RESEARCH ARTICLE

Association between the XRCC3 Thr241Met Polymorphism and Breast Cancer Risk: an Updated Meta-analysis of 36 Case-control Studies

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Abstract

Background: The X-ray repair cross-complementing group 3 (XRCC3) is a highly suspected candidate gene for cancer susceptibility. Attention has been drawn upon associations of the XRCC3 Thr241Met polymorphism with breast cancer risk. However, the previous published findings remain controversial. Hence, we performed a meta-analysis to accurately evaluate any association between breast cancer and XRCC3 T241M (23, 812 cases and 25, 349 controls) in different inheritance models. Materials and Methods: PubMed and Web of Science databases were searched systematically until December 31, 2013 to obtain all the records evaluating the association between the XRCC3 Thr241Met polymorphism and breast cancer risk. Crude odds ratios (ORs) together with 95% confidence intervals (CIs) were used to assess the strength of associations. Results: When all eligible studies were pooled into the meta analysis of XRCC3 T241M polymorphism, a significantly increased breast cancer risk was observed in heterozygote comparison (OR=1.06, 95%CI=1.01-1.12). No significant associations were found in other models. In subgroup analysis, this polymorphism seemed to be associated with elevated breast risk in Asians. No publication bias was detected. Conclusions: This meta-analysis suggests that the T241M polymorphism confers a weakly increased breast cancer risk. A study with the larger sample size is needed to further evaluate gene-gene and gene-environment interactions of the XRCC3 T241M polymorphism with breast cancer risk.

Keywords: XRCC3 - Thr241Met - polymorphism - breast cancer - DNA repair

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Introduction

Breast cancer is one of the most common cancers among females worldwide so far and is the leading cause of cancer-related mortality for almost 14% of all cancer deaths (Jemal et al., 2011). It is a heterogeneous disease caused by interactions of environmental and genetic factors. Gage et al. (2012)have confirmed a strong genetic component underlying the etiology of breast cancer. However, to determine which genetic determinants are actually involved in the pathogenesis of breast cancer and the mechanism remain an interpretive challenge.

Growing evidence suggests that DNA damage, caused by UV, ionizing radiation, and environmental chemical agents, can initiate human cancer. DNA Double-strand breaks (DSB) can be produced by exogenous agents such as ionizing radiation. It has been demonstrated that accumulation of unrepaired DSBs can induce cell death and initiate malignancies (Lengauer et al., 1998). Double-strand break repair (DSBR) is the most common form of radiation-induced DNA damage (Ward, 1988) and DNA can be repaired by two pathways-homologous recombination repair (HRR) and non-homologous end-joining (Goode et al., 2002). The XRCC3 (X-ray repair cross-complementing group 3) protein is one of protein components involved in the homologous recombination repair (HRR) pathway, responsible for DNA repair. Studies have found the polymorphisms of XRCC3 gene in the population: XRCC3 Thr241Met (C>T, rs861539), 5'-UTR A>G (rs1799794), IVS5-14 A>G (rs1799796) (Breast Cancer Association, 2006).

Growing studies have been conducted to explore the role of XRCC3 Thr241Met on different cancer. Qing-Hua Yin et al. found the polymorphism could act as a head and neck cancer risk factor (Yin et al., 2012). Ling-Yan Qin et al. showed that the XRCC3 Thr241Met polymorphism might not act as a cervical cancer risk factor. However, in subgroup analysis, a significant association was found in Asians under all genetic models (Qin et al., 2013). The association should be studied with a larger, stratified population.

Attention has been also drawn upon the association of Thr241Met with breast cancer risk at a meta-analytical level (Han et al., 2006; Lee et al., 2007; Economopoulos and Sergentanis, 2010; He et al., 2012; He et al., 2013); the most recent meta-analysis on the field has reported

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that XRCC3 T241M polymorphism is associated with increased cancer risk when all studies were pooled together. But the results remain controversial rather than conclusive. Given the essential role of XRCC3gene in tumorigenesis, we conducted a meta-analysis to evaluate the impact of the XRCC3 Thr241Met polymorphism on susceptibility of breast cancer.

Materials and Methods

Identification and eligibility of relevant studies

We performed a comprehensive search of PubMed, Wiley Online Library and Web of Science for relevant articles published with the following keywords : "x-ray repair cross-complementing group 3", "XRCC3", "polymorphisms" or "single nucleotide polymorphism" and "breast neoplasm" or "breast cancer" (last search: December 31, 2013). We also identified additional studies by hand searching references in review articles and original articles. The search was limited to human studies. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications.

Inclusion criteria

The following criteria were adopted for the included studies: (a) evaluation of the XRCC3 T241M polymorphism and breast cancer risk, (b) independent case-control studies, and (c) provision of sufficient genotype frequencies for both patients and control populations.

Data extraction

For each eligible publication, the following information was selected independently by two investigators (Mao CF and Qian WY): first author's name, year of publication, source of controls, country, ethnicity, genotype frequencies for cases and controls and the Hardy-Weinberg equilibrium (HWE) among the controls. The descents of different ethnicity were categorized as Asian, African, and Caucasian. When a study did not declare which ethnic groups were included, or if it was impossible to separate participants according to the phenotype, the study was termed as ''mixed population''. Disagreement was settled by the discussion of two investigators.

Statistical analysis

Crude odds ratios (ORs) together with 95% confidence intervals (CIs) were used to evaluate the strength of association between the XRCC3 polymorphism and breast cancer risk. The pooled ORs were performed for homozygote comparison (MM *vs* TT), heterozygote comparison (MM *vs* TM), dominant model (TM+MM *vs* TT), recessive model (TT+TM *vs* MM), respectively. The Z-test was used to determine the significance of the pooled ORs, and p-value<0.05 was considered as statistically significant. Subgroup analyses were done by racial descent and source of controls. Between-study heterogeneity was checked by the chi-square-based Q-test (Heterogeneity was considered statistically significant if p<0.05) (Egger et al., 1997). The fixed-effects model (the Mantel-Haenszel method) was used when there was no heterogeneity among studies (Mantel and Haenszel, 1959);otherwise, the random-effects model (the DerSimonian-Laird method) was applied (DerSimonian and Laird, 1986). Selective bias among the control group was evaluated by the HWE using the chi-square test, and a p-value <0.05 was considered as significant. Moreover, sensitivity analysis was performed.Begg's funnel plots and Egger's linear regression test were used to assess publication bias (Egger et al., 1997). All analyses were performed using STATA version 11.0 (STATA Corporation, College Station, TX).

Results

Literature search and meta-analysis databases

Figure 1 illustrated graphically the study flow chart. A total of 26 articles involving 36 eligible studies with 23, 812 cases and 25, 349 controls were included in the pooled analyses (Jacobsen et al., 2003; Smith et al., 2003a; 2003b; Figueiredo et al., 2004; Forsti et al., 2004; Han et al., 2004; Dufloth et al., 2005; Millikan et al., 2005; Webb et al., 2005; Zhang et al., 2005; Thyagarajan et al., 2006; Breast Cancer Association, 2006; Garcia-Closas et al., 2006; Costa et al., 2007; Sangrajrang et al., 2007; Lee et al., 2007; Loizidou et al., 2008; Smith et al., 2008; Brooks et al., 2008; Krupa et al., 2009; Jara et al., 2010; Santos et al., 2010; Silva et al., 2010; Sterpone et al., 2010; Romanowicz-Makowska et al., 2011; Romanowicz-Makowska et al., 2012). Out of the 100 abstracts retrieved through the search criteria, fifty-four were irrelevant, nine articles were excluded because they were conducted on other XRCC3 polymorphisms. Four studies (Bewick et al., 2006; Popanda et al., 2006; Dufloth et al., 2008; Falvo et al., 2011)was excluded given that it has not included controls , seven articles were reviews or meta-analyses. As a result, 26 case-control articles involving 36 studies were included in this meta-analysis. Main characteristics of the included publications investigating the association of XRCC3 T241M polymorphism and breast cancer risk were presented in Table 1.

Meta-analysis results

As shown in Table.2, significantly increased breast cancer risk was observed in heterozygote comparison (OR=1.06, 95%CI=1.01-1.12) when all studies were pooled in the meta-analysis. However, no significant associations were found for MM *vs* TT (OR=1.06, 95%CI=0.97-1.16, $P_{heterogeneity}$=0.003), TT/TM *vs* MM (OR=0.93, 95%CI=0.87-1.01, $P_{heterogeneity}$=0.008), TM/MM *vs* TT (OR=1.02, 95%CI=0.96-1.07, $P_{heterogeneity}$=0.017). Interestingly enough, in the subgroup analysis by ethnicity, significantly increased risks were found among Asians (TM/MM *vs* TT: OR=1.34, 95%CI=1.09-1.64, $P_{heterogeneity}$=0.819) and Mixed ethnicities (MM *vs* TM: OR=1.18, 95%CI=1.02-1.35, $P_{heterogeneity}$=0.215; TT/TM *vs* MM: OR=0.87, 95%CI=0.76-0.99, $P_{heterogeneity}$=0.137). When stratified by source of controls, We also found that there was a statistically significant link between the XRCC3 T241M polymorphism and breast cancer risk in population-based studies (MM *vs* TT: OR=1.10, 95%CI=1.03-1.18, $P_{heterogeneity}$=0.246; MM *vs* TM: OR=1.10, 95%CI= 1.03-1.18, $P_{heterogeneity}$=0.520; TT/TM

Table 1. General Characteristics of Studies Included in the Meta-Analysis

First author	Year	SOC	Country	Ethnicity	Case			Control			HWE
					TT	TM	MM	TT	TM	MM	
Smith TR	2003	HB	USA	Caucasian	96	105	51	104	129	35	0.611
Jacobsen	2003	PB	Denmark	Caucasian	163	203	59	160	198	65	0.772
Smith TR	2003	PB	USA	Caucasian	62	74	26	112	141	49	0.680
Han	2004	PB	USA	Mixed	388	429	135	468	607	170	0.225
Figueiredo	2004	PB	Canada	Caucasian	139	186	77	146	200	56	0.341
Forsti	2004	PB	Finland	Caucasian	111	80	32	161	110	27	0.198
Forsti	2004	PB	Poland	Caucasian	72	85	15	89	88	25	0.654
Dufloth	2005	HB	Brazil	Mixed	88	57	29	68	35	15	0.005
Millikan	2005	PB	USA	Caucasian	505	578	171	435	555	142	0.086
Millikan	2005	PB	USA	African	482	222	41	421	211	44	0.015
Zhang	2005	HB	China	Asian	107	80	33	166	115	29	0.170
Webb	2005	PB	Australia	Mixed	91	44	14	59	54	15	0.625
Webb	2005	PB	Australia	Caucasian	500	612	184	248	321	91	0.425
Thyagarajan	2006	HB	USA	Caucasian	160	192	67	126	157	40	0.405
BCAC HBBCS	2006	HB	Germany	Caucasian	95	119	42	77	88	29	0.640
BCAC Madrid	2006	HB	Spain	Caucasian	255	274	92	281	287	105	0.028
BCAC SEARCH	2006	PB	UK	Caucasian	1177	1462	465	1607	1898	549	0.760
BCAC Seoul	2006	HB	Korea	Asian	502	53	1	355	31	0	0.411
BCAC Sheffield	2006	HB	UK	Caucasian	458	555	168	437	534	195	0.144
BCAC USRTS	2006	PB	USA	Caucasian	281	336	98	402	480	155	0.550
Garcia-Closas	2006	PB	USA	Caucasian	1102	1419	457	973	1213	368	0.748
Garcia-Closas	2006	PB	Poland	Caucasian	785	907	282	980	1039	266	0.709
Costa	2007	HB	Portugal	Caucasian	108	106	43	346	201	95	0.000
Sangrajrang	2007	HB	Thai	Asian	437	69	1	384	38	2	0.322
Lee	2007	HB	Korean	Asian	437	51	1	349	29	0	0.438
Loizidou	2008	PB	Cyprus	Mixed	312	560	220	351	600	226	0.285
Smith TR	2008	HB	USA	Caucasian	124	137	54	158	184	59	0.649
Smith TR	2008	HB	USA	African	32	19	1	48	20	5	0.169
Brooks	2008	PB	USA	Mixed	254	259	98	249	286	76	0.661
Krupa	2009	HB	Poland	Caucasian	29	68	38	29	107	39	0.003
Silva	2010	HB	Portugal	Caucasian	109	138	42	178	276	94	0.460
Santos	2010	HB	Brazil	Mixed	28	31	6	49	29	7	0.370
Jara	2010	HB	Chilean	Mixed	149	91	27	296	182	22	0.366
Sterpone	2010	HB	Italy	Caucasian	18	21	4	14	14	3	0.853
Romanowicz-Makowska	2011	HB	Poland	Caucasian	190	348	162	158	354	196	0.939
Romanowicz-Makowska	2012	HB	Poland	Caucasian	210	370	180	178	366	216	0.343

SOC: source of controls; PB:Population-based; HB:Hospital-based; HWE:Hardy-Weinberg equilibrium

Table 2. Meta-Analysis of the XRCC3 Thr241Met Polymorphism on Breast Cancer

Variables	N of studies	MM *vs* TT OR (95% CI)	p[b]	MM *vs* TM OR (95% CI)	p[b]	TT/TM *vs* MM (recessive) OR (95% CI)	p[b]	TM/MM *vs* TT (dominant) OR (95% CI)	p[b]
Total	36	1.06 (0.97-1.16)c	0.003	1.06 (1.01-1.12)*	0.052	0.93 (0.87-1.01)[c]	0.008	1.02 (0.96-1.07)c	0.017
Ethnicity									
Asian	4	1.66 (0.99-2.80)	0.731	1.49 (0.87-2.54)	0.579	0.62 (0.38-1.02)	0.720	1.34 (1.09-1.64)*	0.819
African	2	0.77 (0.50-1.19)	0.381	0.82 (0.52-1.28)	0.217	1.27 (0.83-1.95)	0.312	0.92 (0.75-1.13)	0.465
Caucasian	23	1.03 (0.94-1.14)[c]	0.004	1.04 (0.98-1.11)	0.065	0.96 (0.88-1.05)[c]	0.010	1.02 (0.98-1.07)	0.088
Mixed	7	1.13 (0.98-1.30)	0.073	1.18 (1.02-1.35)*	0.215	0.87 (0.76-0.99)*	0.137	1.00 (0.85-1.19)[c]	0.028
Study design									
PB	16	1.10 (1.03-1.18)*	0.246	1.10 (1.03-1.18)*	0.520	0.91 (0.86-0.97)*	0.340	1.02 (0.98-1.07)	0.223
HB	20	1.08 (0.90-1.29)[c]	0.002	1.06 (0.91-1.24)[c]	0.028	0.92 (0.79-1.07)[c]	0.006	1.06 (0.96-1.18)[c]	0.010

*indicate that the results are statistically significant. [a]Number of comparisons [b]P-value of Q-test for heterogeneity test [c]Random-effects model was used when P-value for heterogeneity test <0.05; otherwise, fix-effects model was used

vs MM: OR=0.91, 95%CI=0.86-0.97, $P_{heterogeneity}$=0.340).

Sensitive analysis

Selective bias among the control group was evaluated by the HWE using the chi-square test. Significant deviation from HWE was detected in the five studies[24]. After the exclusion of these studies, the result of XRCC3 T241M was practically unchanged in the overall analysis, given that the pooled ORs were as follows:1.06 (0.96-1.17) for homozygote comparison, 1.08 (1.00-1.17) for hetero -zygote comparison, 0.93 (0.86-1.02) for the recessive model and 1.02 (0.98-1.06) for the dominant model. Additionally, a single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered,

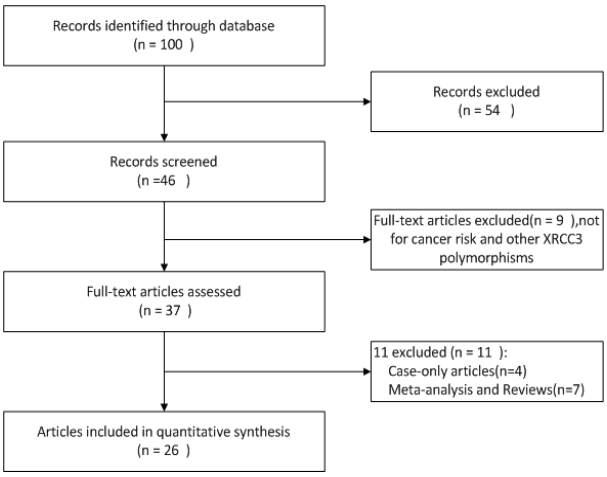

Figure 1. Study Flow Chart Explaining the Selection of the 26 Eligible Articles

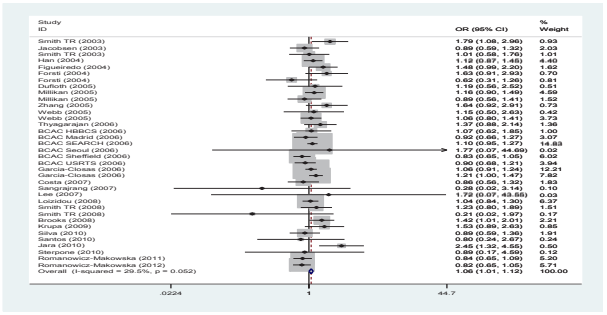

Figure 2. Forest plot of XRCC3 T241M Polymorphism And Breast Cancer when All the Eligible Studies were Pooled Into the Meta-Analysis (heterozygote comparison:MM *vs* TM)

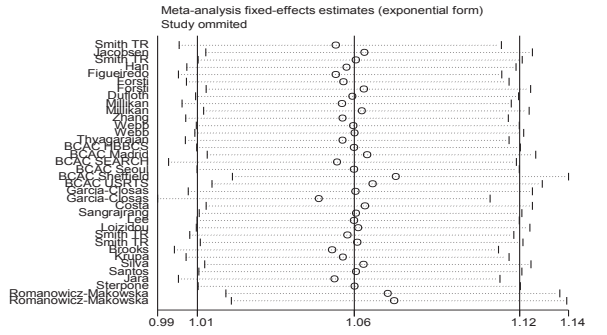

Figure 3. Sensitivity Analysis on the Association T241M Polymorphism and Breast between the XRCC3 Cancer (Heterozygote Comparison: MM *vs* TM). No statistically different results were obtained by excluding every single study in sequence

indicating that our results were stable and credible (Figure 3).

Publication bias

Both Begg's funnel plot and Egger's test were used to assess the publication bias of literatures. No significant publication bias was observed (p=0.054 for homozygote comparison, p=0.724 for heterozygote comparison, p=0.724 for the dominant model, p=0.621 for the recessive model). Figure 4 lists the funnel plot in heterozygote comparison.

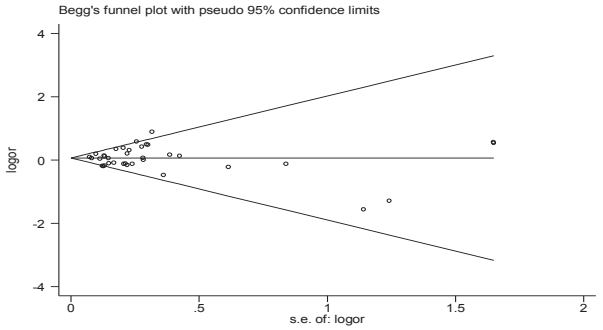

Figure 4. Funnel Plot of Heterozygote Comparison (MM *vs* TM). Funnel plot of all 36 eligible studies (p=0.595, Egger's test p=0.724)

Discussion

Many epidemiological studies have reported the role of XRCC3 T241M (rs861539) with breast cancer risk, but the results remained controversial. Some original studies thought that the polymorphism was associated with elevated breast cancer risk, but others had different opinions. In order to resolve this conflict, we performed the updated meta-analysis of 36 eligible studies involving 23,812 cases and 25,349 controls to derive a more precise estimation of the association between XRCC3 T241M polymorphism and breast cancer risk.

When all eligible studies were pooled into the meta analysis of XRCC3 T241M polymorphism, significantly increased breast cancer risk was observed in heterozygote comparison (OR=1.06, 95%CI=1.01-1.12) (Figure 2). No significant associations were found in other models (homozygote comparison:OR=1.06, 95%CI=0.97-1.16; recessive model:OR=0.93, 95%CI=0.87-1.01; dominant model: OR=1.02, 95%CI=0.96-1.07). However, there was significant heterogeneity between studies. Hence, we further performed subgroup analysis by ethnicity and source of controls. In the stratified analysis of ethnicity, we found significantly increased risks among Asians (TM/MM *vs* TT: OR=1.34, 95%CI=1.09-1.64) and Mixed ethnicities (MM *vs* TM: OR=1.18, 95%CI=1.02-1.35; TT/TM *vs* MM: OR=0.87, 95%CI=0.76-0.99). More importantly, the results of our meta-analysis are in accordance with those reported by Lee et al. (Lee et al., 2007) concerning Asian women. Lee et al. found the TM/MM was more strongly associated with breast cancer compared to TT in Asian women. However, the results of Economopoulos et al. (Economopoulos and Sergentanis, 2010)were inconsistent. Economopoulos et al. found the XRCC3 Thr241Met M allele may be associated with elevated breast cancer risk in non-Chinese subjects. It should be considered that the apparent inconsistency may underlie differences in lifestyle and disease prevalence as well as possible limitations due to the small number of studies.At any case, the association between T241M and breast cancer risk in Asian subject essentially remains an open field, as the number of studies (n=4) is smaller than that needed for the achievement of robust conclusions (Higgins and Green, 2008).

We also examined the association of the XRCC3 T241M polymorphism and breast cancer risk according to source of controls (Table 2). For the population-based

studies, the XRCC3 T241M polymorphism was associated with breast cancer, given that the pooled ORs were as follows: 1.10 (1.03-1.18) for homozygote comparison, 1.10 (1.03-1.18) for heterozygote comparison, 0.91 (0.86-0.97) for the recessive model.

For the hospital-based studies, no significant risks were found (Table 2). However, significantly between-studies heterogeneity was observed in the hospital-based controls for breast cancer. The reason may be that such controls in these hospital-based studies may contain certain benign diseases which are prone to develop malignancy and may not be very representative of the general population.

In addition, some limitations of this study should be considered in our meta-analysis. First, the case subjects were simply defined as breast cancer patients, including both familial and triple-negative breast cancer patients in some of the studies. Second, lack of available information impeded a more precise evaluation with the adjustment by age, status, smoking , alcohol consumption, and menopausal status, etc .Third, it was difficult to get all articles published in various language. We only the studies published in English and Chinese were involved. Finally, this meta-analysis was based on unadjusted OR estimates. Therefore, further and larger studies regarding the association among the XRCC3 T241M polymorphism, XRCC3 T241M levels and the factors mentioned above will be urgently needed.

In conclusion, this meta-analysis supports that T241M polymorphism show a weakly increased breast cancer risk. A study with the larger sample size is needed to further evaluated gene-gene and gene-environment interactions on XRCC3 T241M polymorphism and breast cancer risk.

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