RESEARCH ARTICLE

Association between the XRCC3 Thr241Met Polymorphism and Gastrointestinal Cancer Risk: A Meta-Analysis

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Abstract

Background: The x-ray repair cross-complementing group 3 (XRCC3) encodes a protein involved in the homologous recombination repair (HRR) pathway for double-strand DNA repair. Associations of the XRCC3 Thr241Met polymorphism with various cancers have been widely reported. However, published data on links between XRCC3 Thr241Met and gastrointestinal (GI) cancer risk are inconsistent. **Objective and Methods:** A meta-analysis was conducted to characterize the relationship between XRCC3 Thr241Met polymorphisms and GI cancer risk. Pooled odds ratios (ORs) and 95.0% confidence intervals were assessed using random- or fixed- effect models for 28.0 relevant articles with 30.0 studies containing 7,649.0 cases and 11,123.0 controls. **Results:** The results of the overall meta-analysis suggested a borderline association between the XRCC3 Thr241Met polymorphism and GI cancer susceptibility (T vs. C: OR=1.18, 9 % CI=1.0–1.4, POR=0.04; TT vs. CT+CC: OR=1.3, 95 % CI=1.0–1.6, POR=0.04). After removing studies not conforming to Hardy–Weinberg equilibrium (HWE), however, this association disappeared (T vs. C: OR=1.00, 95 % CI=0.9–1.1, POR=0.96; TT vs. CT+CC: OR=0.9, 95 % CI=0.8–1.1, POR=0.72). When stratified by ethnicity, source of controls or cancer type, although some associations between XRCC3 Thr241Met polymorphism and GI cancer susceptibility were detected, these associations no longer existed after removing studies not conforming to HWE. **Conclusion:** Our meta-analysis suggests that the XRCC3 Thr241Met polymorphism is not associated with risk of GI cancer based on current evidence.

Keywords: X-ray repair cross complementing group 3- polymorphism- gastrointestinal cancer- Meta-analysis

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Introduction

Gastrointestinal cancer (GI) mention to malignant conditions of the gastrointestinal tract including the esophagus, stomach, colon and rectum. Esophageal, gastric and colorectal cancers are the sixth, third and second most common cause of cancer-related death, respectively (Torre et al., 2015). Despite the advancement of diagnostic methods, surgical techniques and medical treatment, the cancer-related mortality remained high due to the invasion and metastasis of tumor at the time of diagnosis(Redig and McAllister, 2013). A majority of studies suggest pathogenesis of cancer is influenced by multiple environmental factors, genetic susceptibility and acquired susceptibility (Yang et al., 2015). Allelic variations in oncogenes are nomination genetic risk factors that may vary the onset and outcome of GI cancer. There has been evidence that human susceptibility to cancer could be influenced by single nucleotide polymorphisms (SNPs) located in DNA repair genes (Chiurillo, 2014).

Homologous recombination is one of the DNA repair mechanisms and the gene encoding X-ray repair cross-complementing group 3 (XRCC3) encodes a member of the RecA/Rad51-related protein family that contributes in homologous recombination to retain chromosome stability and repair DNA damage (Moynahan, 2010). XRCC3 gene is located on chromosome 14q32.3 and consists of 21670 base pair. This gene codifies a mature polypeptide with 346 amino acids (Talar-Wojnarowska et al., 2016). Many studies have demonstrated the role of X-ray repair cross-complementing group in cancer.

Abnormal activity or expression of XRCC3 reported in many types of cancer, like gastric, breast, ovarian and cervix cancer has been suggested as an important marker in tumorigenesis (Abdel-Fatah et al., 2013; Bajpai et al., 2013; Engin, 2013; Sultana et al., 2013). Many single nucleotide polymorphisms in the XRCC3 gene have been reported. Moreover, a common polymorphism in XRCC3 gene is at nucleotide 1,8607C/T (rs861,539) that results in substitution of amino acid threonine to methionine at codon 241 (Thr241Met) in exon seven of XRCC3 gene. Inherited functional polymorphisms in DNA repair genes

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may influence the capacity of DNA repair process, thus leading to increased cancer risk (Aka et al., 2004).

To date, several case-control studies have been conducted to assess the role of XRCC3 Thr241Met polymorphism in predisposition to GI cancer but the published results are controversial and inconsistent. In 2006, Huang et al. found that gastric cancer occurrence was associated with the XRCC3 Met/Met polymorphic variant (OR=1.8, 95% CI=1.1-2.9 for TT genotype) in a Chinese population (Huang et al., 2006) and Mucha et al. (2013) suggested significant association of heterozygotes (OR=0.6, 95% CI=0.4-0.9) and the Met allele (OR=0.7, 95% CI=0.5-0.9) with reduced colorectal cancer risk (Mucha et al., 2013). However, in 2010, Palli et al. reported that XRCC3 Thr241Met polymorphism may not play a significant role in the risk of gastric cancer in Italian population (OR=0.8 and 95% CI= 0.7–1.78 for TT genotype) (Palli et al., 2010)and Moghtit et al. (2014) suggested that the XRCC3 Thr241Met polymorphism may not be associated with the colorectal cancer risk in West Algerian population (Moghtit et al., 2014). We carried out an updated meta-analysis of all available case–control literatures applying multiple genetic statistical models to gain a more reliable conclusion. Besides, stratified analysis by Hardy-Weinberg equilibrium (HWE), ethnicity, source of controls and cancer type were also accomplished for further study.

Materials and Methods

Identification of eligible studies

A literature research was conducted using PubMed Database updated on March 2016 for all publications on the association between XRCC3 Thr241Met polymorphism and GI cancer susceptibility. The search strategy was performed by combination of the following keywords: polymorphism, Thr241Met, XRCC3, esophageal, gastric, colorectal, carcinoma and cancer. All eligible studies were retrieved and their references were reviewed for other eligible studies. The literature retrieval was carried out in duplication by independent investigators.

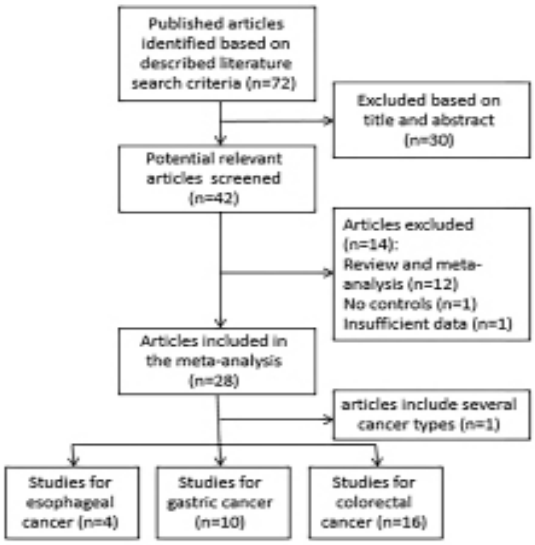

Figure 1. Flow Chart of Study Selection in the Meta-analysis

Inclusion and exclusion criteria

The eligible studies included in present meta-analysis had to comprise all the following inclusion criteria: (a) the study was published in English, (b) case-control studies about the association of XRCC3 Thr241Met polymorphism with GI cancer risk, (c) the study provided sufficient genotype distribution data to compute odds ratios (ORs) and 95% confidence intervals (CIs). Studies such as letters, review, case reports, case-only studies, unpublished data and duplicated studies must be excluded.

Data extraction

Data extracted from relevant articles comprised the first author's name, country of origin, year of publication, ethnicity, number of cases and controls, genotype frequencies for cases and controls and Hardy-Weinberg equilibrium (HWE) for controls (P value). To ensure the accuracy of the extracted data, the investigators reviewed the information extraction results and reached consensus on all of the data extracted.

Statistical analysis

The HWE of genotypes distribution in the control group was assessed by chi-square test and deviation was considered when $P < 0.05$. The risk of GI cancer associated with the XRCC3 Thr241Met polymorphism was estimated for each study by the odds ratio (OR) and

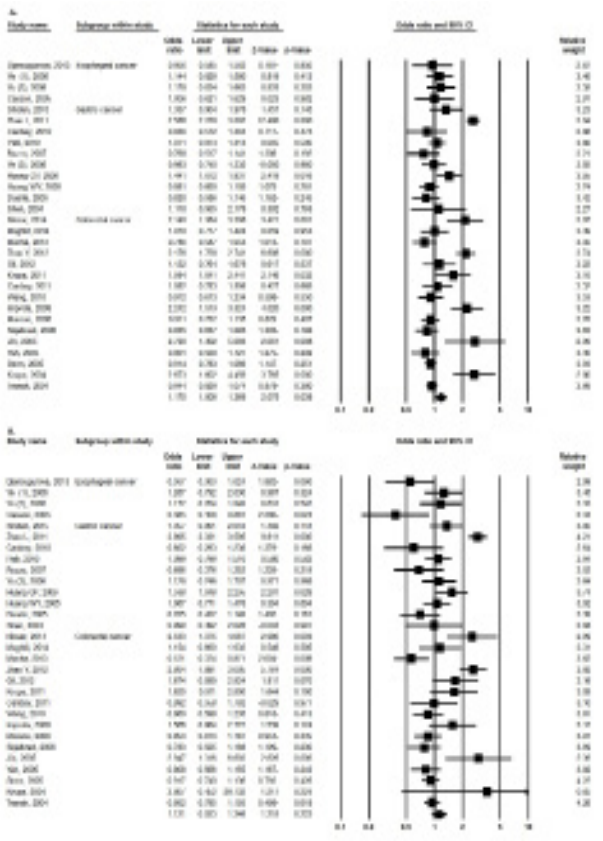

Figure 2. Forest Plot of Associations between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: Allelic Model (T vs. C); B: Heterozygous model (TT vs. CC)

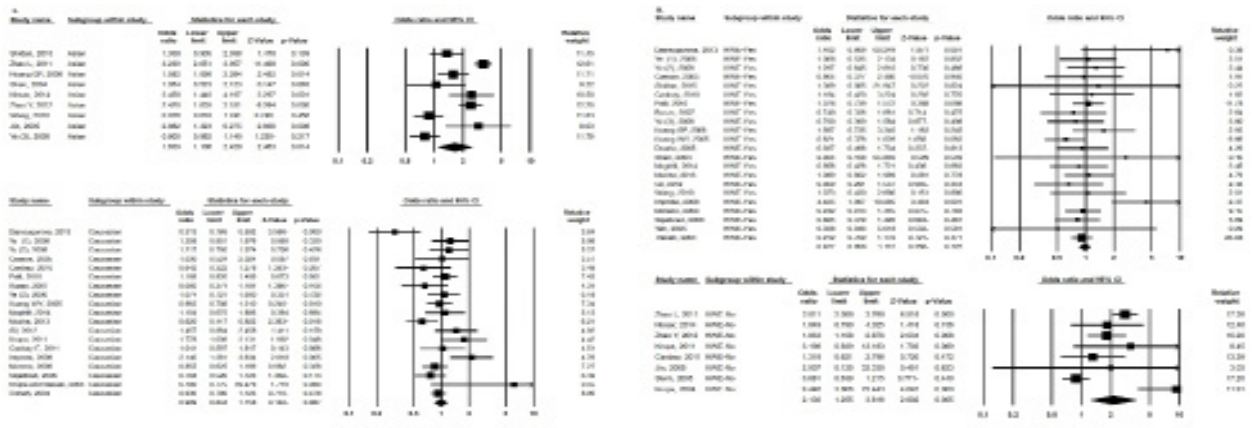

Figure 3. Forest Plot of Subgroup Analysis by Ethnicity and HWE on the Association between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: dominant model of Ethnicity Subgroup (TT+CT vs. CC); B: Recessive model of HWE Subgroup (TT vs. CT+CC)

95.0% confidence interval (CI) under the Allelic model (T vs. C), heterozygote model (CT vs. CC), homozygote model (TT vs. CC), dominant model (TT+ CT vs. CC) and recessive model (TT vs. CT+CC). The significance of the pooled OR was evaluated with the Z test, and it was considered statistically significant for P <0.05. Subgroup analyses were conducted based on ethnicity, source of controls and cancer type. Heterogeneity assumption was checked by a chi-square-based Q test, and the index I2 was used to quantify the effect of heterogeneity (Higgins and Thompson, 2002). A p-value of >0.1 for the Q-test or I^2 <40.0% demonstrated a lack of heterogeneity among different studies; so that the combined OR estimate of each study was computed by the fixed-effects model. Otherwise, the random-effects model was used (DerSimonian and Laird, 1986). In order to confirm the stability and reliability of our combined results in the meta-analysis, a sensitivity analysis was conducted by sequential deletion of a individual study. Begg's funnel plots and Egger's linear regression test were used to estimate of publication bias. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test (P <0.05 was determined a significant publication bias) (Song et al., 2002). Statistical analysis was conducted using Comprehensive Meta-Analysis software (version 2.2)

Results

Characteristics of included studies

Relevant articles published before March 1st, 2016 were identified through a search in PubMed database. Flow chart of the study selection process was illustrated in Figure 1 Based on the search criteria, 7,649.0 multiple cancer cases and 11,123.0 controls from 28.0 eligible articles with 30.0 studies were recruited for this meta-analysis.(Krupa and Blasiak, 2004; Shen et al., 2004; Tranah et al., 2004; Casson et al., 2005; Duarte et al., 2005; Huang et al., 2005; Jin et al., 2005; Stern et al., 2005; Yeh et al., 2005; Huang et al., 2006; Moreno et al., 2006; Skjelbred et al., 2006; Ye et al., 2006; Ruzzo et al., 2007; Improta et al., 2008; Pardini et al., 2008; Canbay et al., 2010; Palli et al., 2010; Wang et al., 2010; Canbay et al., 2011; Krupa et al., 2011; Zhao et al., 2011; Gil et al., 2012; Zhao et al., 2012; Djansugurova et al., 2013; Mucha et al., 2013; Moghtit et al., 2014; Nissar et al., 2014; Cheng et al., 2015) . One of the articles included gastric cancer and two types of esophageal cancer (Ye et al., 2006). Eight of eligible articles deviated from HWE (Krupa and Blasiak, 2004; Jin et al., 2005; Stern et al., 2005; Canbay et al., 2011; Krupa et al., 2011; Zhao et al., 2011; Zhao et al., 2012; Nissar et al., 2014) among these publications, 19 studies were conducted in Caucasian descent (Krupa and Blasiak, 2004; Tranah et al., 2004; Casson et al., 2005; Huang et al., 2005; Moreno et al., 2006; Skjelbred et al., 2006; Ye et al., 2006; Ruzzo et al., 2007; Improta et al., 2008; Canbay et al., 2010; Palli et al., 2010; Canbay et al., 2011; Krupa et al., 2011; Gil et al., 2012; Djansugurova et al., 2013; Mucha et al., 2013;

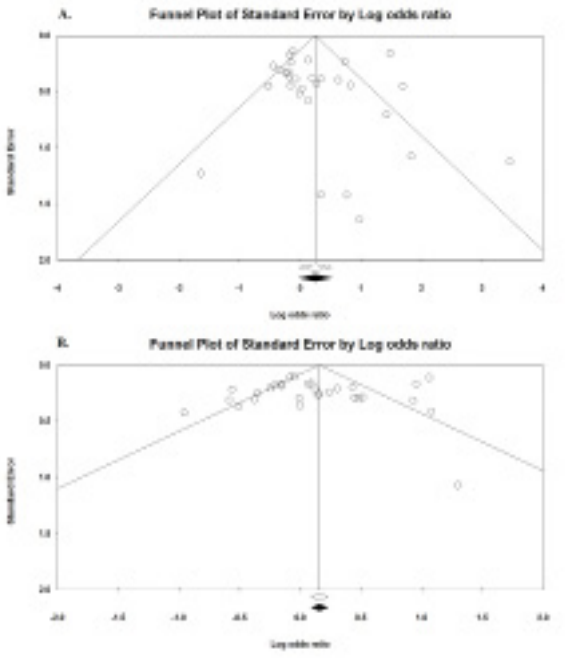

Figure 4. Forest Plot of Association between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: Homozygous genetic model (A vs. C); B: Heterozygous genetic model (AA vs. CC)

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

Cancer location	First author	Year	Country	Ethnicity	Source of controls	Cases	Controls	Genotyping method	P HWE
Esophageal cancer	Djansugurova	2013	Kazakhstan	Caucasian	HB	115.0	100.0	PCR-RFLP	0.108
	Ye (1)	2006	Sweden	Caucasian	PB	96.0	472.0	PCR-RFLP	0.506
	Ye (2)	2006	Sweden	Caucasian	PB	81.0	472.0	PCR-RFLP	0.506
	Casson	2005	Canada	Caucasian	HB	56.0	95.0	PCR-RFLP	0.748
Gastric cancer	Shidan	2015	China	Asian	PB	440.0	602.0	PCR-LDR	0.841
	Zhao L	2011	China	Asian	HB	721.0	989.0	TaqMan	<0.001
	Canbay	2010	Turkey	Caucasian	HB	40.0	247.0	PCR-RFLP	0.861
	Palli	2010	Italy	Caucasian	PB	294.0	546.0	TaqMan	0.713
	Ruzzo	2007	Italy	Caucasian	HB	90.0	121.0	PCR-RFLP	0.214
	Ye (3)	2006	Sweden	Caucasian	PB	126.0	472.0	PCR-RFLP	0.506
	Huang GP	2006	China	Asian	HB	309.0	188.0	PCR-RFLP	0.946
	Huang WY	2005	Poland	Caucasian	PB	281.0	390.0	PCR-RFLP	0.138
	Duarte	2005	Brazil	Others	HB	160.0	150.0	PCR-RFLP	0.127
	Shen	2004	China	Asian	PB	188.0	166.0	PCR-RFLP	0.514
Colorectal cancer	Nissar	2014	Kashmir	Asian	PB	120.0	150.0	PCR-RFLP	<0.001
	Moghtit	2014	Algeria	Caucasian	PB	129.0	148.0	Sequencing	0.741
	Mucha	2013	Poland	Caucasian	HB	194.0	209.0	PCR-RFLP	0.317
	Zhao Y	2012	China	Asian	HB	485.0	970.0	PCR-CTPP	<0.001
	Gil	2012	Poland	Caucasian	HB	132.0	100.0	PCR-RFLP	0.113
	Krupa	2011	Poland	Caucasian	HB	100.0	100.0	PCR-RFLP	0.039
	Canbay E	2011	Turkey	Caucasian	PB	79.0	247.0	PCR-RFLP	<0.001
	Wang	2010	India	Asian	PB	302.0	291.0	PCR-RFLP	0.963
	Improta	2008	Italy	Caucasian	HB	109.0	121.0	PCR-RFLP	0.978
	Moreno	2006	spain	Caucasian	HB	361.0	316.0	APEX	0.447
	Skjelbred	2006	Norwegian	Caucasian	PB	157.0	399.0	TaqMan	0.342
	Jin	2005	China	Asian	PB	140.0	280.0	PCR-RFLP	0.025
	Yeh	2005	Taiwan	Asian	HB	721.0	734.0	PCR-RFLP	0.958
	Stern	2005	USA	Mixed	PB	737.0	787.0	PCR-RFLP	0.033
	Krupa and blasiak	2004	Poland	Caucasian	HB	51.0	100.0	PCR-RFLP	<0.001
	Tranah	2004	UK	Caucasian	PB	835.0	1161.0	TaqMan	0.508

HB, hospital-based; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphisms; PCR-CTPP, polymerase chain reaction-the confronting-two-pair primer; APEX, arrayed primer extension; HWE, Hardy-Weinberg equilibrium

Moghtit et al., 2014) , and nine studies were performed in Asian descent (Shen et al., 2004; Jin et al., 2005; Yeh et al., 2005; Huang et al., 2006; Wang et al., 2010; Zhao et al., 2011; Zhao et al., 2012; Nissar et al., 2014; Cheng et al., 2015). There were 15 hospital-based case–control studies (Casson et al., 2005; Duarte et al., 2005; Yeh et al., 2005; Huang et al., 2006; Moreno et al., 2006; Ruzzo et al., 2007; Improta et al., 2008; Canbay et al., 2010; Krupa et al., 2011; Zhao et al., 2011; Gil et al., 2012; Zhao et al., 2012; Djansugurova et al., 2013; Mucha et al., 2013) involving 3,644 cases and 4,540 controls and 15 population based case–control studies (Shen et al., 2004; Tranah et al., 2004; Huang et al., 2005; Jin et al., 2005; Stern et al., 2005; Skjelbred et al., 2006; Ye et al., 2006; Palli et al., 2010; Wang et al., 2010; Canbay et al., 2011; Moghtit et al., 2014; Nissar et al., 2014; Cheng et al., 2015) including 4,005 cases and 6,583 controls in current meta-analysis. For the meta-analysis of XRCC3 Thr241Met polymorphism for GI cancer, there were four studies on esophageal cancer (Casson et al., 2005; Ye et al., 2006; Djansugurova et al., 2013), 10 studies on gastric cancer (Shen et al., 2004; Duarte et al., 2005; Huang et al., 2005; Huang et al., 2006; Ye et al., 2006; Ruzzo et al., 2007; Canbay et al., 2010; Palli et al., 2010; Zhao et al., 2011; Cheng et al., 2015), and 16 study on colorectal cancer (Krupa and Blasiak, 2004; Tranah et al., 2004; Jin et al., 2005; Stern et al., 2005; Yeh et al., 2005; Moreno et al., 2006; Skjelbred et al., 2006; Improta et al., 2008; Wang et al., 2010; Canbay et al., 2011; Krupa et al., 2011; Gil et al., 2012; Zhao et al., 2012; Mucha et al., 2013; Moghtit et al., 2014; Nissar et al., 2014). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was the most common technique used for the genotype analyzing. All the articles were written in English and the data collected

Table 2. Investigating the Association between XRCC3 Thr241Met Polymorphism and Gastrointestinal Cancer in Overall Studies

				Test of association	95% CI		Test of heterogeneity		
	Number Of study	Cases	controls	OR	Lower	Upper	P_{OR}	$P_{Q\text{-test}}$	I^2 (%)
Overall	30.0	7,649.0	11,123.0						
T vs. C				1.2	1.0	1.4	0.038	<0.001	87.9
TT vs. CC				1.3	1.0	1.7	0.072	<0.001	77.9
CT vs. CC				1.1	0.9	1.4	0.223	<0.001	82.7
TT+CT vs. CC				1.2	0.9	1.4	0.169	<0.001	86.7
TT vs. CT+CC				1.3	1.0	1.6	0.042	<0.001	70.1
HWE in controls									
YES	22.0	5,216.0	7,500.0						
T vs. C				1.0	0.9	1.1	0.965	0.01	46.0
TT vs. CC				1.0	0.8	1.2	0.98	0.08	31.4
CT vs. CC				1.0	0.9	1.1	0.537	0.008	47.4
TT+CT vs. CC				1.0	0.9	1.1	0.649	<0.001	57.2
TT vs. CT+CC				1.0	0.9	1.1	0.722	0.248	16.0
NO	8.0	2,433.0	3,623.0						
T vs. C				1.8	1.2	2.7	0.003	<0.001	93.6
TT vs. CC				2.5	1.3	4.9	0.009	<0.001	88.0
CT vs. CC				1.9	1.2	3.0	0.007	<0.001	89.8
TT+CT vs. CC				2.0	1.2	3.2	0.006	<0.001	92.3
TT vs. CT+CC				2.1	1.3	3.6	0.005	<0.001	83.4
Ethnicity									
Asian	9.0.	3,423.0	4,370.0						
T vs. C				1.5	1.1	2.1	0.009	<0.001	82.9
TT vs. CC				2.1	1.3	3.4	0.004	0.008	61.1
CT vs. CC				1.6	1.1	2.4	0.014	<0.001	88.0
TT+CT vs. CC				1.6	1.1	2.4	0.014	<0.001	90.1
TT vs. CT+CC				2.2	1.8	2.7	<0.001	0.416	2.2
Caucasian	19.0	3,326.0	5,816.0						
T vs. C				1.1	0.9	1.2	0.364	<0.001	61.4
TT vs. CC				1.1	0.9	1.4	0.454	0.002	54.6
CT vs. CC				1.0	0.8	1.1	0. 694	0.015	46.0
TT+CT vs. CC				1.0	0.8	1.2	0.887	0.001	59.2
TT vs. CT+CC				1.2	0.9	1.5	0.234	<0.001	63.7
Source of control									
HB	15.0	3,644.0	4,540.0						
T vs. C				1.3	1.0	1.6	0.117	<0.001	91.1
TT vs. CC				1.6	1.0	2.6	0.049	<0.001	83.1
CT vs. CC				1.1	0.8	1.5	0.7	<0.001	89.3
TT+CT vs. CC				1.2	0.8	1.7	0.476	<0.001	91.4
TT vs. CT+CC				1.6	1.1	2.4	0.013	<0.001	75.8
PB	15.0	4,005.0	6,583.0						
T vs. C				1.1	0.9	1.2	0.38	0.012	50.8
TT vs. CC				0.95	0.8	1.1	0.5	0.654	<0.001
CT vs. CC				1.1	0.9	1.2	0.2	0.066	38.3
TT+CT vs. CC				1.02	0.9	1.1	0.6	0.024	46.7
TT vs. CT+CC				0.9	0.8	1.1	0.4	0.839	<0.001

Table 2 (Continued). Investigating the Association between XRCC3 Thr241Met Polymorphism and Gastrointestinal Cancer in Overall Studies

			Test of association 95% CI					Test of heterogeneity	
	Number Of study	Cases	Controls	OR	Lower	Upper	P_{OR}	$P_{Q\text{-test}}$	I^2 (%)
Cancer type									
Esophageal cancer	4.0	348.0	1139.0						
T vs. C				1.1	0.9	1.3	0.34	0.884	<0.001
TT vs. CC				1.3	0.8	2.1	0.221	0.478	<0.001
CT vs. CC				0.8	0.5	1.4	0.415	0.023	68.4
TT+CT vs. CC				0.9	0.7	1.2	0.665	0.003	78.8
TT vs. CT+CC				1.2	0.8	1.9	0.365	0.354	7.75
Gastric cancer	10.0	2253.0	3871.0						
T vs. C				1.1	0.8	1.6	0.504	<0.001	92.2
TT vs. CC				1.2	0.7	2.2	0.561	<0.001	86.7
CT vs. CC				1.1	0.8	1.6	0.493	<0.001	86.8
TT+CT vs. CC				1.1	0.8	1.7	0.538	<0.001	90.6
TT vs. CT+CC				1.1	0.7	1.8	0.6	<0.001	77.9
Colorectal cancer	16.0	4652.0	6113.0						
T vs. C				1.2	1.0	1.5	0.033	<0.001	85.4
TT vs. CC				1.3	0.9	1.7	0.14	<0.001	68.1
CT vs. CC				1.2	1.0	1.5	0.144	<0.001	78.5
TT+CT vs. CC				1.2	1.0	1.5	0.1	<0.001	82.1
TT vs. CT+CC				1.1	1.0	1.3	0.139	<0.001	69.4

from the eligible studies were summarized in Table 1.

Main results

Table 2 listed the main results of the association between XRCC3 polymorphism and GI cancer risk. The overall results of meta-analysis showed borderline association between the XRCC3 Thr241Met polymorphism and increased GI cancer susceptibility in allelic and recessive genetic models (T vs. C: OR=1.2, 95 % CI=1.0–1.4, POR=0.04; TT vs. CT+CC: OR=1.3, 95 % CI=1.04-1.6, POR=0.04). However, there was no obvious association between XRCC3Thr194Met polymorphism and GI cancer risk under the homozygous, heterozygous and dominant genetic models (TT vs. CC: OR=1.3, 95 % CI=0.9–1.7, POR=0.07; CT vs. CC: OR=1.1, 95 % CI=0.9–1.3, POR=0.22; TT+CT vs. CC: OR=1.1, 95 % CI=0.9–1.4, POR=0.17; Table 2 and Figure 2)

Stratified analyses were also performed by ethnicities, sources of controls, cancer location and HWE.

Stratified analysis by ethnicity, source of controls and cancer type detected some associations between Thr241Met polymorphism and cancer susceptibility.

In stratified analysis by ethnicity, the present meta-analysis showed that the Thr241Met polymorphism was associated with increased GI cancer risk in Asians (T vs. C: OR =1.5, 95 % CI=1.1–2.1, POR=0.009; TT vs. CC: OR=2.1, 95 % CI=1.2–3.4, POR=0.004; CT vs. CC: OR=1.6, 95 % CI=1.1–2.4, POR=0.014; TT+CT vs. CC: OR=1.6, 95 % CI=1.1–2.4, POR=0.014; TT vs. CT+CC: OR=2.2, 95 % CI=1.8–2.7, POR<0.001)

In stratified analysis according to source of control, significant increased GI cancer risk was found in hospital-based studies (TT vs. CC: OR=1.6, 95 % CI=1.0–2.6, POR=0.049; TT vs. CT+CC: OR=1.6, 95 % CI=1.1-2.3, POR=0.013), but not in population-based studies.

In subgroup analysis by cancer type, significant increased GI cancer risk was observed in colorectal cancer (T vs. C: OR=1.2, 95 % CI=1.0–1.5, POR=0.033), but not in esophageal and gastric cancer (Table 2 and Figure 3).

When limiting the meta-analysis to the 22.0 studies conforming to HWE, the results altered and no statistical significant association found in all genetic models. In addition, studies conforming to HWE stratified by ethnicity, source of controls and cancer type. Statistical analysis demonstrated no significant association between Thr241Met XRCC3 and GI cancer in all genetic models (Table 3).

Publication bias

Publication bias of the selected studies was evaluated by the Begg's funnel plot and Egger's regression test. The funnel plot did not represent obvious asymmetry in any genetic model (Figure 4). Similarly, no evidence of publication bias was observed by Egger's regression test (P=0.989 for allelic genetic model; P=0.803 for homozygous genetic model; P=0.527 for heterozygous genetic model; P=0.553 for dominant genetic model; P=0.511 for recessive genetic model). The results demonstrate lack of publication bias among all genetic models.

Test of heterogeneity

Table 3. Investigating the Association between XRCC3 Thr241Met Polymorphism and Gastrointestinal Cancer in Studies Conforming HWE

			Test of association 95% CI					Test of heterogeneity	
	Number Of study	Cases	controls	OR	Lower	Upper	P_{OR}	$P_{Q\text{-}test}$	I^2 (%)
Studies conforming HWE	22.0	5,216.0	7,500.0						
T vs. C				1.0	0.9	1.1	0.965	0.01	46.0
TT vs. CC				1.0	0.8	1.2	0.98	0.08	31.4
CT vs. CC				1.0	0.9	1.1	0.537	0.008	47.4
TT+CT vs. CC				1.0	0.9	1.1	0.649	<0.001	57.2
TT vs. CT+CC				1.0	0.9	1.1	0.722	0.248	16.0
Asian	5.0	1,960.0	1,981.0						
T vs. C				1.1	0.9	1.4	0.5	0.063	55.3
TT vs. CC				1.3	0.8	2.3	0.304	0.449	<0.001
CT vs. CC				1.1	0.8	1.4	0.599	0.074	53.2
TT+CT vs. CC				1.1	0.8	1.5	0.536	0.049	58.1
TT vs. CT+CC				1.3	0.8	2.3	0.341	0.881	<0.001
Caucasian	16.0	3,096.0	5,369.0						
T vs. C				1.0	0.9	1.1	0.984	0.028	44.7
TT vs. CC				1.0	0.8	1.2	0.985	0.041	41.6
CT vs. CC				1.0	0.8	1.1	0.563	0.029	44.5
TT+CT vs. CC				1.0	0.8	1.1	0.666	0.002	57.4
TT vs. CT+CC				1.0	0.8	1.2	0.954	0.08	35.3
HB	11.0	2,287.0	2,381.0						
T vs. C				1.0	0.8	1.2	0.969	0.001	67.6
TT vs. CC				1.1	0.8	1.7	0.57	0.008	58.2
CT vs. CC				0.8	0.7	1.1	0.191	0.001	66.6
TT+CT vs. CC				1.0	0.7	1.3	0.899	<0.001	76.8
TT vs. CT+CC				1.2	0.8	1.6	0.373	0.054	44.7
PB	11.0	2,929.0	5,119.0						
T vs. C				1.0	0.9	1.1	0.673	0.628	<0.001
TT vs. CC				0.9	0.8	1.1	0.356	0.82	<0.001
CT vs. CC				1.0	0.9	1.1	0.627	0.752	<0.001
TT+CT vs. CC				1.0	0.9	1.1	0.901	0.676	<0.001
TT vs. CT+CC				0.9	0.8	1.1	0.29	0.882	<0.001
Esophageal cancer	4.0	348.0	1,139.0						
T vs. C				1.1	0.9	1.3	0.34	0.884	<0.001
TT vs. CC				1.3	0.8	2.1	0.221	0.478	<0.001
CT vs. CC				0.8	0.5	1.4	0.415	0.023	68.4
TT+CT vs. CC				0.9	0.7	1.2	0.665	0.003	78.8
TT vs. CT+CC				1.2	0.8	1.9	0.365	0.354	7.8
Gastric cancer	9.0	1,928.0	2,882.0						
T vs. C				1.0	0.9	1.1	0.793	0.106	39.3
TT vs. CC				0.9	0.7	1.2	0.608	0.446	<0.001
CT vs. CC				1.1	0.9	1.2	0.323	0.142	34.4
TT+CT vs. CC				1.0	0.9	1.2	0.749	0.09	41.6
TT vs. CT+CC				0.9	0.8	1.2	0.526	0.639	<0.001
Colorectal cancer	9.0	2,940.0	3,479.0						
T vs. C				1.0	0.8	1.1	0.777	0.004	65.0
TT vs. CC				1.0	0.7	1.4	0.925	0.02	55.9
CT vs. CC				0.9	0.8	1.1	0.361	0.059	46.6
TT+CT vs. CC				0.9	0.8	1.1	0.541	0.016	57.6
TT vs. CT+CC				1.0	0.8	1.3	0.901	0.071	44.6

Significant heterogeneity revealed among literatures for the XRCC3 Thr241Met polymorphism and GI cancer risk (allelic: P <0.001, I^2=87.9%; homozygous: P <0.001, I^2=77.9%; heterozygous: P <0.001, I2=82.7%, dominant: P <0.001, I^2=86.7% and recessive: P <0.001, I^2=70.1). Hence, random-effect model was applied to generate CIs for these genetics models comparison (P <0.05).

Sensitivity analysis

Some studies with deviated from HWE, were included in this meta-analysis. Sensitivity analysis was performed to assess whether this deviation have an impact on the overall estimate. Sensitivity analysis was conducted by sequential deletion of single study to determine the influence of each individual study on the pooled OR and P-value for various genetic models. Individual studies involved in the meta-analysis were omitted and deletion of studies that deviated from HWE altered P-value of statistical significant associations. Also, sensitivity analysis was conducted in statistical results of studies conforming to HWE and statistical significances of the overall results did not alter. The sensitivity analysis confirmed the stability and reliability of the results.

Discussion

Different DNA repair systems preserve the integrity of the human genome. DNA repair mechanisms are various and intricate, involving more than 100.0 genes (Sancar et al., 2004). Some important pathways in DNA repair have been characterize: nucleotide excision repair (NER), base excision repair (BER), and double-strand break repair (DSBR) (Christmann et al., 2003). Deficiency in the repair capacity because of polymorphisms or mutations in genes involved in DNA repair can ultimate genomic instability that lead to chromosomal instability syndromes and increased risk of developing different types of cancer (Manuguerra et al., 2006).

Double strand breaks (DSBs) are the most dangerous DNA damage and XRCC3 is required for the formation of the protein complex necessary for homologous recombination repair (HRR) of DNA DSB (Brenneman et al., 2000). The Thr241Met (T241M) is the most frequent polymorphism in XRCC3, resulting in the amino acid substitution of threonine to methionine in codon 241, which may modify the function of enzyme and its interaction with other proteins involved in the DNA repair mechanisms.

Mounting evidence by meta-analysis indicates that XRCC3 Thr241Met polymorphism is associated with risk of particularly cancer (e.g., melanoma skin cancer (Fan et al., 2015), prostate cancer (Xuan et al., 2015), lung cancer (Bei et al., 2015), and hepatocellular carcinoma (Wu et al., 2013).Several previous studies have evaluated the association between the XRCC3 Thr241Met polymorphism and GI cancer susceptibility; however, existing results are inconsistent. This meta-analysis was performed to derive a more precise estimation of the association between Thr241Met polymorphism and GI cancer risk.

The overall results indicated a borderline association between the Thr241Met polymorphism and increased GI cancer susceptibility in allelic and recessive genetic models. Subgroup analyses were carried out to further investigate the potential association. In stratified analysis by ethnicity, significant increased GI cancer susceptibility was found in Asians (all genetic models). However, no significant association was detected in Caucasians. The different effect of XRCC3 Thr241Met polymorphism between ethnicity may result from different genetic background and environmental exposures, which may contribute to the discrepancy. In stratified analysis according to source of control, significant increased GI cancer susceptibility was observed in hospital based studies (homozygous and recessive genetic models). The results of hospital-based case-control studies are not reliable because the controls from hospital-based studies may not be truly representative of general population. In subgroup analysis by cancer type, significant increased GI cancer risk was found in colorectal cancer (allelic genetic model).

Departure from HWE may be as a result of methodological and genetic reasons. Methodological reasons include genotyping errors or biased selection of subjects from the population and genetic reasons comprise non-random mating, or the alleles show recent mutations that have not reached equilibrium (Mitchell et al., 2003; Hosking et al., 2004). Because of the reasons of disequilibrium, the findings of genetic association studies might be counterfeit if the distribution of genotypes in the control groups were not in HWE (Salanti et al., 2005; Trikalinos et al., 2006). Hence, we excluded the studies that deviated from HWE in controls. When excluding the studies that deviated from HWE, a borderline association between XRCC3 polymorphism and GI cancer susceptibility altered in allelic and recessive genetic models in overall results. Also, all significant associations between XRCC3 Thr241Met and GI cancer in Asian, hospital based studies and colorectal cancer subgroup were disappeared.

Publication bias and sensitivity analysis were used in current meta-analysis to make our results more guaranteed. Both the Egger's test and Begg's funnel plot demonstrate no publication bias in this meta-analysis. Sensitivity analysis was conducted by sequential deletion of single study to determine the influence of each individual study on the pooled OR and P-value for various genetic models. Individual studies involved in the meta-analysis were omitted and deletion of studies that deviated from HWE altered P-value of statistical significant associations. Also, sensitivity analysis was conducted in statistical results of studies conforming to HWE and statistical significances of the overall results did not alter. The sensitivity analysis confirmed the stability and reliability of the results.

In interpreting results of the present meta-analysis, some limitations need to be considered. First, 7,649.0 cases and 11,123.0 controls were included in this meta-analysis; the sample size was relatively small and may not have provided sufficient statistical power to estimate the association between XRRC3 Thr241Met polymorphism and GI cancer risk. Therefore, more studies with a larger sample size are needed to prepare a more statistical analysis. Second, the original studies in the current meta-analysis

mainly provided data towards Asians and Caucasians. Other ethnicities including Africans and mixed should be investigated to evaluation of probably association in future studies. In addition, Because of limited available data about association between XRCC3 Thr241Met polymorphism and GI cancer in Asian population and esophageal cancer, our results should be interpreted with caution. Larger and more studies are required to clarify the association of this polymorphism and risk of GI cancer in different ethnicities and cancer types. Third, the results of present meta-analysis were based on unadjusted estimates; data were not stratified by other factors such as gender, age, family history, smoking status, alcohol consumption and other lifestyle factors, because sufficient relevant information could not be extracted from the primary studies. Fourth, we did not conduct analyses on the potential role of gene-environment or gene–gene interactions because included studies did not provide usable data. Finally, it was difficult to achieve all articles published in various language and the studies published in English were included. Also, only published papers were included in current meta-analysis.

In spite of these limitations, our meta-analysis still has some advantages. According to our knowledge, this is the first meta-analysis to investigate the association of xrcc3 Thr241Met polymorphism with GI cancer, and the influence of this gene polymorphism on GI cancer susceptibility in different ethnic populations. The identified case-control studies in present meta-analysis were met our inclusion criteria. In addition, the methodological issues for meta-analysis, such as, stability of results, publication bias and heterogeneity were all well investigated.

In conclusion, present meta-analysis suggested that the XRCC3 Thr241Met polymorphism might influence GI cancer risk in Asians, although after removing studies not conforming to HWE, this association disappeared. Further studies with good design and larger sample sizes are required to provide a more precise estimation on the gene–gene or gene–environment interactions in the GI cancer.

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