also performed for further investigation.

Results

Literature search and meta-analysis databases

Figure 1 demonstrates the data collection flow chart for the current study. According to our search criteria, 271 items were identified. In the 271 items, we first excluded books and articles which were not case-control studies and/or were published before Jan 1st, 2000, and ended up with 65 articles. We then further selected against articles which did not aim at investigating association between XRCC3 T241M polymorphisms and breast cancer risks, leading to exclusion of another 45 articles. Finally, by excluding articles with duplicated studies, studies where raw data cannot be retrieved, and studies without control groups, 17 articles with 23 studies including 13 513 cases and 14 100 controls were used for the meta-analysis [7,9–28]. All studies selected for our meta-analysis aimed at evaluating the association between XRCC3 T241M polymorphism and human breast cancer risk. The characteristics of all studies are presented in Tables 1, and 2 shows the pooled information for the patients with or without family history of breast cancer.

Meta-analysis results

First of all, we performed the analysis for the entire database. The M-H fixed-effects model was applied on the subgroup dataset as well as the entire database with 3 different analysis models (dominant, recessive, and homozygote) to assess the heterogeneity. Based on the results, we selected different methods (M-H fixed-effects model or D-L random-effects model [29]) for different analyses. By definition, with I^2<25%, the fixed-effects model should be applied, whereas with I^2>75%, the random-effects model should be used due to significant heterogeneity. For medium heterogeneity, it is reasonable to use either fixed- or random-effects models. However, for databases smaller than 10 studies, it is more reasonable to apply the fixed-effects model in the analysis. ORs were derived based on the analysis, and corresponding p value was acquired as well. Final results for the entire database are presented in Table 3. Corresponding forest plots for each model are shown in Figure 2. For recessive and homozygote models, the fixed-effects model was applied based on their medium heterogeneity. A significant increase of risk of breast cancer was observed in both models, with the overall OR as 1.10 [95% CI, 1.03–1.18, p=0.005] and 1.09 [95% CI, 1.01–1.18, p=0.023], respectively. For the dominant model, the overall OR was 1.01 [95% CI, 0.06–1.06, p=0.765]. No significant heterogeneity was observed (I^2=24%). However, there was no evidence of a strong association between the polymorphism and the risk of breast cancer. In the subgroup analysis, as shown in Table 4, significantly increased risks were detected in recessive and homozygote models within Asian populations. We could not find a significant association between XRCC3 T241M and the risk of breast cancer in white and American populations. A shift pattern was observed with all 3 models within these 2 subgroups. For the white subgroup, overall OR for the dominant model was 0.97 [95% CI, 0.91–1.04, p=0.364] and heterogeneity index I^2 was 29%. For the recessive model, the overall OR was 1.07 [95% CI, 0.98–1.17, p=0.117] and heterogeneity index I^2 was 54.8%. For homozygote comparison, the overall OR was 1.04

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Table 1. All studies used for XRCC3 Thr241Met polymorphism meta-analysis.

Study	Year	Case				Control				HWE
		TT	TM	MM	Total	TT	TM	MM	Total	
Caucasian										
Smith a	2003	96	105	51	252	104	129	35	268	Yes
Smith b	2003	62	74	26	162	112	141	49	302	Yes
Figueiredo	2004	139	186	77	402	146	200	56	402	Yes
Han	2004	388	429	135	952	468	607	170	1245	Yes
Millikan a	2005	505	578	171	1254	435	555	142	1132	NA
Garcia-Closas a	2006	785	907	282	1974	980	1039	266	2285	NA
Thyagarajan	2006	160	192	67	419	126	157	40	323	No
Costa	2007	40	29	12	81	225	140	66	431	No
Smith c	2008	124	137	54	315	158	184	59	401	No
Krupa	2009	29	68	38	135	29	107	39	175	NA
Romanowicz	2011	190	348	162	700	158	354	196	708	No
Romanowicz	2012	210	370	180	760	178	366	216	760	Yes
Smolarz	2014	19	35	16	70	15	35	20	70	No
American										
Dufloth a	2005	88	57	29	174	68	35	15	118	NA
Garcia-Closas b	2006	1102	1419	457	2978	973	1213	368	2554	Yes
Dufloth b	2008	14	12	8	34	29	23	6	58	Yes
Jara	2009	149	91	27	267	296	182	22	500	No
Santos	2010	28	31	6	65	49	29	7	85	Yes
Millikan b	2005	482	222	41	745	421	211	44	676	No
Smith d	2008	32	19	1	52	48	20	5	73	No
Asian										
Zhang	2005	107	80	33	220	166	115	29	310	No
Lee	2006	437	51	1	489	349	29	0	378	Yes
Sangrajrang	2007	507	437	69	1013	424	384	38	846	No

Table 2. Pooled data for the patients with or without family history of breast cancer.

Study	Year	Case				Control			
		TT	TM	MM	Total	TT	TM	MM	Total
With FH									
Costa	2007	40	29	12	81	225	140	66	431
Dufloth b	2008	27	18	7	52	68	35	15	118
Fjgueiredo	2004	29	38	16	83	13	20	4	37
Smith b	2003	10	14	3	27	42	55	4	101
Without FH									
Costa	2007	68	77	31	176	121	61	29	211
Dufloth b	2008	15	16	2	33	68	35	15	118
Fjgueiredo	2004	110	148	61	319	133	180	52	365
Smith b	2003	30	40	17	87	39	55	15	109

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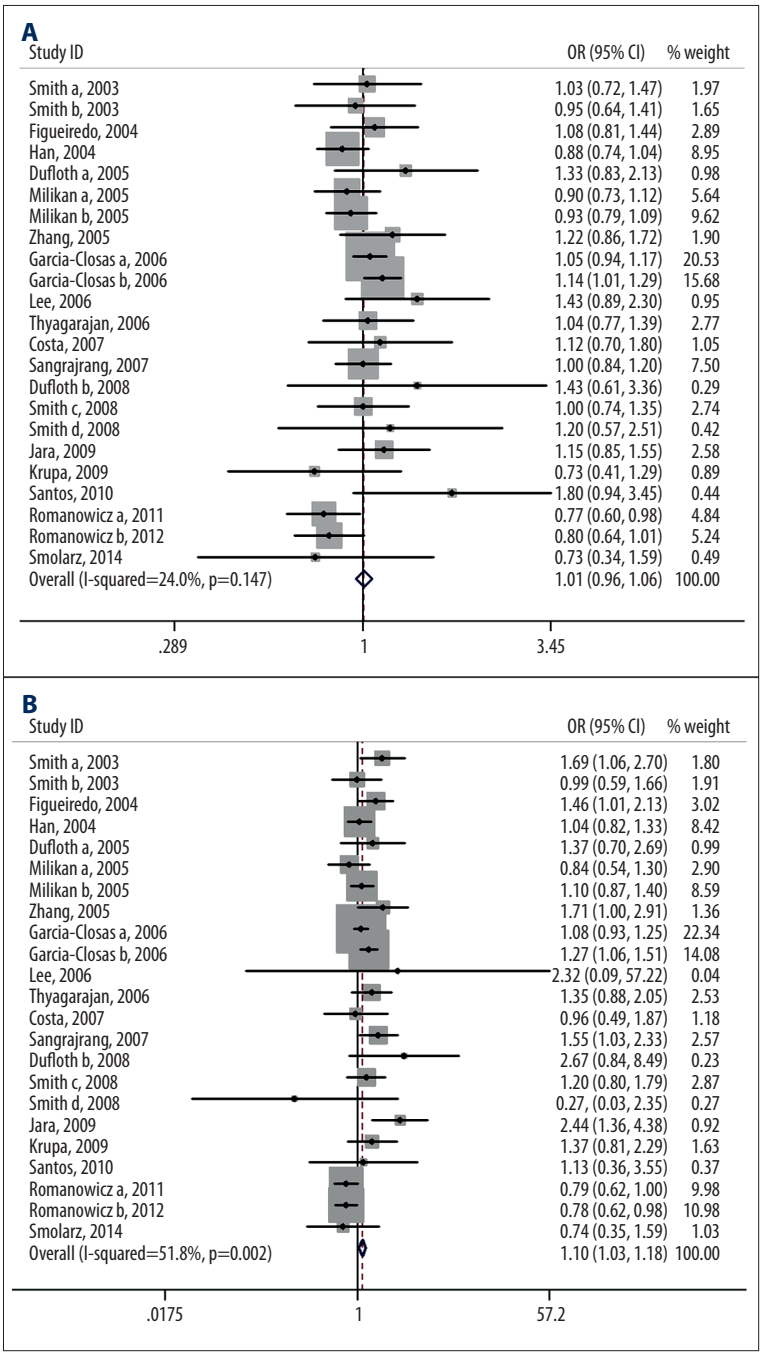
Table 3. Meta-analysis of entire database with dominant (TM+MM *vs.* TT), Recessive (MM *vs.* TM+TT) and homozygote (MM *vs.* TT) models.

Analysis model	Analysis method	Heterogeneity		OR				Publication bias	
		I^2 (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
Dominant	Fixed	24.0	0.147	1.008	0.959	1.059	0.765	0.224	0.633
Recessive	Fixed	51.8	0.002	1.104	1.030	1.184	0.005	0.673	0.233
Homozygote	Fixed	54.5	0.001	1.093	1.012	1.181	0.023	0.792	0.459



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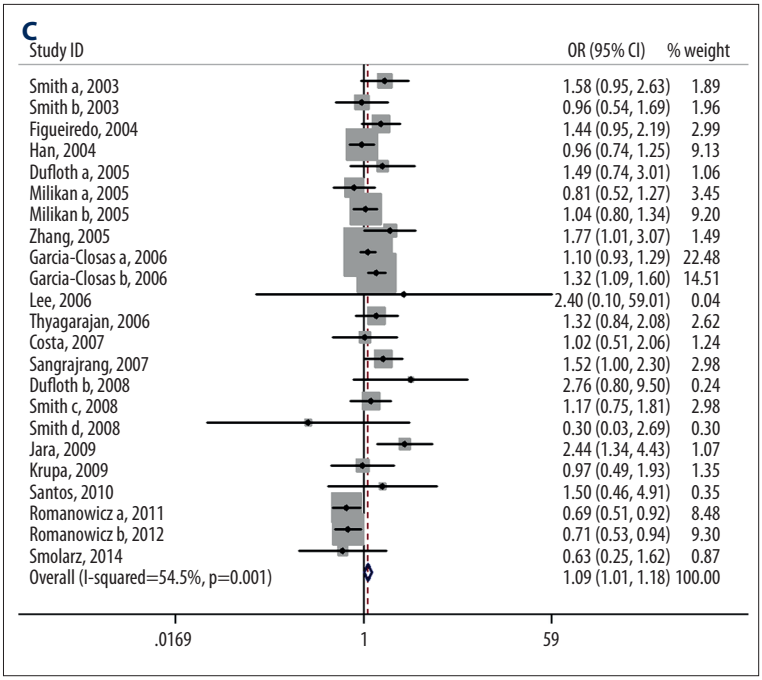

Figure 2. Forest plots for entire database. (**A**) Dominant model: TM+MM *vs.* TT. (**B**) Recessive model: MM *vs.* TM+TT. (**C**) Homozygote model: MM *vs.* TT.

Table 4. Meta-analysis of Caucasian, American, and Asian subgroup with dominant (TM+MM *vs.* TT), recessive (MM *vs.* TM+TT) and homozygote (MM *vs.* TT) models.

Analysis model	Analysis method	Heterogeneity		OR				Publication bias	
		I^2 (%)	p-value	Overall	Lower	Upper	p-value	Begg	Egger
Caucasian									
Dominant	Fixed	29.1	0.152	0.970	0.908	1.036	0.364	0.760	0.272
Recessive	Fixed	54.8	0.009	1.071	0.983	1.166	0.117	0.669	0.604
Homozygote	Fixed	58.1	0.004	1.039	0.945	1.143	0.429	0.583	0.853
American									
Dominant	Fixed	0.0	0.499	1.065	0.959	1.184	0.239		
Recessive	Fixed	27.0	0.254	1.105	0.945	1.276	0.176		
Homozygote	Fixed	27.4	0.252	1.131	0.967	1.322	0.124		
Asian									
Dominant	Fixed	18.3	0.294	1.082	0.929	1.260	0.314		
Recessive	Fixed	0.0	0.937	1.615	1.170	2.228	0.004		
Homozygote	Fixed	0.0	0.886	1.609	1.154	2.241	0.005		

[95% CI, 0.95–1.14, p=0.429] and heterogeneity index I^2 was 58.1%. For the American subgroup, with the dominant model the overall OR was 1.07 [95% CI, 0.96–1.18, p=0.239]. For the recessive model, the overall OR was 1.11 [95% CI, 0.95–1.28, p=0.176]. For the homozygote model, the overall OR was 1.13 [95% CI, 0.97–1.32, p=0.124]. Similar to the white subgroup, no association between XRCC3 Thr241Met and increased risk of breast cancer was found within the American population. With the Asian subgroup, the forest plots of all 3 models are shown in Figure 3. Overall OR was 1.08 [95% CI, 0.93–1.26, p=0.314] with the dominant model. For the recessive model, the overall OR was 1.62 [95% CI, 1.17–2.23, p=0.004]. For the homozygote model, the overall OR was 1.61 [95% CI, 1.15–2.24, p=0.005]. An association between the SNP and breast cancer risk was observed among Asian populations with the recessive model and homozygote comparison.

Similar analysis was performed on subgroups with or without family history of breast cancer. For patients with family history, there was no significant difference between case and control

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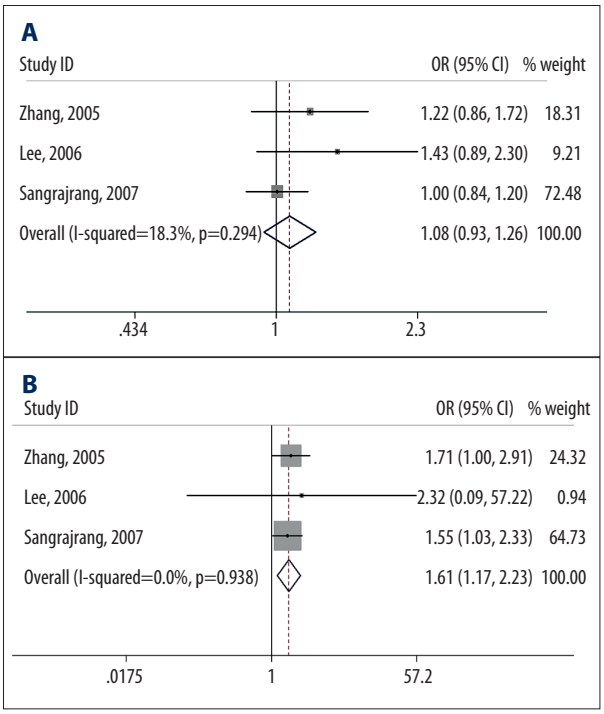
Table 5. Meta-analysis for the breast cancer patients with family history.

Analysis model	Analysis method	Heterogeneity		OR			
		I^2 (%)	p-value	Overall	Lower	Upper	p-value
Dominant	Fixed	0	0.978	1.145	0.829	1.581	0.410
Recessive	Fixed	0	0.474	1.228	0.775	1.948	0.382
Homozygote	Fixed	0	0.607	1.272	0.778	2.079	0.338

Table 6. Meta-analysis for the breast cancer patients without family history.

Analysis model	Analysis method	Heterogeneity		OR			
		I^2 (%)	p-value	Overall	Lower	Upper	p-value
Dominant	Fixed	60.1	0.057	1.364	1.096	1.698	0.005
Recessive	Fixed	0	0.53	1.336	0.999	1.788	0.051
Homozygote	Fixed	0	0.579	1.492	1.085	2.051	0.014



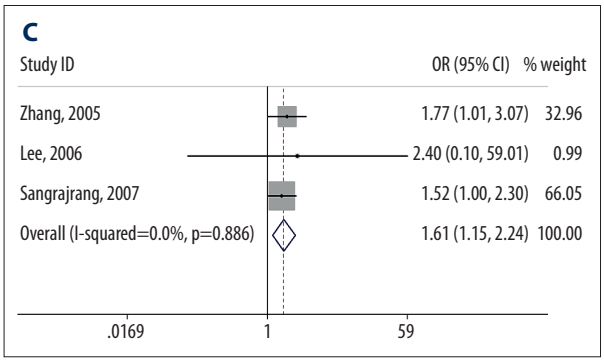


Figure 3. Forest plots for Asian subgroup. (**A**) Dominant model: TM+MM *vs.* TT. (**B**) Recessive model: MM *vs.* TM+TT. (**C**) Homozygote model: MM *vs.* TT.

groups (Table 5). However, among patients without family history, a higher risk was detected within the case group using the dominant model and homozygote comparison (p value smaller than 0.05) (Table 6 and Figure 4). Even though a slightly shifted pattern was observed with the recessive model, we can still hypothesize that there might be a higher risk for the patients without a breast cancer family history, but who carry a MM genotype on XRCC3 T241M.

Publication bias

To test the publication bias for the entire database, both Begg's funnel plot and Egger's test were performed. For all 3 models, the shapes of the funnel plots did not show any evidence of obvious asymmetry, suggesting no significant publication bias was present in the database (Figure 5). As shown in Table 3, for the dominant model, the funnel plot p value was 0.224 and Egger's test p value was 0.633. For the recessive model, the funnel plot p value was 0.673 and Egger's test p value was 0.233. For the homozygote model, the funnel plot p value was 0.792 and Egger's test p value was 0.459. In addition, we also performed funnel plot (data not shown) and Egger's test to assess the publication bias in the white subgroup study. As shown in Table 4, no significant bias was detected in all 3 comparison models. Due to the small database of American and Asian subgroups, no publication bias test was

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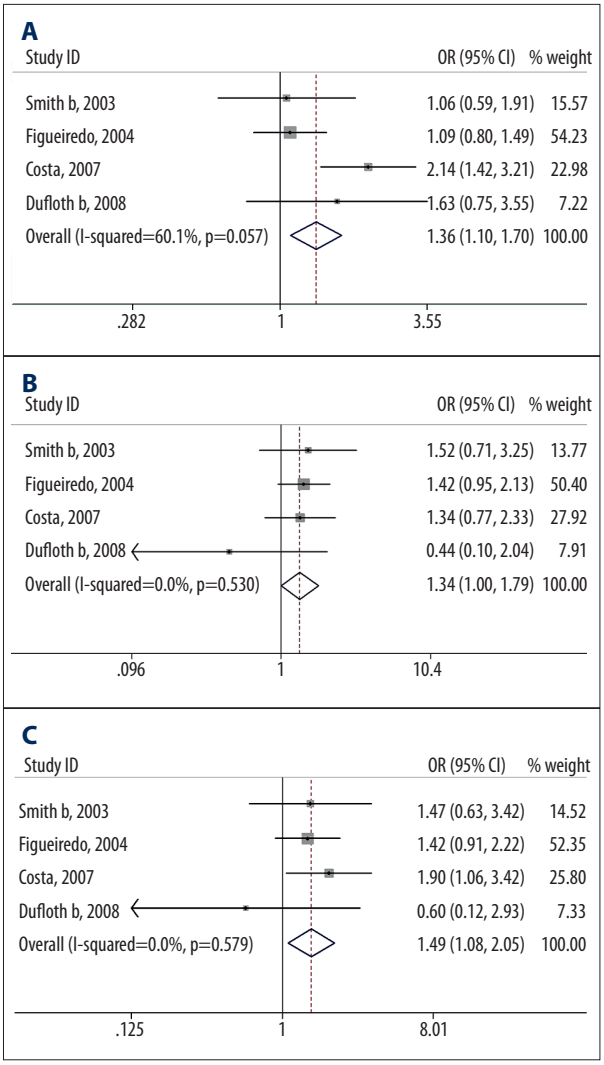

Figure 4. Forest plots for patients without family history of breast cancer. (**A**) Dominant model: TM+MM *vs.* TT. (**B**) Recessive model: MM *vs.* TM+TT. (**C**) Homozygote model: MM *vs.* TT.

performed for these 2 subgroups. Publication bias might exist due to the size of the database.

Discussion

For this study, we performed a meta-analysis of association between XRCC3 T241M polymorphism and the risk of breast cancer; 23 studies consisting of 13 513 cases and 14 100 controls were included in our study. Results of meta-analysis on the entire database in both homozygote and recessive models showed that there was an association between T241M polymorphism and breast cancer risk, but no significant association was found in the dominant model. In terms of subgroups with different ethnic populations, the association was

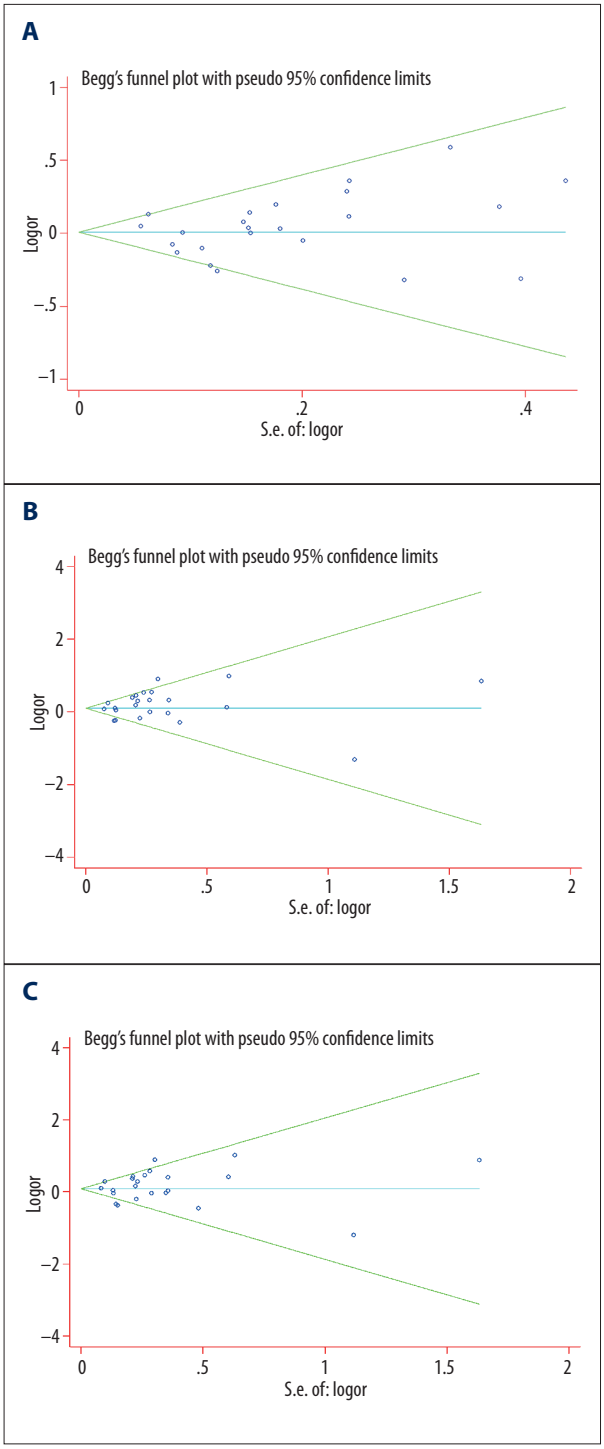

Figure 5. Funnel plots for entire database. (**A**) Dominant model: TM+MM *vs.* TT. (**B**) Recessive model: MM *vs.* TM+TT. (**C**) homozygote model: MM *vs.* TT.

also detected in both homozygote and recessive model within Asian populations. For white and American subgroups, no significant association between the SNP and the risk of breast cancer was observed in all 3 models applied. For the patients'

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family history of breast cancer, the patients who did not have a family history of breast cancer but who carried a MM genotype on XRCC3 T241M were susceptible to breast cancer.

To date, the exact mechanisms of tumorigenesis of breast cancer has not been fully elucidated. However, research has uncovered a spectrum of well-established risk factors relating to breast cancer, such as age, inherited genetic mutations, family history, and exposure to ionizing radiation [30]. About 5% of breast cancer cases are present with rare but highly penetrant genes, such as *BRCA1* and *BRCA2*. However, low-penetrant cancer susceptibility genes, like the ones in drug metabolism and DNA repair, might account for more than 90% of breast cancer cases because they are more common than the high-penetrant genes [31]. Research on the possible association of breast cancer risk and 4 amino acid substitution variants in 3 DNA repair genes which were involved in base excision repair, homologous recombination repair and nucleotide excision repair suggested that genetic variants found in multiple DNA repair pathways might have a joint or addictive effect on the increased risks of breast cancer [32]. As a member of an emerging RAD-5 protein-related family, XRCC3 plays an important role in homologous recombination repair of double DNA strand breaks, which can be induced by exposure to ionizing ration [33]. Three different types of polymorphisms of *XRCC3* in population have been identified, and results from some studies suggested that the SNP XRCC3 T241M might be associated with the increased risks of breast cancer. However, other studies failed to reach the same conclusion. As a result, whether there is an association between T241M polymorphism of *XRCC3* gene and breast cancer risk remains controversial. In 2002, the first study suggesting possible association of T241M polymorphism and the increased risks of breast cancer was published. To evaluate risks of breast cancer in association with 15 polymorphisms in 7 genes, Dunning et al. conducted a case-control study. They reported that in comparison to homozygote AA-carriers, *XRCC3* IVS5 17893 G-allele had a dominant protective effect in both heterozygote and homozygote G-carriers against breast cancer, whereas T241M polymorphism-induced amino acid change was associated with increased risk of breast cancer [34]. Based on experimental evidence, the possible association of T241M and increased risks of breast cancer is biologically plausible. T241M polymorphism changes neutral threonine, which has a hydrophilic hydroxyl group to hydrophobic methionine with a methyl sulfur group [34]. Studies have shown that amino acid substitution variants in DNA repair genes might contribute to hereditary hypersensitivity to ionizing radiation and breast cancer susceptibility [31]. In addition, there was also evidence that XRCC3 T241M variants were significantly associated with higher DNA adducts level [35]. In 2007, Lee et al. reported that although no significant association between XRCC3 T241M polymorphism and breast cancer in Korean women was identified, results of their meta-analysis on 10 white studies and 2 Asian studies showed a positive relationship between the SNP and risk of breast cancer in both white and Asian populations, and Asian populations showed a slightly stronger trend as compared to whites [32]. In another meta-analysis study, the T allele was found to be associated with increased breast cancer risk, mainly following a recessive model, and the effect was more pronounced in homozygous carriers. However, the association was only limited to non-Chinese populations [7]. Therefore, it seems that these 2 results are inconsistent since the Chinese population is one of the major Asian populations. In order to form a clearer conclusion about Asian patients, we collected more updated studies related to Asians, such as the study on a Thai population reported by Sangrajrang et al., for our meta-analysis. In comparison to their findings, we detected a positive association between T241M SNP in the entire database and Asian population; however, we did not detect the association in whites. Therefore, during the diagnosis of breast cancer, we should pay more attention to Asian population with T241M SNP. Besides the Asian population, more diagnosis work also should be given to those patients having no family history of breast cancer while carrying with T241M SNP since the high risk trend for them to have breast cancer was clearly shown in our three model analyses.

It's of note that our study may be improved. First of all, although our subgroup analysis on Asian population showed there was increased risk of breast cancer in recessive and homozygote model, our results were based on three studies. Similarly, only a few studies were used for American subgroup. Consequently, the lack of power due to the small number of studies leaves it an open field for Asian and American population. Subsequent analysis involving more studies on these two populations is needed to further confirm our findings. Second, due to the lack of original information of the entire data, we did not evaluate interactions of gene and environmental factors in all pooled studies. As a result, further assessment of potential interactions, which might be the important elements of the association of the polymorphism and breast cancer risk, was not conducted. Last, due to limited information of cases and controls, we did not have enough information of individual cases and controls, such as age, alcohol consumption, smoking history, previous exposure to radiation, *BRCA-1/2* mutation status and menopausal status, etc. Thus, our results were produced on unadjusted published findings.

Conclusions

We performed a meta-analysis to investigate the association between XRCC3 T241M polymorphism and the risk of human breast cancer. By studying the entire pooled data, except for the dominant model, a significant association was found between

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XRCC3 T241M polymorphism and the increased risk of breast cancer in both the recessive model and homozygote model. In subgroup analysis, we did not observe any association among white and American populations. In the Asian subgroup, we observed results which were similar to the ones derived from the entire database, indicating an association between XRCC3 T241M and the risk of human breast cancer. We also observed that there was a higher risk for the patients without family history of breast cancer to have breast cancer if they carried the MM genotype on XRCC3 T241M. Instead of evaluating multiple SNPs with small databases, we performed a comprehensive study using more databases to acquire a thorough evaluation. According to our results, there might be an association between XRCC3 T241M and the increased risk of human breast cancer. In the future, studies with larger sample sizes are required to further assess the role of XRCC3 T241M polymorphism in risk of breast cancer for Asian and American populations.

Conflict of interest statement

No conflict of interest is declared.

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