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RESEARCH ARTICLE

XRCC3 T241M polymorphism is associated risk of hepatocellular carcinoma in the Chinese

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Abstract The X-ray repair cross-complementing group 3 (*XRCC3*) gene has been suggested to play an important role in the pathogenesis of hepatocellular carcinoma (HCC). However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the association of *XRCC3* Thr241Met variant with HCC. The published literature from PubMed, Chinese National Knowledge Infrastructure, and Wan Fang data was retrieved. Pooled odds ratio (OR) with 95 % confidence interval (CI) was calculated using fixed or random effects model. A total of five studies (1,531 HCC cancer cases and 1,952 controls) for *XRCC3* Thr241Met variant were included in the meta-analysis. The meta-analysis showed that *XRCC3* Thr241Met variant was associated with HCC risk under homogeneous codominant model (OR=3.99, 95 % CI=1.74–9.13) and recessive model (OR=5.22, 95 % CI=3.65–7.48), but not under heterogeneous codominant model (OR=1.18, 95 % CI=0.68–2.05) and dominant model (OR=1.37, 95 % CI=0.73–2.57). Subgroup analysis by ethnicity suggested that *XRCC3* Thr241Met variant was associated with HCC risk in Chinese population, but not in Pakistani population. The present meta-analysis supported the positive association of *XRCC3* Thr241Met variant with HCC in the Chinese. Further large-scale studies with the consideration for gene–gene/gene–environment interactions should be conducted to investigate the association.

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Introduction

Hepatocellular carcinoma (HCC), accounting for 85–90 % of all primary liver cancer, ranks as the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. High incidence of HCC is found especially in Eastern Southeastern Asia and sub-Saharan African; low rate is estimated in developed regions except for Southern Europe [2]. HCC is a complex disease influenced by genetic and environmental factors. Epidemiological studies have shown that the main risk factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), exposure to dietary aflatoxin B1 (AFB1), and alcohol consumption. Moreover, genetic factors also play important roles in the pathogenesis of this disease.

As is known, the environmental risk factors can cause HCC in relationship with unrepaired DNA-damaged pathways. The DNA repair pathways protect against carcinogenesis by repairing DNA damage caused either by endo- or exogenous carcinogens. DNA repair systems are designed to protect the integrity of the genome, and any deficiency in this system likely leads to the development of cancers [3]. Polymorphisms in DNA repair genes that can substitute an amino acid can alter the function of DNA repair enzymes and may decrease the ability of the host to repair DNA damage, thus making it susceptible to cancer [4]. The X-ray repair cross-complementing group 3 (*XRCC3*) gene codes for an enzyme functioning in the homologous recombination repair of DNA cross-links and double-strand breaks. The main SNP in the *XRCC3* gene leads to an amino acid substitution at codon 241 (exon 8, C → T, Thr → Met)

[5]. To date, several studies have investigated the association between *XRCC3* Thr241Met variant and HCC [6–11]. However, the conclusions have been inconsistent. Thus, in this study, we performed a meta-analysis to clarify the association between *XRCC3* Thr241Met variant and HCC risk.

Materials and methods

Literature and search strategy

Literature databases including PubMed, Chinese National Knowledge Infrastructure, and Wan Fang data were searched. The search strategy to identify all possible studies involved the use of the following key words: (X-ray repair cross-complementing group 3 or XRCC3) and (hepatocellular carcinoma or HCC). All related studies published in English and Chinese languages were included. The reference lists of retrieved articles were manually searched. If more than one article were published using the same data, only the study with the largest sample size was included. The literature search was updated on February 17, 2013.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluating the association between *XRCC3* Thr241Met variant and HCC, (2) using case–control or cohort design, and (3) providing sufficient data for calculation of odds ratio (OR) with 95 % confidence interval (CI). The following information was extracted from each study: (1) name of the first author, (2) year of publication, (3) country, (4) ethnicity, (5) sample size of cases and controls, (6) genotype distribution in cases and controls, and (7) p value for Hardy–Weinberg equilibrium test in controls. The two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements, and reached a consistent decision.

Statistical analysis

The association between *XRCC3* Thr241Met variant and HCC was estimated by calculating pooled OR and 95 % CI under a codominant, a dominant, or a recessive model. The significance of pooled OR was determined by Z test ($p<0.05$ was considered statistically significant). Q test was performed to evaluate the between-study heterogeneity. A random (DerSimonian–Laird method [12]) or fixed (Mantel–Haenszel method [13]) effects model was used to calculate pooled OR in the presence ($p\leq0.10$) or absence ($p>0.10$) of heterogeneity, respectively. Subgroup analysis by ethnicity was performed to examine the source of heterogeneity. Sensitivity analysis was performed by excluding one study at a time. Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of the studies

A flow chart to describe the study inclusion/exclusion is shown in Fig. 1. The literature search identified a total of 19 potentially relevant papers. Of these, 12 papers were excluded because of obvious irrelevance by reading the titles and abstracts. In addition, one paper was excluded because it was a duplicated publication [14]. Then, six papers met the primary inclusion criteria. However, one paper was excluded since it did not detect Thr/Met and Met/Met genotypes [6]. At last, five studies (1,531 HCC cancer cases and 1,952 controls) for *XRCC3* Thr241Met variant were included in the final meta-analysis [7–11]. The characteristics of the included studies are listed in Table 1.

Meta-analysis results

There was a significant between-study heterogeneity under codominant model (Met/Met vs. Thr/Thr, $I^2=61.5$ %, $p=0.034$; Thr/Met vs. Thr/Thr, $I^2=86.9$ %, $p<0.001$) and dominant model ($I^2=91.1$ %, $p<0.001$); then, random effects model was used; there was no between-study heterogeneity under recessive model ($I^2=36.4$ %, $p=0.178$); then, fixed effects model was used. The meta-analysis showed that *XRCC3* Thr241Met variant was associated with HCC risk under homogeneous codominant model (OR=3.99, 95 % CI=1.74–9.13; Fig. 2) and recessive model (OR=5.22, 95 % CI=3.65–7.48; Fig. 5), but not under heterogeneous codominant model (OR=1.18, 95 % CI=0.68–2.05; Fig. 3) and dominant model (OR=1.37, 95 % CI=0.73–2.57; Fig. 4). Subgroup analysis by ethnicity suggested that *XRCC3* Thr241Met variant was associated with HCC risk in Chinese population, but not in Pakistani population (Figs. 2 and 5).

Sensitivity analysis

Sensitivity analysis was performed to evaluate the stability of the results. By excluding one study at a time, the significant association between *XRCC3* Thr241Met and HCC risk was stable, with OR and 95 % CI ranging from 2.93 (1.48–5.81) to 4.82 (2.28–10.18) under homogeneous codominant model and ranging from 3.03 (1.55–5.92) to 5.65 (3.87–8.25) under recessive model.

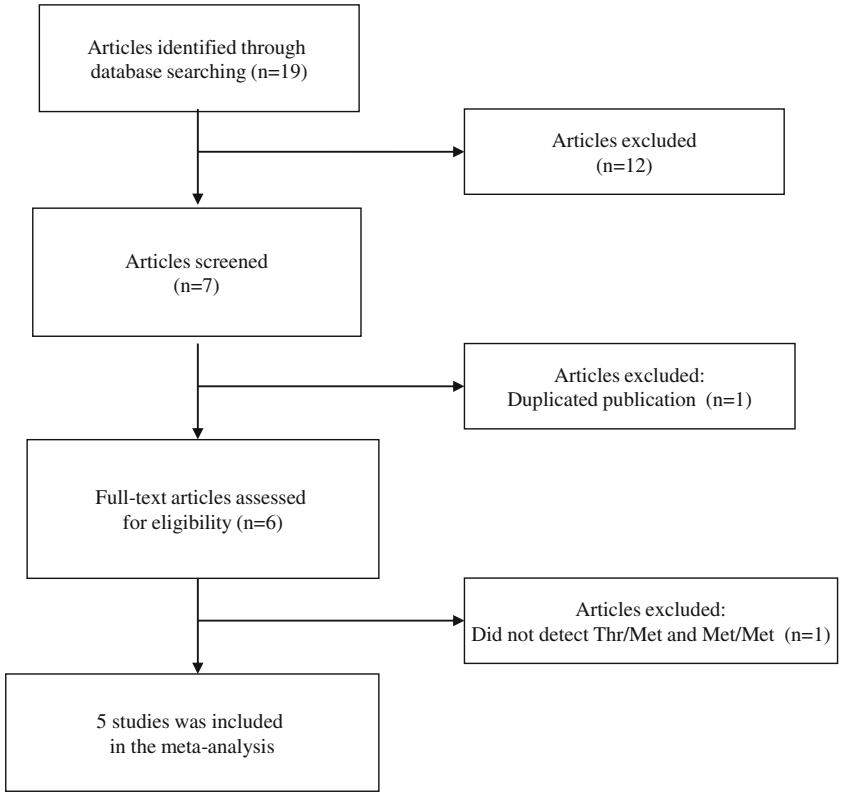

Fig. 1 Flow chart describing the study inclusion/exclusion

Potential publication bias

We did not assess the publication bias for *XRCC3* Thr241Met variant based on the knowledge of Cochrane Handbook for Systematic Reviews of Interventions (www.cochranehandbook.org) which states that the test for publication bias yields unreliable results when less than ten studies are included in a meta-analysis.

Discussion

To our knowledge, this is the first meta-analysis investigating the association of *XRCC3* Thr241Met variant with HCC risk. Our study showed that *XRCC3* Thr241Met variant might be associated with HCC risk, especially in the Chinese. The sensitivity analysis further confirmed the positive association.

To date, six studies have investigated the association of *XRCC3* Thr241Met variant with HCC risk, while the conflicting results have been reported. The discrepancy might be due to the modest effect of the studies variant and the low statistical power of included individual studies. Xu firstly reported the association in a Chinese population, but they did not detect Thr/Met and Met/Met genotypes in both cases and controls [6]. In 2008, Long et al. found that the *XRCC3* Thr241Met polymorphism may be associated with the risk of AFB1-related HCC among the Guangxi population [7]. However, a recent study on Pakistani population suggested the null association of *XRCC3* Thr241Met polymorphism with HCC risk. There are no related studies on European and African populations, and further studies

Table 1 Characteristics of the included studies of the association between *XRCC3* Thr241Met and HCC risk

Study	Country	Ethnicity	Sample size		Genotype frequency in cases			Genotype frequency in controls			p_{HWE}
			Cases	Controls	Thr/Thr	Thr/Met	Met/Met	Thr/Thr	Thr/Met	Met/Met	
Long [7]	China	East Asian	491	862	198	200	93	585	248	29	0.667
Liu [8]	China	East Asian	344	358	319	25	0	337	20	1	0.240
Han [9]	China	East Asian	149	158	75	55	19	87	66	5	0.071
Zeng [10]	China	East Asian	497	500	440	50	7	432	65	3	0.745
Gulnaz [11]	Pakistan	Pakistani	50	74	25	18	7	39	31	4	0.495

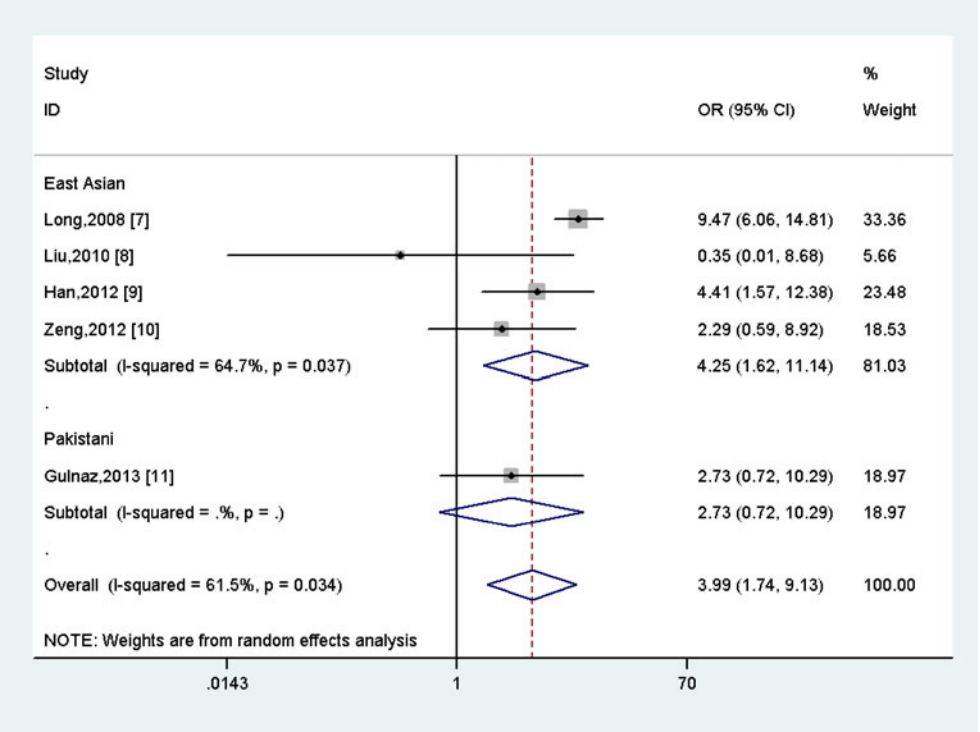

Fig. 2 Meta-analysis of the association between *XRCC3* Thr241Met variant and HCC risk under homogeneous codominant model (Met/Met vs. Thr/Thr) by ethnicity

are necessary to examine the association in these populations to confirm or refute the findings.

Recently, several meta-analyses have examined the association of *XRCC3* Thr241Met variant with other types of cancers [15–20]. The results demonstrated that *XRCC3* Thr241Met variant might be associated with head and neck [17], breast [18], bladder [19], and gastric cancers [20], but not with lung [15] and colorectal cancers [16]. The inconsistent results for different cancer types need further investigation.

Several limitations of our study should be considered. First, our meta-analysis was based on unadjusted estimates, and the confounding factors could not be controlled for because most studies did not provide these data. However, most included studies used age- and sex-matched controls for HCC cases. Second, gene–gene

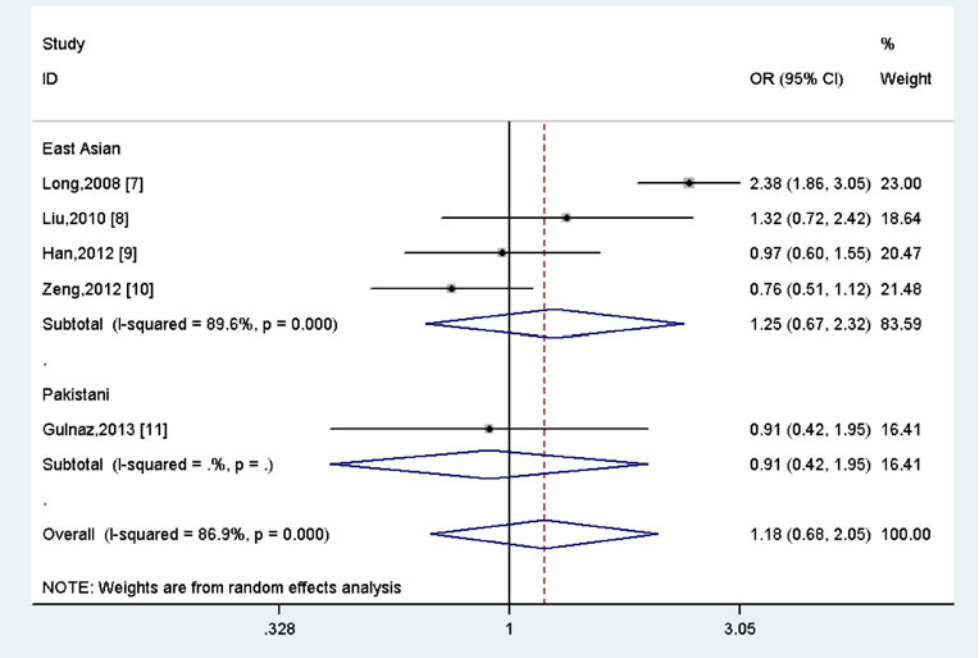

Fig. 3 Meta-analysis of the association between *XRCC3* Thr241Met variant and HCC risk under heterogeneous codominant model (Thr/Met vs. Thr/Thr) by ethnicity

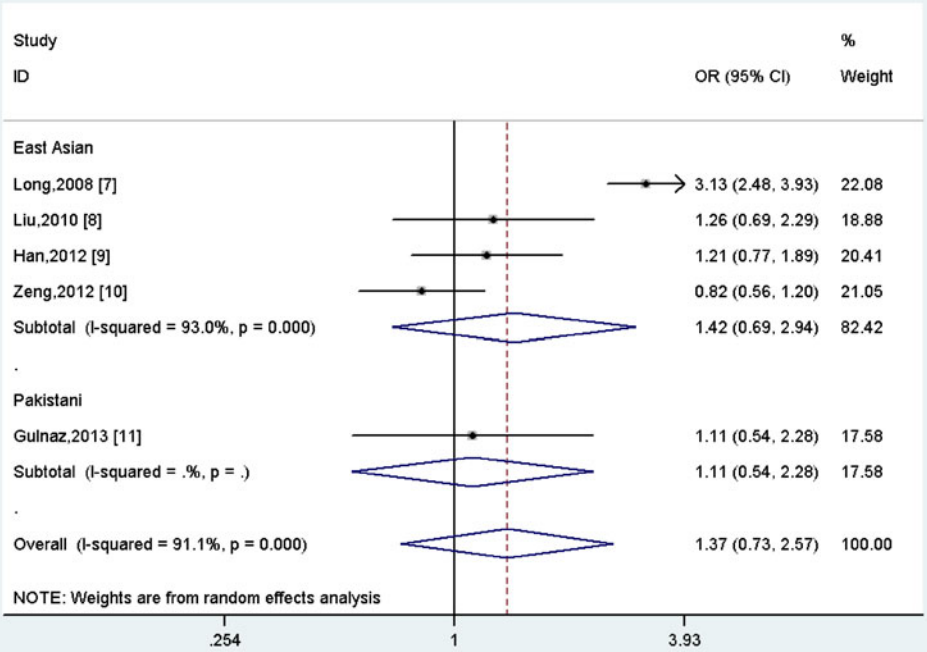

Fig. 4 Meta-analysis of the association between *XRCC3* Thr241Met variant and HCC risk under dominant model (Met/Met + Thr/Met vs. Thr/Thr) by ethnicity

and gene–environment interactions were not addressed in our meta-analysis. However, several studies indicated that *XRCC3* Thr241Met polymorphism could interact with environmental factors, such as HBV/HCV, exposure to dietary AFB1, and alcohol consumption, to increase the risk of HCC. Third, all the included studies used case–control design, which did not allow for drawing casual conclusion. Fourth, since most studies were based on Chinese population, the conclusions should not be generated to other populations such as Caucasian population. In addition, the nonsignificant association in Pakistan population might be due to the low statistical power for one study only. Fifth, the authors did not assess the publication bias for *XRCC3* Thr241Met variant since less than ten studies were included

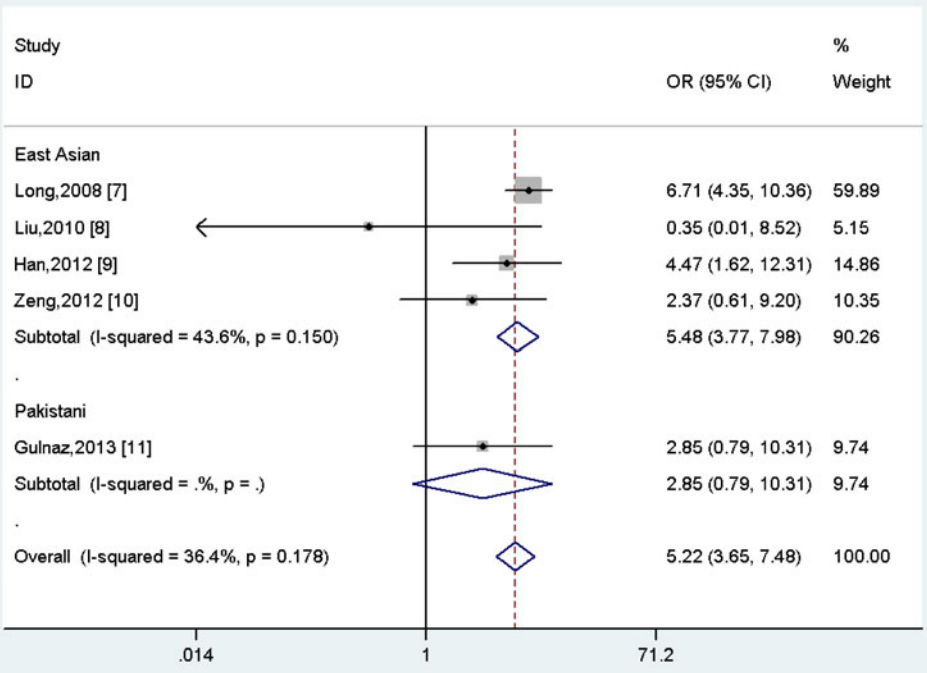

Fig. 5 Meta-analysis of the association between *XRCC3* Thr241Met variant and HCC risk under recessive model (Met/Met vs. Thr/Met + Thr/Thr) by ethnicity

in a meta-analysis. Thus, we could not rule out the possibility of publication bias.

In summary, the present meta-analysis supported the positive association of *XRCC3* Thr241Met polymorphism with HCC risk in the Chinese. Further large-scale studies with the consideration for gene–gene/gene–environment interactions should be conducted to investigate the association.

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Conflicts of interest None.

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