

XRCC3 Thr241Met polymorphism and breast cancer risk: a meta-analysis

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Abstract XRCC3 (X-ray repair complementing defective repair in Chinese hamster cells 3) is a member of the RecA/Rad51-related protein family that participates in homologous recombination, maintaining chromosome stability and participating in DNA repair. Attention has been drawn upon the association of XRCC3 Thr241Met polymorphism with breast cancer risk. The present meta-analysis aims to examine whether XRCC3 Thr241Met polymorphism status is associated with breast cancer risk. Apart from the overall meta-analysis, separate analyses were performed on Chinese and non-Chinese populations, in order to investigate race-specific effects. Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to August 2009. Twenty case-control studies on non-Chinese subjects (19,575 cases and 21,125 controls) and three case-control studies on Chinese subjects (1,216 cases and 1,112 controls) were eligible. Pooled odds ratios (OR) were appropriately derived from fixed-effects or random-effects models. At the overall analysis, the T allele was associated with elevated breast cancer risk mainly following a recessive model (pooled OR = 1.064, 95% CI: 1.007–1.124, fixed effects), given that the effect was more pronounced in homozygous carriers (pooled OR = 1.073, 95% CI: 1.010–1.140, fixed effects). The association seemed confined in non-Chinese populations, once again following a recessive model (pooled OR = 1.072, 95% CI: 1.014–

1.133, fixed effects). Concerning Chinese populations, no consistent results were demonstrated. In conclusion, the XRCC3 Thr241Met T allele seems associated with elevated breast cancer risk in non-Chinese subjects. The need for additional studies on Chinese populations seems warranted.

Keywords XRCC3 · Thr241 Met · Polymorphism · Breast cancer · DNA repair

Introduction

XRCC3 (X-ray repair complementing defective repair in Chinese hamster cells 3) is a member of the RecA/Rad51-related protein family that participates in homologous recombination, maintaining chromosome stability and participating in DNA repair [1]. XRCC3 gene has been found polymorphic in the population; three polymorphisms have been identified: XRCC3 Thr241Met (C to T, rs861539), 5'-UTR A > G (rs1799794), IVS5-14 A > G (rs1799796) [2].

Attention has been mainly drawn at a meta-analytical level upon the association of Thr241Met with breast cancer risk [2–5]; the most recent meta-analysis on the field has reported that the Met allele is associated with elevated breast cancer risk both in Asian and Caucasian populations [3]. Interestingly enough, however, close inspection of the published meta-analyses on Thr241Met reveals the need for a comprehensive approach, as the sizeable studies analyzed by the Breast Cancer Association Consortium [2] have not been included in the most recent meta-analysis by Lee et al. [3].

Under the light of the above, the present meta-analysis aims to examine whether XRCC3 Thr241Met polymorphism status is associated with breast cancer risk. Separate

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analyses were performed on Chinese and non-Chinese populations, in an attempt to investigate race-specific effects.

Methods

Trial identification

Eligible articles were identified by a search of MEDLINE bibliographical database for the period up to August 2009 (last search: August 31, 2009) using combinations of the following keywords: “XRCC3”, “Thr241Met”, “T241M”, “polymorphism”, “rs861539”, “breast cancer”, “breast”. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used and two investigators (KPE and TNS), working independently, searched the literature and extracted data from each eligible case–control study.

Eligible studies and data abstraction

All case–control studies with any sample size examining the association between breast cancer and XRCC3 Thr241Met were considered eligible for this meta-analysis. For each one of the eligible case–control studies, the following data were collected: journal name, year of publication, inclusion and exclusion criteria, demographic characteristics of the population being studied, frequencies of genotypes in cases and controls.

Statistics

Based on the genotype frequencies in cases and controls, crude odds ratios (OR) as well as their standard errors (SE) were calculated. Four different ORs were calculated: (i) CT versus CC (heterozygous carriers), (ii) TT versus CC (homozygous carriers), (iii) T allele carriers (CT and TT grouped together) versus CC (dominant model) and (iv) TT genotype versus (CT and CC grouped together) (recessive model). Separate analyses were performed in Chinese and non-Chinese populations. In case of zero cells, an appropriate continuity correction (addition of 0.5) was implemented.

The fixed-effects model (Mantel–Haenszel method), as well as the random effects (DerSimonian Laird) model were used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2 , respectively [6]. In case no significant heterogeneity was detected, the fixed effects model was chosen. Evidence of publication bias was determined using Egger’s formal

statistical test [7] and by visual inspection of the funnel plot. For the interpretation of Egger’s test, statistical significance was defined as $P < 0.1$. Meta-analysis was performed using the STATA “metan” command.

In addition, meta-regression was performed to assess whether odds ratio (OR) was associated with publication year. The exponentiated coefficient is provided, since the dependent variable in the meta-regression model is $\log(\text{OR})$. Meta-regression was performed with the “meta-reg” STATA command. Analyses were conducted using STATA 10.0 (STATA Corp. College Station, TX, USA).

Results

Figure 1 graphically illustrates the trial flow chart. Out of the 55 abstracts retrieved through the search criteria, 25 were irrelevant, four articles [8–11] were excluded because they were conducted on overlapping populations with other eligible studies [2, 3, 5, 12] (these excluded articles represent smaller studies performed on subsets of larger eligible studies), one study [13] was excluded given that it has not included controls in its study design, three articles [4, 14, 15] were reviews/meta-analyses, and three studies [16–18] were excluded due to other reasons (two of them [16, 17] were excluded due to reporting reasons, i.e. no

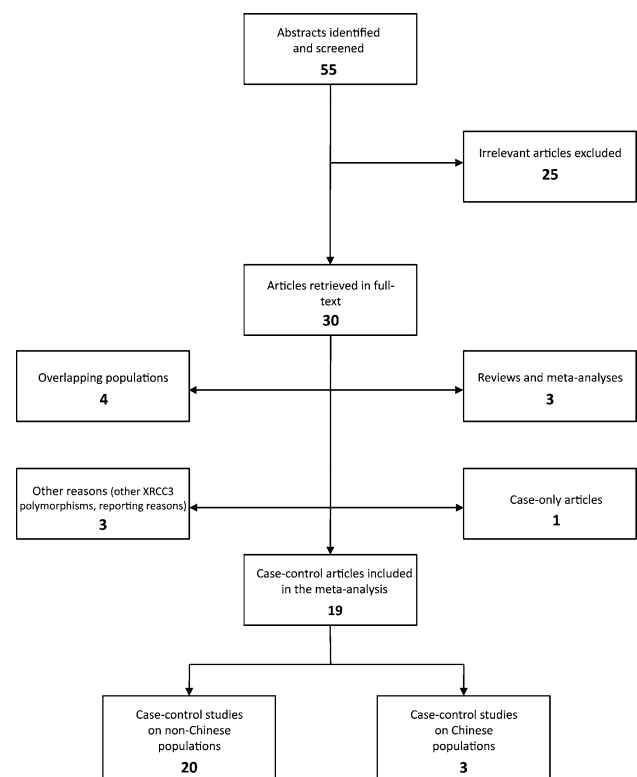


Fig. 1 Study flow chart explaining the selection of the 23 eligible case-control studies

reporting of the relevant genotype frequencies, whereas the other [18] was excluded for examining the association between other XRCC3 polymorphisms and premenopausal breast cancer risk). As a result, 19 case–control articles [2, 3, 5, 12, 19–33] (23 case–control studies, considering that Breast Cancer Association Consortium has more than one studies included) were included in this meta-analysis; 20 case–control studies on non-Chinese subjects (19,575 cases and 21,125 controls) and three case–control studies [3, 24, 29] on Chinese subjects (1,216 cases and 1,112 controls).

Table 1 presents in detail the results of the meta-analysis. At the overall analysis, the T allele was associated with elevated breast cancer risk mainly following a recessive model (pooled OR = 1.064, 95% CI: 1.007–1.124, fixed effects), given that the effect was more pronounced in homozygous carriers (pooled OR = 1.073, 95% CI: 1.010–1.140, fixed effects).

Interestingly enough, stratification by race pointed to discrepancy between non-Chinese and Chinese studies. The association seemed confined in non-Chinese populations, once again following a recessive model (pooled OR = 1.072, 95% CI: 1.014–1.133, fixed effects, Fig. 2). Concerning Chinese populations, no consistent results were found, as the dominant model (pooled OR = 1.102, 95% CI: 0.693–1.949, random effects) and the recessive model (pooled OR = 0.815, 95% CI: 0.580–1.147, fixed effects, Fig. 3) pointed to opposite directions. Interestingly enough, a reverse association, pointing to protective effects of the T allele in homozygous carriers emerged (pooled OR = 0.574, 95% CI: 0.336–0.979, fixed effects); nevertheless, this result should be interpreted with caution given the small number of studies on Chinese populations ($n = 3$).

Meta-regression with publication year did not point to any major modifying effects of publication year (for heterozygous carriers: exponentiated coefficient = 1.037, 95% CI: 0.987–1.089, $P = 0.138$; for homozygous carriers: exponentiated coefficient = 1.048, 95% CI: 0.986–

1.114, $P = 0.127$; for the recessive model: exponentiated coefficient = 1.041, 95% CI: 0.988–1.096, $P = 0.128$), apart from a trend of borderline significance in the dominant model (exponentiated coefficient = 1.041, 95% CI: 0.995–1.089, $P = 0.080$).

No significant publication bias was detected ($P = 0.957$ for heterozygous carriers, $P = 0.116$ for homozygous carriers, $P = 0.690$ for the dominant model, $P = 0.334$ for the recessive model).

Discussion

The principal message of this meta-analysis is that the T allele of the XRCC3 Thr241Met polymorphism is associated with elevated breast cancer risk in non-Chinese populations; the results are principally compatible with a recessive model. Although controversy exists at a functional level, with studies supporting [34] or not [35] the functioning properties of the Thr241Met polymorphism, this meta-analysis points to significant effects in terms of breast cancer risk.

Having analyzed an almost twofold larger number of studies than the previous meta-analysis [3], our results seem to confirm and establish the positive trend in non-Chinese populations that the data by Lee et al. had indicated. Specifically, under the light of the larger number of studies in the present, formal statistical significance has been reached in the subanalysis of non-Chinese studies; in the most recent meta-analysis [3] solely a trend of borderline significance had emerged. In other words, the accumulation of data has led to adequate power.

More importantly, however, the results of the present meta-analysis are not in accordance with those reported by Lee et al. [3] concerning Chinese populations. Although the latter stated that the (positive association) “trend was shown little stronger in Asian than in Caucasian”, the

Table 1 Pooled ORs by race for heterozygous, homozygous carriers, dominant and recessive model

Race	Heterozygous (CT vs. CC)		Homozygous (TT vs. CC)		Dominant model (TT and CT vs. CC)		Recessive model (TT vs. CC and CT)	
	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity	OR (95% CI)	Test for heterogeneity
Overall ($n = 23$)	1.010 (0.949–1.074)	$P = 0.047$	1.073^F (1.010–1.140)	$P = 0.200$	1.020 (0.962–1.081)	$P = 0.045$	1.064^F (1.007–1.124)	$P = 0.304$
Non-Chinese ($n = 20$)	1.010 ^F (0.968–1.054)	$P = 0.165$	1.082^F (1.018–1.150)	$P = 0.308$	1.026 ^F (0.985–1.069)	$P = 0.170$	1.072^F (1.014–1.133)	$P = 0.284$
Chinese ($n = 3$)	1.143 (0.664–1.968)	$P = 0.024$	0.574^F (0.336–0.979)	$P = 0.819$	1.102 (0.623–1.949)	$P = 0.012$	0.815 ^F (0.580–1.147)	$P = 0.803$

All pooled ORs were derived from random-effects models except for cells marked with F (fixed-effects model)

Bold letters denote statistically significant results

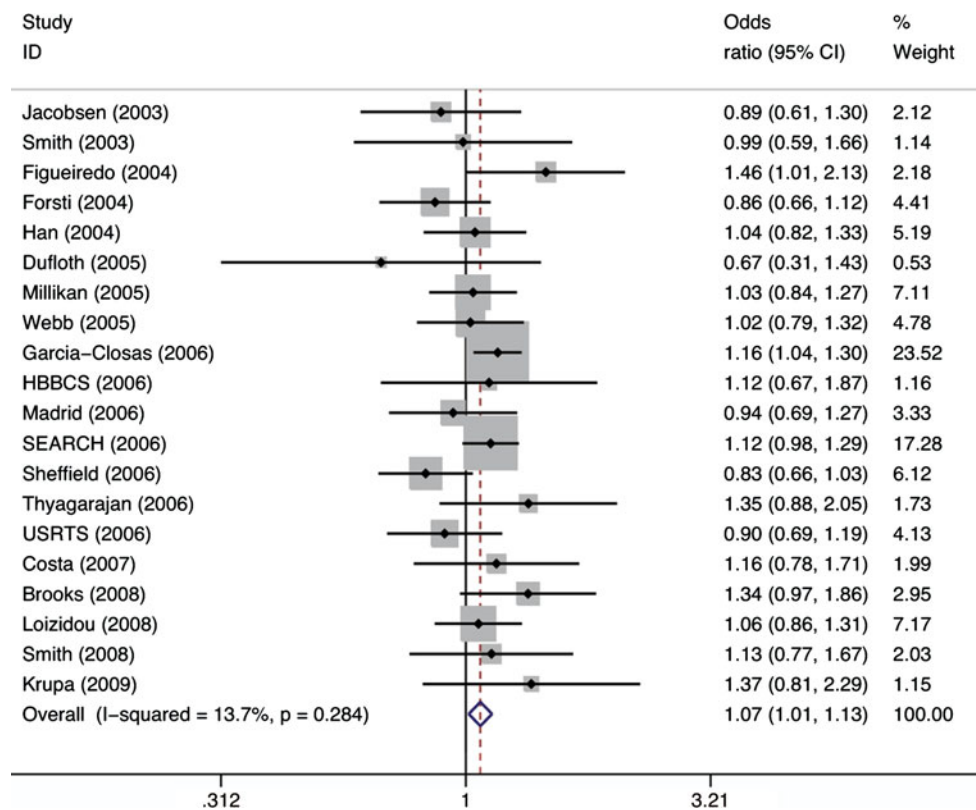


Fig. 2 Forest plot for the overall association between XRCC3 Thr241Met polymorphism and breast cancer risk for non-Chinese subjects following a recessive model. Each study is shown by the point estimate of the Odds Ratio (OR) (the size of the square is

proportional to the weight of each study) and 95% confidence interval for the OR (extending lines); the pooled OR and 95% confidence interval have been appropriately derived from fixed effects model

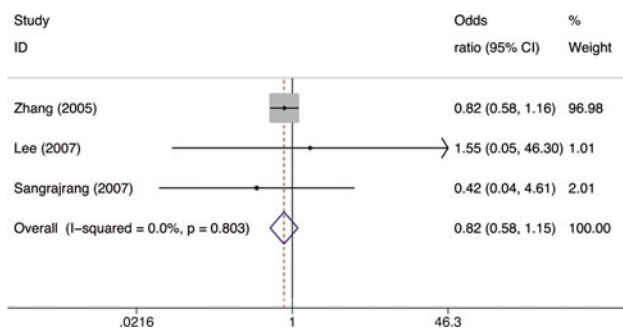


Fig. 3 Forest plot for the overall association between the XRCC3 Thr241Met polymorphism and breast cancer risk for Chinese subjects (fixed effects) following a recessive model

present meta-analysis does not confirm this observation. According to our data, the results in Chinese populations were inconsistent, with dominant and recessive models pointing to opposite directions; worthy of note, a reverse association in homozygous carriers reached significance. At any case, the association between Thr241Met and breast cancer risk essentially remains an open field in Chinese populations, as the number of studies ($n = 3$) is considerably smaller than that needed for the achievement of robust conclusions [36].

In conclusion, the XRCC3 Thr241Met T allele seems associated with elevated breast cancer risk in non-Chinese subjects. The need for additional studies on Chinese populations seems warranted, as the results remain inconclusive.

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