Association Between X-Ray Cross-Complementing Group 3 (XRCC3) Thr241Met Polymorphism and Risk of Thyroid Cancer: A Meta-Analysis

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Background: The X-ray cross-complementing group 3 (XRCC3) gene encodes a protein that plays an important role in homologous recombination repair (HRR) of DNA double-strand break (DSB). Increasing attention has been drawn to the association of XRCC3 T241M polymorphism with various types of human cancers. In this study, a meta-analysis was performed to investigate whether there is an association between XRCC3 T241M polymorphism and thyroid cancer risk.

Material/Methods: A comprehensive search was conducted and a total of 8 studies that covered 963 thyroid cancer cases and 1942 controls were included in this analysis. The meta-analysis was performed on both overall database and 2 ethnic subgroups (Caucasian and Asian). The fixed-effects model was used to calculate odds ratio (OR) with 95% confidence intervals (CIs). The publication bias was evaluated using Begg's funnel plots and Egger's test.

Results: A positive association between XRCC3 T241M polymorphism and thyroid cancer risk was found by the analyses of the overall database using both recessive model (OR=1.40, 95% CI=1.08–1.81, P=0.012) and homozygote comparison (OR=1.41, 95% CI=1.07–1.86, P=0.015), but not by that using the dominant model (OR=1.12, 95% CI=0.95–1.33, P=0.18). However, no significant association of XRCC3 Thr241Met polymorphism with the risk of thyroid cancer was found in individual ethnic subgroups.

Conclusions: We conclude that the XRCC3 Thr241Met polymorphism is associated with an increased risk of thyroid cancer in the overall population, while no significant association was observed in individual ethnic subgroups due to limited population size.

MeSH Keywords: Amplified Fragment Length Polymorphism Analysis • Meta-Analysis as Topic • Parathyroid Neoplasms

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 Thyroid cancer is the most common endocrine malignancy, and its incidence has been increasing in the past 3 decades worldwide [1,2]. It is suspected that environmental factors might play an important role in the development of human cancers under a predisposing genetic background (Hum Reprod. Epub 2015 July 3) [3]. Thyroid cancer is a typical human cancer in which critical genes are frequently mutated [4–6]. In terms of the environmental factors, exposure to ionizing radiation is currently the only well-established risk factor for thyroid cancer, given that the thyroid may have more chances of exposure to irradiation than other tissues due to its position in the body and its ability to concentrate iodine [7,8]. Double-strand breaks (DSBs) of DNA can occur as a result of endogenous metabolic disorders or from exogenous stress such as ionizing radiation, and must be repaired to preserve chromosomal integrity [9]. Furthermore, a reduced capacity of DNA repair can cause genetic instability that contributes to tumorigenesis, thus genes involved in DNA repair have been proposed as candidate cancer susceptibility genes. X-ray cross-complementing group 3 (XRCC3) localizes on human chromosome 14q32.3 and encodes a protein that participates in homologous recombination repair (HRR) of DNA DSBs [10]. Therefore, XRCC3 plays an important role in protecting against DNA mutations and maintaining genomic integrity. Among various single-nucleotide polymorphisms (SNPs) of the XRCC3 gene, Thr241Met, with a Thr-to-Met amino acid conversion, is caused by a C-to-T nucleotide change at codon 241 [11].

During the last decade, various individual studies have been carried out to examine the association between XRCC3 Thr241Met polymorphism and thyroid cancer risk, but the results from these studies were controversial [12–16]. In the present study, we performed a comprehensive meta-analysis that covers 8 studies including 963 tumor cases and 1942 controls, to clarify whether there is an association between XRCC3 Thr241Met and thyroid cancer risk.

**Material and Methods**

**Literature search**

Published studies were searched in NCBI Global Cross-database, including PubMed, PubMed Central, Gene, and Google Scholar, with the following key words: “XRCC3 Thr241Met polymorphism”, “X-ray cross-complementing group 3 polymorphism”, “XRCC3 C18067T polymorphism”, “rs861539” and “thyroid cancer”. Publication language was not restricted in this search as long as the genetic and cancer risk information were retrievable. Reference lists of articles retained for review were examined manually to further identify potentially relevant studies. Unpublished studies were not considered.

**Inclusion and exclusion criteria**

Abstracts of all retrieved studies were reviewed. Studies that meet the following criteria were included: (1) Addressing the association between XRCC3 T241M polymorphism and thyroid cancer risk; (2) Having a case-control study design; and (3) Providing sufficient data for calculating odds ratios (OR) and 95% confidence interval (CI). Studies were excluded for any of the following: (1) Books and other literature that were not case-control studies; and (2) Articles without control group information or without the retrievable original data. For the studies that were covered in different articles, only the ones showing the most extensive results were included in our study. All studies covered in this meta-analysis were determined to be valid using the Newcastle-Ottawa Scale (NOS) (Wells GA, Shea B, O’Connell D, et al.).

**Statistical analysis**

The statistical analysis was conducted using STATA 12.0 (Stata Corp LP, College Station, TX, USA). P-value <0.05 was considered as statistically significant. In addition to the overall database, 2 ethnic subgroups that covered studies from either Caucasians or Asians were created. Odds ratios (ORs) were calculated under the following 3 models with 95% confidence intervals: the dominant model (TM+MM vs. TT), in which the distribution of TM+MM genotype referred to TT genotype was investigated; the recessive model (MM vs. TM+TT), in which the distribution of MM genotype referred to TM+TT genotype was assessed; and the homozygote comparison (MM vs. TT), in which TT was used as reference genotype and the distribution of MM genotype was investigated. For each study, numbers of 3 genotypes in case and control groups were used as pooled data. The heterogeneity among different studies was tested using I² index (I² <25%, no heterogeneity; I²=25–50%, moderate heterogeneity; I² >50%, large or extreme heterogeneity) [17]. In this meta-analysis, 8 studies were included in the final analysis of the association between XRCC3 Thr241Met polymorphism and thyroid cancer risk. For each analysis, because of the small size of the dataset, the M-H fixed-effects model was used first to test the study heterogeneity, and different models were then chosen based on the test result. Forest plots were generated to summarize the results. Publication bias was evaluated with Begg’s funnel plots based on the analysis.
results and database size. Egger’s test was also used for each dataset to better understand publication bias.

**Results**

**Study characteristics**

A total of 297 literatures were retrieved after the initial search, and 289 were excluded from the analysis based on the criteria that were introduced in Methods and Figure 1. As a result, 8 case-control studies that met the inclusion criteria were included in the final meta-analysis, which covered 963 thyroid cancer cases and 1942 controls for XRCC3 T241M [12–16,18]. The data collection flow chart is shown in Figure 1. The characteristics of all studies are illustrated in Table 1.

**Quantitative synthesis**

In this study, we performed the meta-analysis on both the overall database and the 2 ethnic subgroups (Caucasian and Asian). As shown in Table 1, there were 3 studies in each ethnic subgroup, and 2 studies were excluded from either subgroup due to their mixed ethnic composition [16]. The results of the overall database including 8 eligible studies indicated that increased thyroid cancer risk was significantly associated with XRCC3 T241M polymorphism by the analyses using either the recessive model (OR=1.40, 95% CI=1.08–1.81, P=0.012) (Table 2 and Figure 2B) or the homozygote comparison (OR=1.41, 95% CI=1.07–1.86, P=0.015) (Table 2 and Figure 2C), but not by using the dominant model (OR=1.12, 95% CI, 0.95–1.33, P=0.18) (Table 2, Figure 2A).

When studies were stratified by ethnicity, no significant association was observed between XRCC3 T241M polymorphism and thyroid cancer risk in either Caucasian or Asian group in any genetic model. For the Caucasian population, with the dominant model, overall OR was 0.90 (95% CI, 0.70–1.15, p=0.411) (Table 3); with the recessive model, the overall OR was 1.27 (95% CI, 0.89–1.80, p=0.187) (Table 3); with homogygote comparison, the overall OR was 1.12 (95% CI, 0.77–1.65, p=0.549) (Table 3). For the Asian population, with dominant model, overall OR was 1.12 (95% CI, 0.81–1.55, p=0.483) (Table 3); with recessive model, the overall OR was 1.46 (95% CI, 0.80–2.67, p=0.223) (Table 3); with the homogygote comparison, the overall OR was 1.52 (95% CI, 0.82–2.85, p=0.188) (Table 3).

**Evaluation of heterogeneity**

For the overall database, significant heterogeneity was detected in the dominant model (I²=58%, P-value=0.02) (Table 2), but no significant heterogeneity was observed in either the recessive model (I²=0%, P-value=0.429) (Table 2) or the homozygote comparison (I²=0%, P-value=0.452) (Table 2). Heterogeneity was also analyzed within the 2 ethnic subgroups. In the Caucasian subgroup, no significant heterogeneity was observed by either the dominant model (I²=0%, P-value=0.940) (Table 3) or the homozygote comparison (I²=12%, P-value=0.321) (Table 3), but there was significant heterogeneity in the recessive model (I²=53.4%, P-value=0.429) (Table 3). For the Asian subgroup, no significant heterogeneity was observed in either the recessive model (I²=0%, P-value=0.495) (Table 3) or homozygote comparison (I²=0%, P-value=0.987) (Table 3), but there was significant heterogeneity in the dominant model (I²=67.1%, P-value=0.048) (Table 3).
Publication bias

To test the publication bias of the overall dataset, Begg’s and Egger’s tests were performed. As shown in Table 2, the result of Begg’s test suggested a possible publication bias (P-value=0.000), but the result from Egger’s test showed no bias (P-value=0.818). Funnel plots were also generated, which did not show any significant publication bias in the 3 methods (Figure 3A–3C). Funnel plot and Egger’s test were not used for both ethnic subgroups (Caucasian and Asian) because of the small sample size.

Discussion

XRCC3 plays an important role in repairing DNA DSBs and maintaining chromosomal integrity. The association between different XRCC3 SNPs and the risk of various types of human cancers has been extensively studied [19–23]. Recently, many individual studies have investigated the association between XRCC3 T241M polymorphism and the risk of thyroid cancer, but the results were inconsistent [12–16]. This meta-analysis aimed to get better insight into the association between this SNP and thyroid cancer risk by combing the data from all available studies. After a comprehensive search and careful selection, 8 studies were critically reviewed and included in our analysis. The results of this meta-analysis show that there is a significant association between XRCC3 T241M polymorphism and increased risk of thyroid cancer using either the recessive model (OR=1.40, 95% CI=1.08–1.81, P=0.012) or homozygote comparison (OR=1.41, 95% CI=1.07–1.86, P=0.015), but not by the dominant model (OR was 1.12, 95% CI, 0.95–1.33, P=0.18) when combining all the data from different ethnic databases. It is not surprising that an association was found in the recessive and homozygote models but not in the dominant model, because although M is the risk factor, TM (heterozygous)
is not sufficient for disease induction and development, nor is TT. As such, while there was no association identified when TT was compared with TM plus MM, a significant association was found when MM was compared with TM plus TT or TT alone. The Mantel-Haenszel (M-H) fixed-effects model was applied with 3 different analysis models (dominant, recessive, and homozygote) to test the heterogeneity. Based on the heterogeneity testing results, the M-H fixed-effects model should be applied to analyze datasets that have a low heterogeneity ($I^2 < 25\%$), and DerSimonian and the Laird (D-L) random-effects model should be applied to analyze datasets that show high heterogeneity ($I^2 > 75\%$). However, in our meta-analysis, due to the small size of the dataset, it is more reasonable to apply the M-H fixed-effects model for the XRCC3 Thr241Met dataset. Therefore, the M-H fixed-effect model was applied to the overall dataset in the dominant model, although a medium heterogeneity was observed ($I^2 = 58\%$, Table 2). No significant association (with $p$-value 0.18) was observed in the dominant model, indicating that the M allele acts in a recessive manner in enhancing thyroid cancer risk. In the recessive model, the overall OR was 1.40 [95% CI, 1.08–1.81, $P=0.012$]. Because no significant heterogeneity was detected ($I^2=0\%$),

![Figure 2. Forest plots of XRCC3 T241M polymorphism and thyroid cancer risk for the entire database with different models: (A) dominant model (TM+MM vs. TT); (B) recessive model (MM vs. TM+TT); (C) homozygote comparison (MM vs. TT).]
the fixed-effects model was used. Similarly, for the homozygote comparison, the overall OR was 1.41 [95% CI, 1.07–1.86, P=0.015] and the fixed-effects model ($I^2=0\%$) was also applied.

When studies were stratified by ethnicity, no significant associations were observed between XRCC3 T241M polymorphism and thyroid cancer risk in either the Caucasian or Asian group for any genetic models. We excluded 2 out of 8 studies from the ethnic stratification (Table 1) because of mixed ethnic composition [16]. Thus, only 3 studies were included in each ethnic group (Caucasian Asian). The small sample size and limited number of studies in each ethnic subgroup in this meta-analysis could have contributed to the discrepancies between the overall and subgroup analyses. A very recent meta-analysis that included 6 studies showed no association between XRCC3 Thr241Met and the risk of thyroid cancer in an overall population that contained both Caucasian and Asian groups [24]. Interestingly, with 2 more studies included, the result from our meta-analysis evidently showed significant association, supporting the importance of increased sample size and number of studies for meta-analysis.

Figure 3. Funnel plots of the entire database with different models: (A) dominant model (TM+MM vs. TT); (B) recessive model (MM vs. TM+TT); (C) homozygote model (MM vs. TT).
Conclusions

In conclusion, the results of our meta-analysis suggest that there is a significant association between XRCC3 Thr241Met polymorphism and an increased risk of thyroid cancer for the overall population. To determine the effect of Thr241Met polymorphism on the development of thyroid cancer in different ethnic populations, studies with larger sample sizes are needed. This finding suggests that the XRCC3 Thr241Met polymorphism might be used as a genetic biomarker, in combination with other molecular biomarkers [6], for improving the prediction and diagnosis of thyroid cancer, especially in cases with indeterminate cytology.

Conflict of interest

None of the authors have any relevant financial conflicts of interest in this study and no competing financial interests exist.

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