

## RESEARCH ARTICLE

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

Mohammad Hossein Sahami-Fard<sup>1</sup>, Ali Reza Mousa Mayali<sup>2,3</sup>, Ahmad Tajehmiri<sup>4\*</sup>

### 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, 95 % 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

*Asian Pac J Cancer Prev*, 17 (10), 4599-4608

### 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

<sup>1</sup>Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, <sup>2</sup>Young researchers and Elite club, <sup>3</sup>Department of Genetics, Science and Research Branch, Islamic Azad University Tehran, <sup>4</sup>Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran. \*For correspondence: ahmadtajehmiri@kums.ac.ir

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

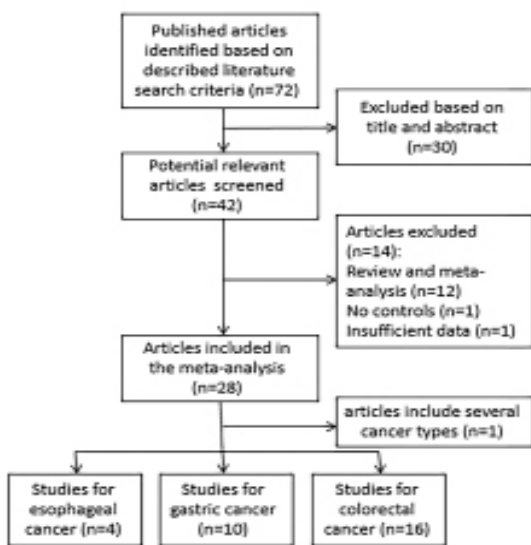


Figure 1. Flow Chart of Study Selection in the Meta-analysis

eligible studies. The literature retrieval was carried out in duplication by independent investigators.

*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

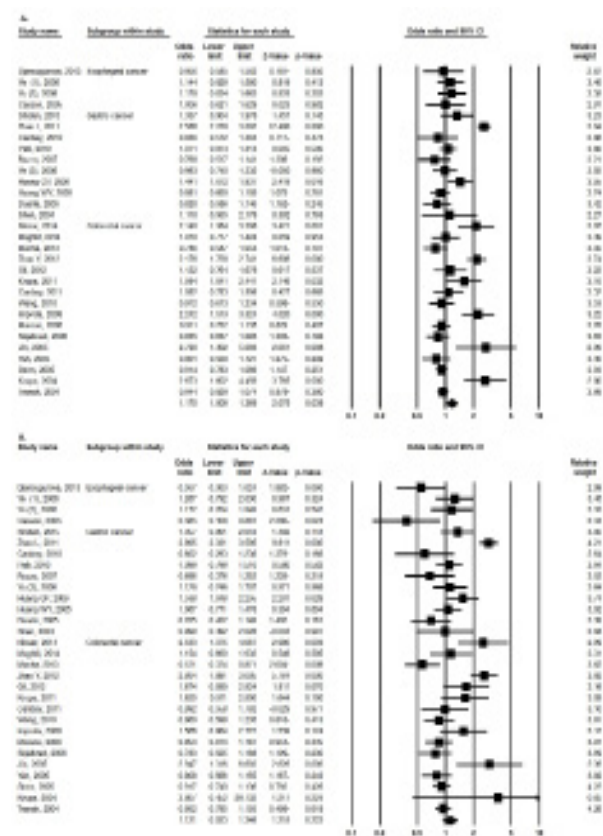


Figure 2. Forest Plot of Associations between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: Allelic Model (T vs. C); B: Heterozygous model (TT vs. CC)

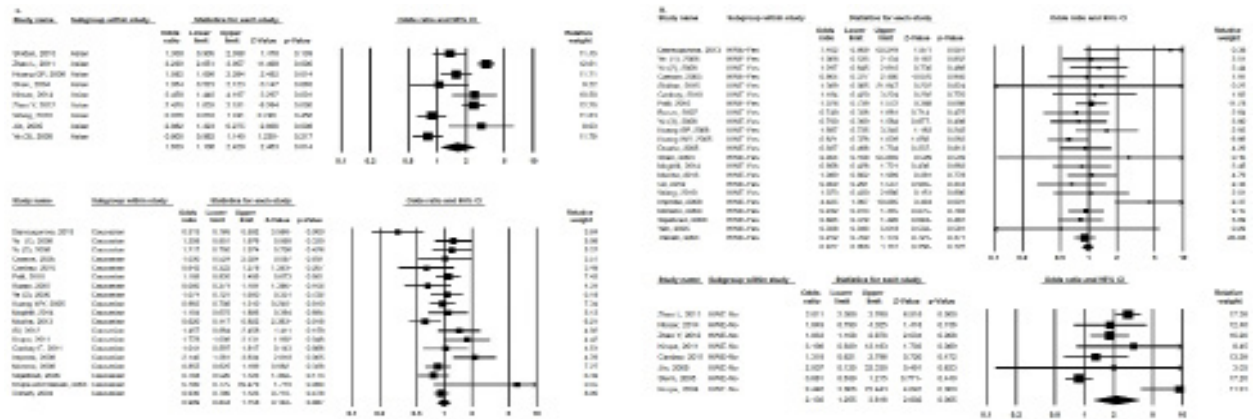


Figure 3. Forest Plot of Subgroup Analysis by Ethnicity and HWE on the Association between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: dominant model of Ethnicity Subgroup (TT+CT vs. CC); B: Recessive model of HWE Subgroup (TT vs. CT+CC)

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 I<sup>2</sup> 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;

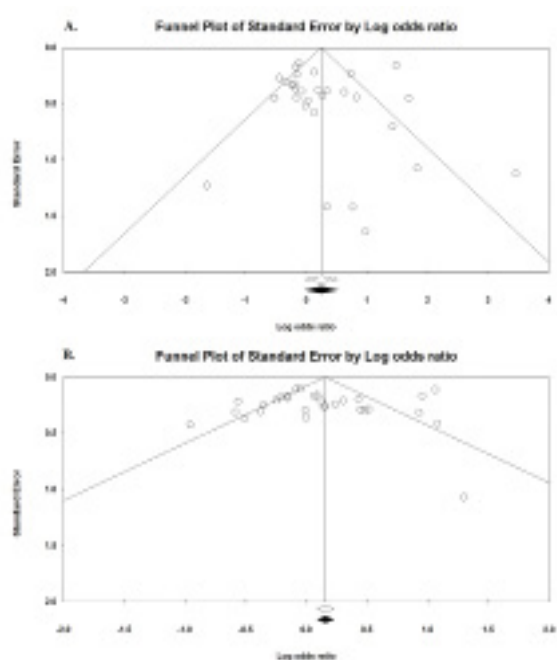


Figure 4. Forest Plot of Association between XRCC3 Thr241Met Polymorphism and GI Cancer Risk. A: Homozygous genetic model (A vs. C); B: Heterozygous genetic model (AA vs. CC)

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

|                   | Number<br>Of study | Cases   | controls | Test of association | 95% CI |       | Test of heterogeneity |              |           |
|-------------------|--------------------|---------|----------|---------------------|--------|-------|-----------------------|--------------|-----------|
|                   |                    |         |          | OR                  | Lower  | Upper | $P_{OR}$              | $P_{Q-test}$ | $I^2$ (%) |
| 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

| Of study           | Number | Test of association 95% CI |          |     | Test of heterogeneity |       |                 |                     |                    |
|--------------------|--------|----------------------------|----------|-----|-----------------------|-------|-----------------|---------------------|--------------------|
|                    |        | Cases                      | Controls | OR  | Lower                 | Upper | P <sub>OR</sub> | P <sub>Q-test</sub> | I <sup>2</sup> (%) |
| <b>Cancer type</b> |        |                            |          |     |                       |       |                 |                     |                    |
| 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 | $P_{OR}$              | $P_{Q-test}$ | $I^2$ (%) |
| 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:  $P < 0.001$ ,  $I^2 = 82.7\%$ , 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 XRCC3 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.

## References

- Abdel-Fatah T, Sultana R, Abbotts R, et al (2013). Clinicopathological and functional significance of XRCC1 expression in ovarian cancer. *Int J Cancer*, **132**, 2778-86.
- Aka P, Mateuca R, Buchet JP, et al (2004). Are genetic polymorphisms in OGG1, XRCC1 and XRCC3 genes predictive for the DNA strand break repair phenotype and genotoxicity in workers exposed to low dose ionising radiations? *Mutat Res*, **556**, 169-81.
- Bajpai D, Banerjee A, Pathak S, et al (2013). Decreased expression of DNA repair genes (XRCC1, ERCC1, ERCC2, and ERCC4) in squamous intraepithelial lesion and invasive squamous cell carcinoma of the cervix. *Mol Cell Biochem*, **377**, 45-53.
- Bei L, Xiao-Dong T, Yu-Fang G, et al (2015). DNA repair gene XRCC3 Thr241Met polymorphisms and lung cancer risk: a meta-analysis. *Bull Cancer*, **102**, 332-9.
- Brenneman MA, Weiss AE, Nickoloff JA, et al (2000). XRCC3 is required for efficient repair of chromosome breaks by homologous recombination. *Mutat Res*, **459**, 89-97.
- Canbay E, Agachan B, Gulluoglu M, et al (2010). Possible associations of APE1 polymorphism with susceptibility and HOGG1 polymorphism with prognosis in gastric cancer. *Anticancer Res*, **30**, 1359-64.
- Canbay E, Cakmakoglu B, Zeybek U, et al (2011). Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. *Curr Med Res Opin*, **27**, 1295-302.
- Casson AG, Zheng Z, Evans SC, et al (2005). Polymorphisms in DNA repair genes in the molecular pathogenesis of esophageal (Barrett) adenocarcinoma. *Carcinogenesis*, **26**, 1536-41.
- Cheng S, Wang L, Wang L, et al (2015). Association of XRCC3 gene rs861539 polymorphism with gastric cancer risk: evidence from a case-control study and a meta-analysis. *Int J Clin Exp Pathol*, **8**, 1911-9.
- Chiurillo MA (2014). Role of gene polymorphisms in gastric cancer and its precursor lesions: current knowledge and perspectives in Latin American countries. *World J Gastroenterol*, **20**, 4503-15.
- Christmann M, Tomacic MT, Roos WP, et al (2003). Mechanisms of human DNA repair: an update. *Toxicology*, **193**, 3-34.
- DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.
- Djansugurova LB, Perfilyeva AV, Zhunusova GS, et al (2013). The determination of genetic markers of age-related cancer pathologies in populations from Kazakhstan. *Front Genet*, **4**, 70.
- Duarte MC, Colombo J, Rossit AR, et al (2005). Polymorphisms of DNA repair genes XRCC1 and XRCC3, interaction with environmental exposure and risk of chronic gastritis and gastric cancer. *World J Gastroenterol*, **11**, 6593-600.
- Engin AB (2013). Evaluation of JWA and XRCC1 expressions in gastric cancer. *Translational Gastrointestinal Cancer*, 94-7.
- Fan J, Fan Y, Kang X, et al (2015). XRCC3 T241M polymorphism and melanoma skin cancer risk: A meta-analysis. *Oncol Lett*, **9**, 2425-9.
- Gil J, Ramsey D, Stembalska A, et al (2012). The C/A polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer. *Mol Biol Rep*, **39**, 527-34.
- Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.
- Hosking L, Lumsden S, Lewis K, et al (2004). Detection of genotyping errors by Hardy-Weinberg equilibrium testing. *Eur J Hum Genet*, **12**, 395-9.
- Huang GP, Zheng ZL, Cai L (2006). [DNA repair gene XRCC3 Thr241Met polymorphism and susceptibility to cardia and non-cardia gastric cancer: a case-control study]. *Zhonghua Liu Xing Bing Xue Za Zhi*, **27**, 420-3.
- Huang WY, Chow WH, Rothman N, et al (2005). Selected DNA repair polymorphisms and gastric cancer in Poland. *Carcinogenesis*, **26**, 1354-9.
- Improta G, Sgambato A, Bianchino G, et al (2008). Polymorphisms of the DNA repair genes XRCC1 and XRCC3 and risk of lung and colorectal cancer: a case-control study in a Southern Italian population. *Anticancer Res*, **28**, 2941-6.
- Jin MJ, Chen K, Song L, et al (2005). The association of the DNA repair gene XRCC3 Thr241Met polymorphism with susceptibility to colorectal cancer in a Chinese population. *Cancer Genet Cytogenet*, **163**, 38-43.
- Krupa R, Blasiak J (2004). An association of polymorphism of DNA repair genes XRCC1 and XRCC3 with colorectal cancer. *J Exp Clin Cancer Res*, **23**, 285-94.
- Krupa R, Sliwinski T, Wisniewska-Jarosinska M, et al (2011). Polymorphisms in RAD51, XRCC2 and XRCC3 genes of the homologous recombination repair in colorectal cancer--a case control study. *Mol Biol Rep*, **38**, 2849-54.
- Manuguerra M, Saletta F, Karagas MR, et al (2006). XRCC3 and

- XPB/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. *Am J Epidemiol*, **164**, 297-302.
- Mitchell AA, Cutler DJ, Chakravarti A (2003). Undetected genotyping errors cause apparent overtransmission of common alleles in the transmission/disequilibrium test. *Am J Hum Genet*, **72**, 598-610.
- Moghtit FZ, Aberkane MS, Le Morvan V, et al (2014). No association between XRCC3 Thr241Met and XPD Lys751Gln polymorphisms and the risk of colorectal cancer in West Algerian population: a case-control study. *Med Oncol*, **31**, 942.
- Moreno V, Gemignani F, Landi S, et al (2006). Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. *Clin Cancer Res*, **12**, 2101-8.
- Moynahan M (2010). Mitotic homologous recombination maintains genomic stability and suppresses tumorigenesis. *Nat Rev Mol Cell Biol*, **11**, 196-207.
- Mucha B, Przybyłowska-Sygut K, Dziki AJ, et al (2013). Association of Thr241Met polymorphism of XRCC3 gene with risk of colorectal cancer in the Polish population. *Pol J Pathol*, **64**, 185-90.
- Nissar S, Sameer AS, Lone TA, et al (2014). XRCC3 Thr241Met gene polymorphism and risk of colorectal cancer in Kashmir: a case control study. *Asian Pac J Cancer Prev*, **15**, 9621-5.
- Palli D, Polidoro S, D'Errico M, et al (2010). Polymorphic DNA repair and metabolic genes: a multigenic study on gastric cancer. *Mutagenesis*, **25**, 569-75.
- Pardini B, Naccarati A, Novotny J, et al (2008). DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech Republic. *Mutat Res*, **638**, 146-53.
- Redig AJ, McAllister SS (2013). Breast cancer as a systemic disease: a view of metastasis. *J Intern Med*, **274**, 113-26.
- Ruzzo A, Canestrari E, Maltese P, et al (2007). Polymorphisms in genes involved in DNA repair and metabolism of xenobiotics in individual susceptibility to sporadic diffuse gastric cancer. *Clin Chem Lab Med*, **45**, 822-8.
- Salanti G, Amoutza G, Ntzani EE, et al (2005). Hardy-Weinberg equilibrium in genetic association studies: an empirical evaluation of reporting, deviations, and power. *Eur J Hum Genet*, **13**, 840-8.
- Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, et al (2004). Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annu Rev Biochem*, **73**, 39-85.
- Shen H, Wang X, Hu Z, et al (2004). Polymorphisms of DNA repair gene XRCC3 Thr241Met and risk of gastric cancer in a Chinese population. *Cancer Lett*, **206**, 51-8.
- Skjelbred CF, Saebo M, Wallin H, et al (2006). Polymorphisms of the XRCC1, XRCC3 and XPD genes and risk of colorectal adenoma and carcinoma, in a Norwegian cohort: a case control study. *BMC Cancer*, **6**, 67.
- Song F, Khan KS, Dinnes J, et al (2002). Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. *Int J Epidemiol*, **31**, 88-95.
- Stern MC, Siegmund KD, Corral R, et al (2005). XRCC1 and XRCC3 polymorphisms and their role as effect modifiers of unsaturated fatty acids and antioxidant intake on colorectal adenomas risk. *Cancer Epidemiol Biomarkers Prev*, **14**, 609-15.
- Sultana R, Abdel-Fatah T, Abbotts R, et al (2013). Targeting XRCC1 deficiency in breast cancer for personalized therapy. *Cancer Res*, **73**, 1621-34.
- Talar-Wojnarowska R, GaSiorowska A, Olakowski M, et al (2016). Analysis of XRCC2 and XRCC3 gene polymorphisms in pancreatic cancer. *Biomedical Reports*, **4**, 236-40.
- Torre LA, Bray F, Siegel RL, et al (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, **65**, 87-108.
- Tranah GJ, Giovannucci E, Ma J, et al (2004). XRCC2 and XRCC3 polymorphisms are not associated with risk of colorectal adenoma. *Cancer Epidemiol Biomarkers Prev*, **13**, 1090-1.
- Trikalinos TA, Salanti G, Khoury MJ, et al (2006). Impact of violations and deviations in Hardy-Weinberg equilibrium on postulated gene-disease associations. *Am J Epidemiol*, **163**, 300-9.
- Wang J, Zhao Y, Jiang J, et al (2010). Polymorphisms in DNA repair genes XRCC1, XRCC3 and XPD, and colorectal cancer risk: a case-control study in an Indian population. *J Cancer Res Clin Oncol*, **136**, 1517-25.
- Wu D, Jiang H, Yu H, et al (2013). Significant association between XRCC3 C241T polymorphism and increased risk of hepatocellular carcinoma: a meta-analysis. *Tumour Biol*, **34**, 3865-9.
- Xuan G, Hui Y, Fang H (2015). The association of XRCC3 Thr241Met genetic variant with risk of prostate cancer: a meta-analysis. *Afr Health Sci*, **15**, 117-22.
- Yang CH, Lin YD, Yen CY, et al (2015). A systematic gene-gene and gene-environment interaction analysis of DNA repair genes XRCC1, XRCC2, XRCC3, XRCC4, and oral cancer risk. *OmicS*, **19**, 238-47.
- Ye W, Kumar R, Bacova G, et al (2006). The XPD 751Gln allele is associated with an increased risk for esophageal adenocarcinoma: a population-based case-control study in Sweden. *Carcinogenesis*, **27**, 1835-41.
- Yeh CC, Sung FC, Tang R, et al (2005). Polymorphisms of the XRCC1, XRCC3, & XPD genes, and colorectal cancer risk: a case-control study in Taiwan. *BMC Cancer*, **5**, 12.
- Zhao L, Long XD, Yao JG, et al (2011). Genetic polymorphism of XRCC3 codon 241 and Helicobacter pylori infection-related gastric antrum adenocarcinoma in Guangxi Population, China: a hospital-based case-control study. *Cancer Epidemiol*, **35**, 564-8.
- Zhao Y, Deng X, Wang Z, et al (2012). Genetic polymorphisms of DNA repair genes XRCC1 and XRCC3 and risk of colorectal cancer in Chinese population. *Asian Pac J Cancer Prev*, **13**, 665-9.