Asian Pac J Cancer Prev, 18 (1), 263-270

Introduction

Thyroid cancer (TC) is the most common malignancy of the endocrine system in human, which accounts for nearly 3.8% of newly diagnosed cancers annually (Visciano et al., 2015; SEER, 2016). According to the last reports, the incidence of TC is the third fastest rising cancer diagnosis in the USA, which its incidence is rapidly increasing from 7.6 to 14.9 per 100,000 in a decade (between 2000 and 2012) (De Lellis, 2004; Morris et al., 2013).

Thyroid malignancies are categorized into several subtypes including follicular (FTC), papillary (PTC), medullary (MTC), undifferentiated, Hurthle cell and a subgroup of rare morphologies such as mucoepidermoid, oncocytic carcinomas and squamous (De Lellis, 2004; Schneider et al., 2013). In addition, TC could be categorized as either sporadic or familial, which only 5-7% of TC cases are familial (Nagy and Ringel, 2015; Haugen et al. 2016). According to the studies, a TC risk factors is very complex, simply is anything that causes to increase the susceptibility of TC. However, a combination of genetic and environmental factors (predominantly including: age, gender, ethnicity, family history, radiation exposure and iodine intake) likely contributes to the development of TC. The underlying genetics cause of TC varies based on its histology. The genetic cause of MTC is well identified. Hereditary MTC is caused by mutations in the RET proto-oncogene that cause multiple endocrine neoplasia 2A (MEN2A) syndrome characterized by MTC, parathyroid hyperplasia and pheochromocytoma, and multiple endocrine neoplasia 2A (MEN2B) syndrome characterized by MTC, pheochromocytoma, mucosal neuromas, and tall, asthenic habitus. However, the genetic causes of familial non-medullary thyroid carcinoma (FNMTc) are less understood (Morrison et al., 2009;
Associations between X-ray cross complementary group 1 protein (XRCC1) gene polymorphisms and multiple cancers have already been reported. Three major polymorphisms of the XRCC1 gene have been identified at codon 194 (rs1799782, C > T substitution at position 26304, exon 6, Arg to Trp), at codon 280 (rs25489, C > T substitution at position 43552260, exon 9, Arg to His), and at codon 399 (rs25487, G > A substitution at position 28152, exon 10, Arg to Gln) (Garcia et al. 2011; Santos et al. 2012; and Halkova et al. 2016). Recently, several studies have demonstrated that the polymorphism of XRCC1 gene was associated with the TC. However, these results were inconsistent. And for the relatively small sample size of the published studies, it is necessary to accumulate data from different studies to provide evidence on the association of XRCC1 gene polymorphisms with risk of TC. Moreover, in recent years more studies with large sample have been published. Therefore, we performed a meta-analysis to further estimate the overall risk of TC caused by the XRCC1 rs1799782 (Arg194Trp), rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms in patients.

Materials and Methods

Literature search strategy

The databases include Pubmed, Google Scholar, MEDLINE, ISI Web of Science and SCOPUS database up to January 5th, 2017 to identify all relevant articles on the subject. We have used various combinations of keywords to screen for potentially relevant studies, including “Thyroid cancer”; “DNA repair gene”, “XRCC1” or “XRCC1 DNA repair protein”; “Genetic polymorphism” or “single nucleotide polymorphism” or “polymorphism” or “SNP” or “mutation” or “variation”, with restricted to English language and only published studies with full-text articles available. All eligible studies were retrieved, then we also manually searched the references of included studies to identify more potentially relevant articles.

Including and Excluding Criteria

Studies included to the meta-analysis had to be consistent with the following criteria: (1) only studied on human; (2) only the case–control studies and cohorts, (3) studies have evaluated the XRCC1 rs1799782 (Arg194Trp), rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms and TC risk, and (4) sufficient published data (specially frequency of the genotypes) for estimating an odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were as follows: (1) not on human, (2) not cancer research (3) only on patients, (4) duplicate of previous papers, and (5) have not sufficient data about frequency of genotypes.

Data extraction

Two authors carefully and independently were extracted the data from all eligible publications using a structured table. The following items were considered: first author’s name, year of publication, ethnicity, and country of study population, number of cases and controls, genotype number in cases and controls, and p-value for Hardy-Weinberg equilibrium (HWE). The subject’s ethnicities were categorized as Caucasian, Asian, or African. Disagreements were resolved in consultation with the third reviewer.

Statistical Analysis

An ethical approval was not necessary needed as this is a meta-analysis based on previous studies. The strength of association between XCCR1 gene polymorphism and TC risk was tested by odds ratios (ORs) with 95% confidence intervals (CIs) using Z test. The summarized ORs were performed for rs1799782 (allele model: T vs. C, heterozygote model: TC vs. CC, homozygote model: TT vs. CC, dominant model: TT+TC vs. CC, and recessive model: TT vs. TC+CC), rs25487 (allele model: A vs. G, heterozygote model: AG vs. GG, homozygote model: AA vs. GG, dominant model: AA+AG vs. GG, and recessive model: AA vs. AG+GG), and rs25489 (allele model: A vs. G, heterozygote model: AG vs. GG, homozygote model: AA vs. GG, dominant model: AA+AG vs. GG, and recessive model: AA vs. AG+GG) polymorphisms.

The Chi-squared Q-test and I2 statistics were used to identify the heterogeneity among included publications (Zintzaras et al., 2005). The fixed-effects model (the Mantel–Haenszel method) is used when the effects are assumed to be homogenous (P ≥ 0.1 or I2 < 50%). Otherwise, the random effects model (the DerSimonian and Laird method) is used when they are heterogeneous (P < 0.1 or I2 ≥ 50%). Subgroup analyses by ethnicity was also performed to identify the substantial heterogeneity. Additionally, the effect of each single study on the overall estimate was determined by application of one-way sensitivity analysis. The sensitivity analysis was performed by omitting 1 study at a time. To examine the potential publication bias in the meta analysis, Begg’s funnel plot and Egger’s test were used; P<0.05 indicated that the result was statistically significant (Song et al., 1998; Peters et al., 2006). All the statistical analyses were performed by comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA). Two-sided P values < 0.05 were considered statistically significant.

Results

Characteristics of the published studies

Initially, we have identified 39 publications, among which 18 irrelevant articles were excluded. Thus, 21 publications were eligible. Among these publications, six publications were excluded because they were review articles and other polymorphisms of XRC1 gene, and also one paper was excluded because of it subject overlapped with other included study. As seen in Tables 1-3, 14 case–control studies were selected in the final meta-analysis, including 8 case–control studies with a total of 1,672 cases and 2,805 controls concerning the XRC1 rs1799782 polymorphism (Table 1), 14 studies with a total of 2,506 cases and 5,180 controls for XRC1 rs25487 polymorphism (Table 2), and 11 studies with a total of 2,197 cases and 4,761 controls for XRC1 rs25489 polymorphism (Table 3). The article performed

Nagy and Ringel, 2015).
| First author | Country (Ethnicity) | Case/Control | Cases | Controls |
|--------------|--------------------|--------------|-------|----------|
| Chiang et al. 2008 | China (Asian) | 283/469 | 127 | 119 |
| Ho et al. 2009 | USA (Caucasian) | 251/503 | 203 | 45 |
| Esfahani et al. 2011 | Iran (Asian) | 157/187 | 136 | 18 |
| Ryu et al. 2011 | Korea (Asian) | 111/100 | 59 | 43 |
| Santos et al. 2012 | Portugal (Caucasian) | 109/217 | 98 | 8 |
| Yan et al. 2015 | China (Asian) | 276/403 | 124 | 112 |
| Wang et al. 2015 | China (Asian) | 276/552 | 181 | 52 |
| Halkova et al. 2016 | Czech (Caucasian) | 209/374 | 178 | 31 |

**Table 1. Characteristics of Studies Included in the Meta Analysis of XRCC1 rs1799782 Polymorphism and TC**
by Akulevich et al. was separated as 2 studies for they evaluated different Russian and Belarus population. The year of publication ranged between 2008 and 2016. There were 7 studies of Caucasian descendants (Sigurdsson et al., 2009; Akulevich et al., 2009; Ho et al., 2009; Garcia et al., 2011; Santos et al. 2012; and Halkova et al. 2016) and 7 studies of Asian descendants (Zhu et al., 2004; Chiang et al., 2008; Siraj et al. 2008; Esfahani et al. 2011; Ryu et al., 2011; Wang et al., 2015 and Yan et al., 2015). The populations came from different countries, including China, India, Iran, Brazil, Russia, Belarus, Korea, Spain, Portugal, Czech and Kingdom of Saudi Arabia (KSA). Genotype distributions in the controls of 3 publication (predominantly, the publication of Wang et al., 2015) were not in agreement with HWE.

### Meta-analysis

#### XRCC1 rs1799782 Polymorphism

Table 4 listed the main results of the meta-analysis of XRCC1 rs1799782 (Arg194Trp) polymorphism and TC risk (Figure 1A). When all the eligible studies were pooled into the meta-analysis of XRCC1 Arg194Trp polymorphism, significantly increased risk of TC was observed in homozygote (TT vs. CC: OR = 1.815, 95% CI = 1.115-2.953, p= 0.016) and recessive (TT vs. TC+CC: OR = 1.854, 95% CI = 1.433-2.399, p< 0.001). In the subgroup analysis by ethnicity, significantly increased TC risk was observed in Asians only under recessive model (TT vs. TC+CC: OR = 1.816, 95% CI = 1.398-2.358, p< 0.001) by using fixed-effect model, but not among Caucasians.

#### XRCC1 rs25487 Polymorphism

The main results of XRCC1 rs25487 (Arg399Gln) meta-analysis were presented in Table 4. The odds ratios (OR) and 95% confidence intervals (CI) were calculated for the comparison of genotype frequencies between cases and controls. The meta-analysis revealed a statistically significant increase in risk for the TT vs. CC genotype comparison (OR = 1.854, 95% CI = 1.433-2.399, p< 0.001) and the TT vs. TC+CC genotype comparison (OR = 1.816, 95% CI = 1.398-2.358, p< 0.001). The subgroup analysis showed a significant increase in risk among Asians only under the recessive model (OR = 1.816, 95% CI = 1.398-2.358, p< 0.001), but not among Caucasians.

### Table 3. Characteristics of Studies Included in the Meta-Analysis of XRCC1 rs25489 Polymorphism and TC

| Study | First author | Country (Ethnicity) | Case/Control | Genotype | Allele |
|-------|--------------|---------------------|--------------|----------|--------|
| Chiang et al. 2008 | China (Asian) | 283/469 | GG | G |
| Ho et al. 2009 | USA (Caucasian) | 251/503 | GA | A |
| Garcia et al. 2011 | Spain (Caucasian) | 276/552 | AA | A |
| Akulevich et al. 2009 | Russia (Caucasian) | 132/398 | GG | G |
| Sigurdsson et al. 2009 | Iceland (Caucasian) | 25/896 | GA | A |
| Halkova et al. 2016 | Czech (Caucasian) | 209/374 | AA | A |
| Akulevich et al. 2009 | Belarus (Caucasian) | 123/195 | GG | G |
| Siraj et al. 2008 | India (Asian) | 50/299 | GA | A |
| Chiang et al. 2008 | China (Asian) | 283/469 | AA | A |
| Esfahani et al. 2011 | Iran (Asian) | 170/193 | GG | G |
| Halkova et al. 2016 | Czech (Caucasian) | 209/374 | GA | A |
| Sigurdsson et al. 2009 | Iceland (Caucasian) | 25/896 | GA | A |
| Ho et al. 2009 | USA (Caucasian) | 251/503 | AA | A |
| Garcia et al. 2011 | Spain (Caucasian) | 276/552 | GG | G |
| Akulevich et al. 2009 | Russia (Caucasian) | 132/398 | GG | G |
| Siraj et al. 2008 | India (Asian) | 50/299 | GA | A |
| Chiang et al. 2008 | China (Asian) | 283/469 | AA | A |

### Figure 1. Forest Plots Showed Significant Association between XRCC1 Polymorphisms and TC Risk.

A: XRCC1 rs1799782 polymorphism (Allele model: T vs. C) and B: XRCC1 rs25487 polymorphism (Homzygote model: AA vs. GG)
Association of XRCC1 Gene Polymorphisms with TC polymorphism meta-analysis are listed in Table 5. Overall, there was no evidence of an association between TC risk and the XRCC1 rs25487 polymorphism in the different genetic models when all the eligible studies were pooled into the meta-analysis (A vs. G: OR = 1.131, 95% CI = 0.829-1.543, p = 0.136; AG vs. GG: OR = 0.903, 95% CI = 0.811-1.006, p = 0.063; AA vs. GG: OR = 0.892, 95% CI = 0.690-1.153, p = 0.382, Figure 1B; AA+AG vs. GG: OR = 0.880, 95% CI = 0.766-1.012, p = 0.073; and AA vs. AG+GG: OR = 0.940, 95% CI = 0.797-1.109, p = 0.462). For ethnicity, the results showed XRCC1 rs25487 polymorphism was associated with increased risk of TC among Caucasians under allele genetic comparison (A vs. G: OR = 0.882, 95% CI = 0.794-0.979, p = 0.136) and dominant genetic comparison (AA+AG vs. GG: OR = 0.838, 95% CI = 0.728-0.965, p = 0.014; Table 2), but not among Asians.

**XRCC1 rs25489 Polymorphism**

As shown in Table 6, no significant association was detected between the XRCC1 rs25489 (Arg280His) polymorphism and TC risk under all five genetic models (A vs. G: OR = 1.044, 95% CI = 0.848-1.263, P = 0.507; AG vs. GG: OR = 0.984, 95% CI = 0.948-1.141, P = 0.836; AA vs. GG: OR = 1.154, 95% CI = 0.803-1.658, P = 0.439, AA + AG vs. GG: OR = 1.023, 95% CI = 0.887-1.179, P = 0.758 and AA vs. AG+GG: OR = 1.206, 95% CI = 0.846-1.719, P = 0.300). Furthermore, when stratified by ethnicity, there were no associations between XRCC1 rs25489 polymorphism and TC risk under all five genetic models in both Asians and Caucasians.

**Test of heterogeneity**

For XRCC1 rs1799782 (Arg194Trp) polymorphism, when we have pooled the data a significant heterogeneity observed in heterozygote (I² = 64.0%, P_H = 0.007), homozygote (I² = 51.90%, P_H = 0.042) and dominant (I² = 77.9%, P_H = 0.007) genetic models (Table 4). After

| Genetic model | Type of model | Heterogeneity | Odds ratio |
|---------------|---------------|---------------|------------|
|               |               | F (%)         | P_H        | OR          | 95% CI     | P_OH       |
| Overall       |               |               |            |             |            |            |
| T vs. C       | Random        | 77.5          | <0.001     | 1.276       | 0.980-1.660| 0.07       |
| TC vs. CC     | Random        | 64.0          | 0.007      | 1.122       | 0.856-1.470| 0.406      |
| TT vs. CC     | Random        | 51.9          | 0.042      | 1.815       | 1.115-2.953| 0.016      |
| TT+TC vs. CC  | Random        | 77.9          | <0.001     | 1.232       | 0.895-1.696| 0.201      |
| TT vs. TC+CC  | Fixed         | 37.8          | 0.128      | 1.854       | 1.433-2.399| <0.001     |
| Ethnicity     |               |               |            |             |            |            |
| Caucasian     |               |               |            |             |            |            |
| T vs. C       | Fixed         | 29.1          | 0.244      | 1.202       | 0.919-1.572| 0.179      |
| TC vs. CC     | Fixed         | 19.1          | 0.29       | 1.092       | 0.782-1.527| 0.605      |
| TT vs. CC     | Fixed         | 0.0           | 0.389      | 4.031       | 0.828-19.620| 0.084      |
| TT+TC vs. CC  | Fixed         | 21.3          | 0.281      | 1.161       | 0.872-1.544| 0.307      |
| TT vs. TC+CC  | Fixed         | 0.0           | 0.397      | 3.956       | 0.813-19.246| 0.088      |
| Asian         |               |               |            |             |            |            |
| T vs. C       | Random        | 84.9          | <0.001     | 1.323       | 0.932-1.879| 0.117      |
| TC vs. CC     | Random        | 75.8          | 0.002      | 1.141       | 0.774-1.683| 0.504      |
| TT vs. CC     | Random        | 66.1          | 0.019      | 1.681       | 0.995-2.838| 0.052      |
| TT+TC vs. CC  | Random        | 85.2          | <0.001     | 1.289       | 0.823-2.020| 0.267      |
| TT vs. TC+CC  | Fixed         | 52.9          | 0.075      | 1.816       | 1.398-2.358| <0.001     |

Table 4. Meta-Analysis of the Association of XRCC1 rs1799782 Polymorphism with TC

Figure 2. Begg’s Funnel Plots of XRCC1 Gene Polymorphisms and TC Risk for Publication Bias Test. Each Point Represents a Separate Study for the Indicated Association. A: XRCC1 rs1799782 polymorphism (Allele model: T vs. C) and B: XRCC1 rs25487 polymorphism (Dominant model: AA+AG vs. GG)
subjects stratified by ethnicity, the heterogeneity obviously disappeared in the Caucasians (heterozygote: $I^2=19.13\%$, $P_H=0.290$; homozygote: $I^2=0.0\%$, $P_H=0.389$ and dominant: $I^2=21.3\%$, $P_H=0.281$). However, heterogeneity was still present among the Asians (heterozygote: $I^2=75.8\%$, $P_H=0.002$; homozygote: $I^2=66.1\%$, $P_H=0.019$ and dominant: $I^2=85.2\%$, $P_H<0.001$). Therefore, the observed heterogeneity between the included studies might be due to the ethnicities.

**Sensitivity Analysis**

We have performed sensitivity analysis by omitting

| Ethnicity | Genetic model | Type of model | Heterogeneity | Odds ratio |
|-----------|---------------|---------------|---------------|------------|
|           | Overall       |               | $I^2$ (%)      | $P_H$      | OR          | 95% CI      | $P_{OR}$   |
|           | A vs. G       | Random        | 93.3          | <0.001     | 1.131       | 0.829-1.543 | 0.136      |
|           | AG vs. GG     | Fixed         | 14.4          | 0.296      | 0.903       | 0.811-1.006 | 0.063      |
|           | AA vs. GG     | Random        | 48.4          | 0.022      | 0.892       | 0.690-1.153 | 0.382      |
|           | AA+AG vs. GG  | Random        | 42.3          | 0.048      | 0.88        | 0.766-1.012 | 0.073      |
|           | AA vs. AG+GG  | Fixed         | 33.0          | 0.111      | 0.94        | 0.797-1.109 | 0.462      |

| Ethnicity | Genetic model | Type of model | Heterogeneity | Odds ratio |
|-----------|---------------|---------------|---------------|------------|
|           | Ethnicity     |               | $I^2$ (%)      | $P_H$      | OR          | 95% CI      | $P_{OR}$   |
|           | Caucasian     |               | $I^2$ (%)      | $P_H$      | OR          | 95% CI      | $P_{OR}$   |
|           | A vs. G       | Fixed         | 0.0           | 0.429      | 0.882       | 0.794-0.979 | 0.018      |
|           | AG vs. GG     | Fixed         | 8.6           | 0.363      | 0.861       | 0.742-1.001 | 0.051      |
|           | AA vs. GG     | Fixed         | 1.4           | 0.414      | 0.835       | 0.663-1.051 | 0.124      |
|           | AA+AG vs. GG  | Fixed         | 0.0           | 0.541      | 0.838       | 0.728-0.965 | 0.014      |
|           | AA vs. AG+GG  | Fixed         | 6.8           | 0.376      | 0.89        | 0.716-1.106 | 0.249      |
|           | Asian         |               | $I^2$ (%)      | $P_H$      | OR          | 95% CI      | $P_{OR}$   |
|           | A vs. G       | Random        | 96.2          | <0.001     | 1.435       | 0.762-2.699 | 0.263      |
|           | AG vs. GG     | Fixed         | 23.3          | 0.251      | 0.95        | 0.814-1.108 | 0.512      |
|           | AA vs. GG     | Random        | 67.8          | 0.005      | 0.982       | 0.591-1.631 | 0.944      |
|           | AA+AG vs. GG  | Random        | 62.9          | 0.013      | 0.927       | 0.719-1.195 | 0.559      |
|           | AA vs. AG+GG  | Fixed         | 50.8          | 0.058      | 0.906       | 0.711-1.154 | 0.423      |

Table 5. Meta-Analysis of the Association of XRCC1 rs25487 Polymorphism with TC.
The XRCC1 plays an important role in the base excision repair (BER) pathway and interacts with DNA polymerase Beta (POLB), Poly ADP ribose Polymerase (PARP) and DNA ligase III (Zhang et al., 2006). The XRCC1 gene (Gene ID 37414; OMIM 21171001 and 21174504), is 33 kb long and located at chromosome 19q13.3, consists of 17 exons, and encodes a 2.2 kb transcript, which produces an enzyme called X-ray cross-complementing group 1 that is involved in base excision repair pathway (Wang et al., 2015). XRCC1 polymorphisms disrupt the interaction of XRCC1 with other enzymatic proteins and consequently overwhelm DNA repair capacity, which leads to genetic instability and carcinogenesis (Forat Yazdi et al., 2014).

In the present meta-analysis, we have evaluated the association between three most common XRCC1 gene polymorphisms including rs1799782 (Arg194Trp), rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms and risk of TC. To the best of our knowledge, this is the most comprehensive meta-analysis of the relationship between XRCC1 polymorphisms and the risk of TC. We have found the absence of rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms are significantly associated with an increased risk of TC, while the rs1799782 (Arg194Trp) polymorphism significantly associated with development of TC in the overall analysis. However, there was a significant association between XRCC1 rs25487 polymorphism risk of TC among Caucasians under allele genetic comparison (A vs. G: OR = 0.882, 95% CI = 0.794–0.979, p = 0.136) and dominant genetic comparison (AA+AG vs. GG: OR = 0.838, 95% CI = 0.728–0.965, p = 0.014). Moreover, the T allele of XRCC1 rs1799782 and A allele of XRCC1 rs25487 may be as a marker for increased susceptibility to TC. Similarly, in a meta-analysis Qian et al. have not an association between XRCC1 rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms and TC risk in the overall analysis. However, they have not found such association for third polymorphism with risk of TC, too (Qian et al., 2012). The contribution of rs1799782 (Arg194Trp) polymorphism in development of TC was identified by Zhao et al. in meta-analysis of five studies, comprising 911 patients and 1476 controls, recently. However, inconsistent with our results, Li et al., (2014) and Wu et al., (2014) in the two different meta-analysis of 8 and 10 studies not found a significant association between TC risk and the three polymorphisms of XRCC1 gene in all genetic Models. Due to the difference in genetic backgrounds and the environment in which the subjects were lived, we have performed a subgroup analysis by ethnicity, however we found a significant association between rs1799782 and rs25487 polymorphism and TC risk in Asians and Caucasians, respectively.

Interestingly, in meta-analysis Yan et al., (2015) based on previous studies quoted that the XRCC1 rs25489 polymorphism is related to different cancers in Asian populations, including gastric cancer, bladder cancer, lung cancer, and colorectal cancer. While, this meta-analysis results and three previous meta-analysis by Qian et al., (2012) Li et al., (2014) and Wu et al., (2014) there was not such association between XRCC1 rs25489 polymorphism and risk of TC. Therefore, it seems the A allele of XRCC1 rs25489 may not be as a marker for increased susceptibility to TC.

To the best of our knowledge, the current meta-analysis made a more convincing and detailed evaluation than the previous meta-analysis did. However, there are some limitations should be also recognized in this meta-analysis. First, the included studies were restricted to just English literature, which might bias the results. Second, severe TC is a multifactorial condition that results from complex interactions between genes and environmental factors such as age, gender, ethnicity, family history, radiation exposure and iodine intake. Therefore, we might fail to receive the true associations when we only considered those three XRCC1 gene polymorphisms, but neglect the role of other genetic, polymorphisms, and environmental factors in TC. Finally, the sample size of subgroup analysis by ethnicity was limited, which may causes to reduce the power of analyses. Therefore, further studies with large sample sizes are required to gain more precise results.

In summary, the results of the meta-analysis suggest an increased risk role of the XRCC1 rs1799782 and rs25487 polymorphisms in TC development. However, there was no association between the XRCC1 rs25489 polymorphisms and TC risk. More studies with a larger sample size is needed to further evaluate the association XRCC1 gene polymorphisms and TC risk.

References

Akulevich NM, Saenko VA, Rogounovitch TI, et al (2009). Polymorphisms of DNA damage response genes in radiationrelated and sporadic papillary thyroid carcinoma. *Endocr Relat Cancer*, 16, 491–503

Chiang FY, Wu CW, Hsiao PJ, et al (2008). Association between polymorphisms in DNA base excision repair genes XRCC1, APE1, and ADPRT and differentiated thyroid carcinoma. *Clin Cancer Res*, 14, 5919–24.

DeLellis RA (2004). Pathology of genetics and tumours of endocrine organs. Lyon: IARC Press.

Fard-Esfahani P, Fard-Esfahani A, Fayaz S, et al (2011). Association of Arg194Trp, Arg280His and Arg399Gln polymorphisms in X-ray repair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. *Iran Biomed J*, 15, 73-8.

Forat-Yazdi M, Gholi-Nataj M, Neamtazadeh H, et al (2015). Association of XRCC1 Arg399Gln polymorphism with colorectal cancer risk: A HuGE meta-analysis of 35 studies. *Asian Pac J Cancer Prev*, 16, 3285-91.
Garcia-Quispes WA, Perez-Machado G, Akdi A, et al (2011). Association studies of OGG1, XRCC1, XRCC2 and XRCC3 polymorphisms with differentiated thyroid carcinoma. *Mutat Res*, 67, 709–10.

Halkova T, Dvorakova S, Sykorova V, et al (2016). Polymorphisms in selected DNA repair genes and cell cycle regulating genes involved in the risk of papillary thyroid carcinoma. *Cancer Biomark*, 17, 97-106.

Haugen BR, Alexander EK, Bible KC, et al (2016). 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid*, 26, 1-133.

Ho T, Li G, Lu J, et al (2009). Association of XRCC1 polymorphisms and risk of differentiated thyroid carcinoma: a case-control analysis. *Thyroid*, 19, 129–35.

Kanavos P (2006). The rising burden of cancer in the developing world. *Ann Oncol*, 17, 15-23.

Li C, Xiang X, Zhou Y (2014). No association between XRCC1 genetic polymorphisms and differentiated thyroid carcinoma risk: a meta-analysis. *Mol Biol Rep*, 41, 7613-21.

Morrison PJ, Atkinson AB (2009). Genetic aspects of familial thyroid cancer. *Oncologist*, 14, 571-77.

Nagy R, Ringel MD (2015). Genetic predisposition for nonmedullary thyroid cancer. *Horm Cancer*, 6, 13-20.

Morris LG, Sikora AG, Tosteson TD, et al (2013). The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid*, 23, 885-91.

Namazi A, Abedinzadeh M, Nourbaksh P, et al (2015). Association between the XRCC3 Thr241Met polymorphism and risk of colorectal cancer: a meta-analysis of 5,193 cases and 6,645 controls. *Asian Pac J Cancer Prev*, 16, 2263-8.

Peters JL, Sutton AJ, Jones DR, et al (2006). Comparison of two methods to detect publication bias in meta-analysis. *JAMA*, 295, 676–80.

Qian K, Liu K, Xu F, et al (2012). X-Ray repair cross-complementing group 1(XRCC1) genetic polymorphisms and thyroid carcinoma risk: a meta-analysis. *Asian Pac J Cancer Prev*, 13, 6385-90.

Ryu RA, Tac K, Min HJ, et al (2011). XRCC1 polymorphisms and risk of papillary thyroid carcinoma in a Korean sample. *J Korean Med Sci*, 26, 991–95.

Santos LS, Branco SC, Silva SN, et al (2012). Polymorphisms in base excision repair genes and thyroid cancer risk. *Oncol Rep*, 28, 1859–68.

Schneider D, Chen H (2013). New developments in the diagnosis and treatment of thyroid cancer. *CA Cancer J Clin*, 63, 373-94.

Sigurdson AJ, Land CE, Bhatti P, et al (2009). Thyroid nodules, polymorphic variants in DNA repair and RET-related genes, and interaction with ionizing radiation exposure from nuclear tests in Kazakhstan. *Radiat Res*, 171, 77–88

Siraj AK, Al-Rasheed M, Ibrahim M, et al (2008). RAD52 polymorphisms contribute to the development of papillary thyroid cancer susceptibility in Middle Eastern population. *J Endocrinol Invest*, 31, 893–9.

Song F, Gilbody S (1998). Bias in meta-analysis detected by a simple, graphical test. Increase in studies of publication bias coincided with increasing use of meta-analysis. *BMJ*, 316, 471.

Surveillance, Epidemiology, and End Results Program. (n.d.). Latest Retrieved January 4, 2016, from http://seer.cancer.gov/.

Visciano C, Prevete N, Liotti F, et al (2015). Tumor-associated mast cells in thyroid cancer. *Int J Endocrinol*, 2015, 705169.

Wang C, Ai Z (2014). Association of XRCC1 polymorphisms with thyroid cancer risk. *Tumor Biol*, 35, 4791-97.

Wu FF, He XF, Shen HW, et al (2014). Association between the XRCC1 polymorphisms and thyroid cancer risk: a meta-analysis from case-control studies. *PLoS One*, 9, e87764.

Yan L, Li Q, Li X, et al (2016). Association studies between XRCC1, XRCC2, XRCC3 polymorphisms and differentiated thyroid carcinoma. *Cell Physiol Biochem*, 38, 1075-84.

Yan J, Wang X, Tao H, et al (2015). Meta-analysis of the relationship between XRCC1-Arg399Gln and Arg280His polymorphisms and the risk of prostate cancer. *Sci Rep*, 5, 9905.

Zhao J, Tan X, Zhao M, et al (2016). Association between the X-ray repair cross-complementing group 1 Arg194Trp polymorphism and thyroid carcinoma susceptibility: A meta-analysis. *Genet Mol Res*, 15.

Zhu QX, Bian JC, Shen Q, et al (2004). Genetic polymorphisms in X-ray repair cross-complementing gene 1 and susceptibility to papillary thyroid carcinoma. *Zhonghua Liu Xing Bing Xue Za Zhi*, 25, 702–5.

Zintzaras E, Ioannidis JP (2005). HEGESMA: genome search meta-analysis and heterogeneity testing. *Bioinformatics*, 21, 3672–73