Gene 528 (2013) 67–73

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Review

# *XRCC1* polymorphisms and differentiated thyroid carcinoma risk: A meta-analysis

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ARTICLE INFO

*Article history:*
Accepted 2 July 2013
Available online 17 July 2013

*Keywords:*
*XRCC1*
Polymorphisms
Differentiated thyroid carcinoma
Meta-analysis

ABSTRACT

The objective of this study is to quantitatively derive a more precise estimation of the association between X-ray repair cross-complementing group 1 (*XRCC1*) gene polymorphisms and differentiated thyroid carcinoma risk. A comprehensive literature search of three databases was conducted. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with fixed-effect models and random-effect models when appropriate. Overall, no association of the *XRCC1* Arg399Gln, Arg280His, and Arg194Trp polymorphisms with differentiated thyroid carcinoma risk was found. In subgroup analyses, a decreased differentiated thyroid carcinoma risk was observed among Caucasians (Gln vs. Arg, OR = 0.86, 95% CI = 0.77–0.96, $P = 0.343$ for heterogeneity; Gln/Arg vs. Arg/Arg, OR = 0.84, 95% CI = 0.71–0.98, $P = 0.229$ for heterogeneity; Gln/Gln vs. Arg/Arg, OR = 0.77, 95% CI = 0.60–0.99, $P = 0.477$ for heterogeneity; dominant genetic model, OR = 0.82, 95% CI = 0.71–0.95, $P = 0.272$ for heterogeneity), not among Asians. No publication bias was observed. Our results suggest that *XRCC1* Arg399Gln polymorphism is not associated with differentiated thyroid carcinoma risk, while a decreased risk is observed among Caucasian population.



**Contents**



## 1. Introduction

Thyroid carcinoma is the most prevalent endocrine malignancy (Parkin et al., 2005) and accounts for more than 90% of all endocrine malignancies. The incidence rate of thyroid carcinoma in the world has increased over recent decades (Burgess, 2002; Davies & Welch, 2006; Liu et al., 2001). Among these thyroid carcinomas, more than

*Abbreviation: XRCC1*, X-ray repair cross-complementing group 1; OR, odds ratio; CI, confidence interval; BER, base excision repair; SNP, single nucleotide polymorphism; HWE, Hardy–Weinberg equilibrium.

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http://dx.doi.org/10.1016/j.gene.2013.07.005

90% are differentiated thyroid carcinomas, a category that includes the pathologic subtypes of papillary, follicular, and Hürthle cell carcinoma (Wein & Weber, 2005). However, etiologic risk factors for thyroid carcinoma have puzzled investigators for many years and still remain an enigma. It is believed that thyroid carcinoma is induced by environmental agents (e.g., carcinogens, mutagens) together with genetic factors (e.g., individual genetic susceptibility).

DNA damage occurs through various pathways, including exogenous carcinogens and endogenously-produced reactive oxygen metabolites, which may result in uncontrolled cell proliferation or programmed cell death. DNA repair genes have a critical role for the maintenance of genome integrity. Mutations in DNA repair genes may reduce the DNA repair capacity and result in individual susceptibility to cancer risk (Hoeijmakers, 2001; Wood et al., 2001). Among the DNA repair pathways, the base excision repair (BER) specifically eliminates alterations of a single base when it is methylated, oxidized, or reduced, and it consequently rectifies single-strand breaks in DNA (Hoeijmakers, 2001; Wood et al., 2001). Therefore, inter-individual variation in the BER pathway is one of the individual susceptibility factors that may affect thyroid carcinoma risk.

The BER pathway is a multistep process that requires several activated proteins, among which X-ray repair cross complementing 1 (*XRCC1*) protein plays an important role for repairing single-strand DNA breaks (Hung et al., 2005) in conjunction with a number of other proteins, including poly (ADP-ribose), DNA polymerase beta, and DNA ligase III. Many studies have suggested that XRCC-lacking cells are hypersensitive to exogenous insults such as ionizing radiation, alkylating agents, ultra-violet light and hydrogen peroxide (Izumi et al., 2000; Kubota et al., 1996; Vidal et al., 2001; Zhang et al., 1998). The *XRCC1* gene is located on chromosome 19q13.2, spans a genetic distance of 32 kb, contains of 17 exons and encodes a 70-kDa protein comprising of 633 amino acids (Lindahl & Wood, 1999). Numerous single nucleotide polymorphisms (SNP) of *XRCC1* gene have been reported in the Ensemble database to be associated with increased risk for various cancers (Goode et al., 2002; Hu et al., 2005). Among them, Arg399Gln (exon 10, base G to A, arginine to glutamine, rs25487), Arg280His (exon 9, base G to A, arginine to histidine, rs25489) and Arg194Trp (exon 6, base C to T, arginine to tryptophane, rs1799782) are highly studied and result in amino acid substitutions at evolutionarily conserved regions.

To date, several published studies have explored the association between *XRCC1* Arg399Gln, Arg280His and Arg194Trp polymorphisms and differentiated thyroid carcinoma risk (Akulevich et al., 2009; Chiang et al., 2008; Fard-Esfahani et al., 2011; Garcia-Quispes et al., 2011; Ho et al., 2009; Ryu et al., 2011; Sigurdson et al., 2009; Siraj et al., 2008; Zhu et al., 2004). However, these results are conflicting and inconclusive. Thus, a meta-analysis is conducted with rigorous methods, aiming to pool all available evidence to verify the role of polymorphisms of *XRCC1* polymorphisms (Arg399Gln, Arg280His and Arg194Trp) in differentiated thyroid carcinoma risk.

## 2. Materials and methods

### 2.1. Search strategy and selection criteria

A comprehensive systematic bibliographic search through the digital medical databases Medline, EMBASE, and The Cochrane Library database was conducted for all medical publications up to September 2012. The search strategy used the following keywords: *XRCC1* or X-ray repair cross-complementing group 1, polymorphism, thyroid carcinoma, and thyroid cancer. There were not any language restrictions. Bibliographies of relevant articles and conference proceedings were also reviewed for related original studies. Two investigators (Zhen Hu and Xue-Ying Hu) independently reviewed the relevant initial studies with the titles and abstracts synchronously to determine whether they met the general inclusion and exclusion criteria. Discordance in study inclusion was subsequently reviewed and resolved through discussion and a consensus meeting with a third reviewer (Jian-Xiong Long).

The inclusion criteria were as follows: (1) case–control studies were conducted to investigate the association between *XRCC1* Arg399Gln, Arg280His and/or Arg194Trp polymorphisms and differentiated thyroid carcinoma risk; (2) studies including differentiated thyroid carcinoma cases and thyroid carcinoma-free controls; (3) with sufficient data for calculating the odds ratio (OR) with 95% confidence interval (CI). The major reasons for exclusion of studies were as follows: studies without genotype or allele data of case/control; studies with benign thyroid disease; and case-only studies, case reports, editorials, and review articles (including meta-analysis).

### 2.2. Data extraction

Two reviewers independently extracted data using a standardized form. Study characteristics were collected from each study as follows: first author, year of publication, country, ethnicity of subjects, numbers of genotyped cases and controls, gender, source of controls, genotype studied, genotyping methods, evidence of Hardy–Weinberg equilibrium (HWE), and the available genotype frequency information from *XRCC1* Arg399Gln, Arg280His and Arg194Trp.

### 2.3. Statistical analysis

We used crude odds ratios (ORs) with 95% confidence intervals (CIs) as the metric of choice. The analysis for *XRCC1* Arg399Gln polymorphism genetic polymorphism was performed for variant allele (Gln) vs. wild-type allele (Arg), as well as heterozygote genotype comparison (Gln/Arg vs. Arg/Arg), homozygote genotype comparison (Gln/Gln vs. Arg/Arg), dominant model comparison (Gln/Gln + Gln/Arg vs. Arg/Arg) and recessive model comparison (Gln/Gln vs. Gln/Arg + Arg/Arg). The same contrasts were also performed for *XRCC1* Arg280His and Arg194Trp gene polymorphisms. Both the Cochran's Q statistic to test for statistical heterogeneity (Vangel & Rukhin, 1999) and the I2 statistic to quantify the proportion of the total variation due to heterogeneity (Higgins et al., 2003) were calculated. A $P$ value of $<0.1$ indicated the presence of heterogeneity across studies. Data were combined using both fixed effects (Mantel–Haenszel) and random effects (DerSimonian and Laird) models (DerSimonian & Laird, 1986). The pooled effect estimates were calculated using the Mantel–Haenszel fixed-effect model first (Sutton KRA et al., 2000). A statistical test with a $P$-value less than 0.05 was considered significant. When there was heterogeneity between studies, the DerSimonian and Lair random-effect model was applied instead (Lau et al., 1997) and sources of heterogeneity were explored by conducting subgroup analysis. Further, sensitivity analysis could be employed by excluding one or two outlying studies with results that conflicted with the rest of the studies.

To assess the covariate effects, stratified analyses were conducted by ethnicity, and control source. The ethnic subgroups were defined as two ethnic groups (Caucasian, and Asian), while the control source subgroups were considered as two groups (hospital-based controls and population-based controls). Potential publication bias was diagnosed both visually by using a funnel plot and statistically via Begg and Egger's unweighted regression test (Begg & Mazumdar, 1994; Egger et al., 1997), which measures the degree of funnel plot asymmetry. Statistical analyses were conducted with Stata version 9.2 (Stata Corporation, College Station, Texas, USA). A 2-tailed $P$ value of less than 0.05 was judged as statistically significant.

## 3. Results

### 3.1. Characteristics of relevant studies

We preliminarily identified 11 studies based on the search terms. Two studies were excluded because of not associated with *XRCC1*