



# Association between the X-ray repair cross-complementing group 1 Arg194Trp polymorphism and thyroid carcinoma susceptibility: A meta-analysis

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**ABSTRACT.** Previous case-control studies having investigated the relationship between the X-ray repair cross-complementing group 1 (*XRCC1*) Arg194Trp polymorphism and thyroid cancer (TC) have drawn inconsistent conclusions. The current study aimed to clarify the role of this polymorphism in susceptibility to TC. An up-to-date search of PubMed and Web of Science databases was conducted, including articles published up to August 2015. Crude odds ratios (ORs) with 95% CIs were calculated to establish the association between the *XRCC1* Arg194Trp polymorphism and TC risk. Five studies were used, comprising 911 patients and 1476 controls. Our meta-analysis indicated that this polymorphism is associated with TC risk in Caucasians (TrpTrp vs ArgArg: OR = 5.72, 95%CI = 1.39-23.54; ArgTrp vs ArgArg: OR = 1.20, 95%CI = 0.87-1.66; dominant

model: OR = 1.31, 95%CI = 0.96-1.79; recessive model: OR = 0.18, 95%CI = 0.04-0.73). This investigation demonstrates that the *XRCC1* Arg194Trp polymorphism constitutes a risk factor for TC in Caucasian individuals.

**Key words:** *XRCC1*; Thyroid cancer; Arg194Trp

## INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy and its global incidence has increased over recent decades (Jemal et al., 2011). TC is classified histologically into four major groups: papillary, follicular, medullary, and undifferentiated carcinomas. The mechanism behind thyroid carcinogenesis remains incompletely understood. To date, the only well-established etiological factor in the development of TC is exposure to ionizing radiation (Wang et al., 2013). However, only a small number of individuals exposed to radiation develop TC. This shows that genetic factors may play key roles in its pathogenesis. Recently, attention has focused on the impact of gene polymorphisms on TC, and many sequence variants have been put forward as risk factors, such as the C677T variation in the methylenetetrahydrofolate reductase gene (Yang et al., 2014).

DNA repair systems perform important roles in protecting cells against mutation, and are essential for maintaining genomic stability. To date, numerous proteins implicated in DNA repair have been found. Such proteins have been connected to four major DNA repair pathways in human cells, namely, nucleotide excision repair, base excision repair (BER), double-strand break repair, and mismatch repair (Wood et al., 2001). X-ray repair cross-complementing group 1 (*XRCC1*) is a major DNA repair protein in the BER pathway (Tudek, 2007). Loss of nuclear activity of this protein leads to decreased genome integrity, including an increased frequency of spontaneous and induced chromosome translocations and deletions (Rouse and Jackson, 2002).

The *XRCC1* gene is located on chromosome 19 at q13.2-13.3, and is 33 kb in length, comprising 17 exons. The gene encodes a 70-kDa protein consisting of 633 amino acids (Forat-Yazdi et al., 2015). Although numerous validated single nucleotide polymorphisms (SNPs) of this gene have been identified in the dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>), the Arg194Trp polymorphism has been the most researched of these *XRCC1* variations, and is one of the most frequently studied of any DNA repair gene sequence variant (Custódio et al., 2011). This polymorphism may affect DNA repair by modifying interactions between *XRCC1* and other proteins in the BER pathway, and many recent studies have paid close attention to its relationship with cancer pathogenesis (Tae et al., 2004; Wang et al., 2009).

Over the past decade, numerous epidemiological studies have assessed the association between the *XRCC1* Arg194Trp polymorphism and TC risk. However, the results have been inconsistent. This may have been caused by small sample sizes, low statistical power, and/or clinical heterogeneity in these investigations. The aim of the present work was to assess the association between this polymorphism and TC susceptibility by performing a meta-analysis of all published case-control studies currently available in public databases.

## MATERIAL AND METHODS

### Search strategy

PubMed and Web of Science online databases were searched to retrieve papers published up to August 2015 having examined the connection between the *XRCC1* Arg194Trp polymorphism and TC risk. The following keywords were used, with no language restrictions: “XRCC1”, “Arg194Trp”, “gene polymorphism”, “thyroid cancer/TC”, and “single nucleotide polymorphism”. This search was supplemented by manual research and a review of the reference lists included in retrieved articles. If necessary, attempts were made to contact the corresponding authors of retrieved articles to request additional information.

### Inclusion and exclusion criteria

To be included in the meta-analysis, articles had to: 1) be case-control studies; 2) assess the association between the *XRCC1* Arg194Trp polymorphism and TC risk; 3) provide sufficient information to estimate odds ratios (ORs) and their 95% confidence intervals (95% CIs); and 4) provide data relating to Arg194Trp polymorphism genotype frequencies. The following were excluded: 1) reviews, editorials, or comments; 2) articles lacking genotype frequency data; and 3) duplicated studies.

### Data extraction

Two reviewers (J.Z.Z. and X.R.T.) independently retrieved the following information from each included study: first author, year of publication, location, number of cases and controls, genotype frequencies in case and control groups, and evidence of Hardy-Weinberg equilibrium (HWE) in the control group. Differences of opinion between the two reviewers were resolved by discussion until an agreement was reached.

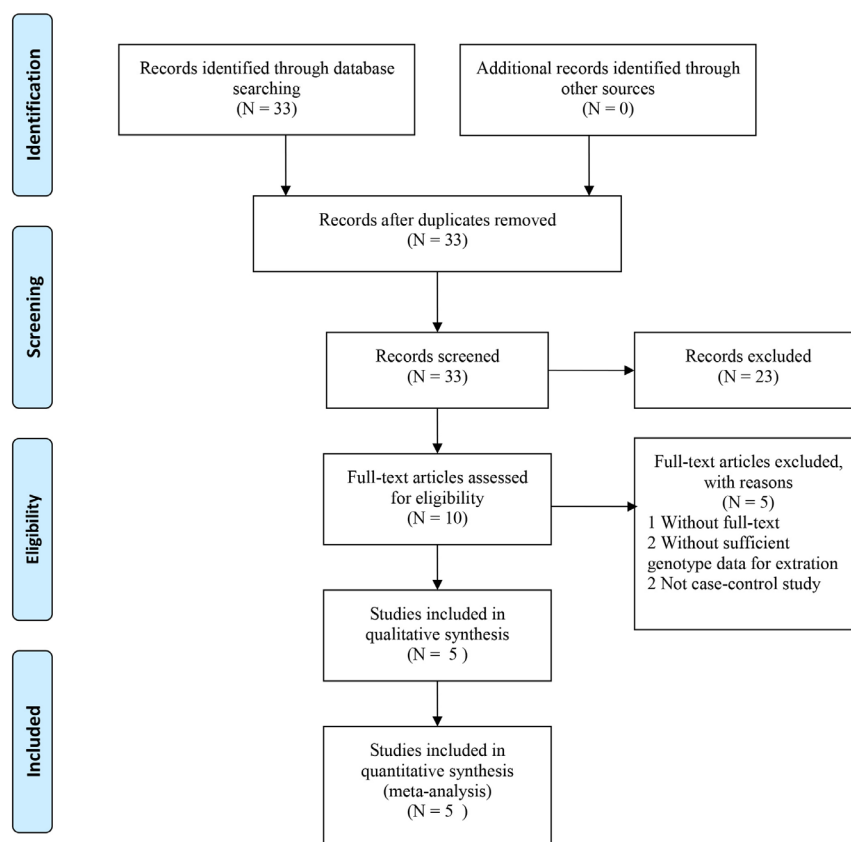
### Statistical analysis

For data analysis, we used Stata software version 12.0 (StataCorp, College Station, TX, USA). HWE was assessed by the Fisher exact test, and  $P < 0.05$  was considered to signify significant disequilibrium. The strength of association between the Arg194Trp polymorphism and susceptibility to TC was estimated by ORs and 95% CIs using homozygote comparison (TrpTrp vs ArgArg), heterozygote comparison (ArgTrp vs ArgArg), and dominant (ArgTrp+TrpTrp vs ArgArg) and recessive (TrpTrp vs ArgArg+ArgTrp) models. Pooled effects were calculated using either the fixed- or random-effects model (Ding and Li, 2015). The presence of heterogeneity was evaluated using the  $I^2$  test. Data were considered to demonstrate significant heterogeneity when  $I^2$  exceeded 50%. Sensitivity analysis was performed by comparing random- and fixed-effects model estimates. Publication bias was assessed using a Begg’s funnel plot, with  $P < 0.05$  being considered to represent statistically significant bias.

## RESULTS

### Study characteristics

As a result of database searches, 33 papers were retrieved, of which five full-text articles were ultimately included in our meta-analysis (Chiang et al., 2008; Ho et al., 2009; Fard-Esfahani et al., 2011; Ryu et al., 2011; Santos et al., 2012). A flow chart representing the study selection process is shown in Figure 1. These five case-control studies included a total of 911 cases and 1476 healthy controls. Three of these investigations involved Caucasian participants (Ho et al., 2009; Fard-Esfahani et al., 2011; Santos et al., 2012), while two focused on Asian populations (Chiang et al., 2008; Ryu et al., 2011). The year of publication ranged from 2008 to 2014. Tests of genotype distributions in the control groups revealed no deviation from HWE. All studies were population-based, and in each case, controls were matched by sex and age to patients. All of the included investigations used a classical polymerase chain reaction-restriction fragment length polymorphism assay. Their main characteristics are listed in Table 1.



**Figure 1.** Flow chart showing the study selection procedure.

**Table 1.** Characteristics of the included studies for meta-analysis.

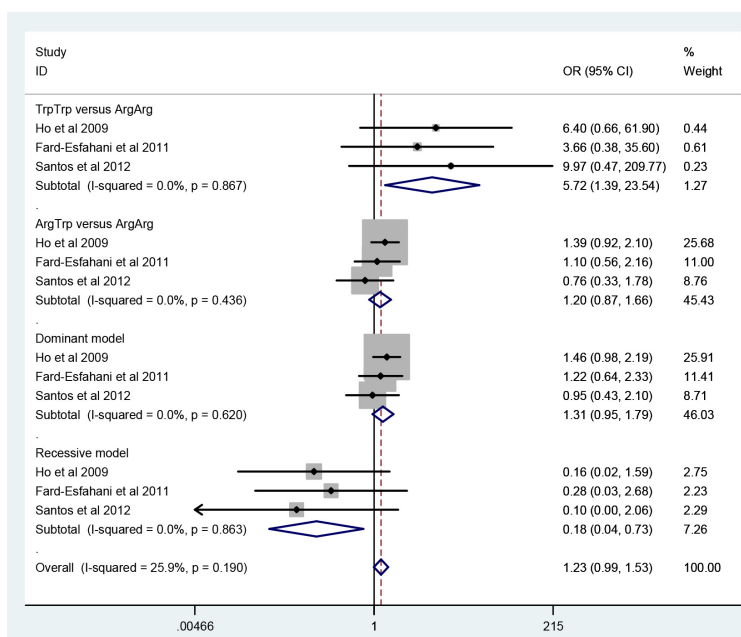
Study	Year	Country	Ethnicity	Cases/controls	<i>XRCCI</i> Arg194Trp polymorphism (Cases/controls)			HWE test
					Arg/Arg	Arg/Trp	Trp/Trp	
Chiang et al.	2008	China	Asian	283/489	127/254	119/199	37/36	0.73
Ho et al.	2009	USA	Caucasian	251/503	203/433	45/69	3/1	0.31
Fard-Esfahani et al.	2011	Iran	Caucasian	157/187	136/166	18/20	3/1	0.64
Ryu et al.	2011	Korea	Asian	111/100	59/37	43/49	9/14	0.72
Santos et al.	2012	Portugal	Caucasian	108/217	98/196	8/21	2/0	0.45

HWE = Hardy-Weinberg equilibrium.

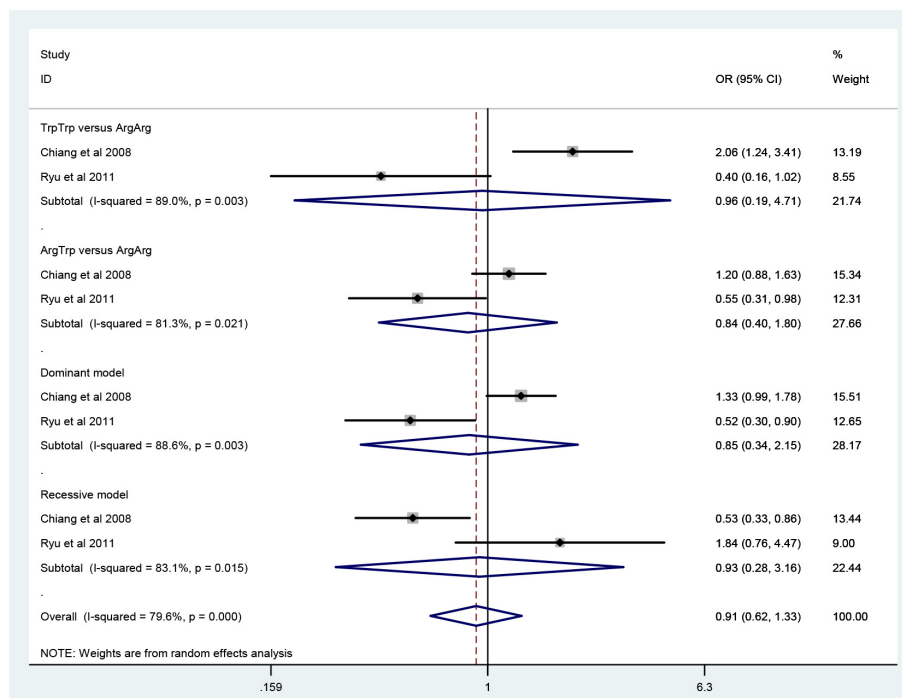
## Meta-analysis results

The results of our meta-analysis of the relationship between the *XRCCI* gene Arg194Trp polymorphism and TC risk are summarized in Figures 2 and 3 and Table 2. This analysis identified no significant interaction between this polymorphism and susceptibility to TC (TrpTrp vs ArgArg: OR = 1.92, 95%CI = 0.64-5.78; ArgTrp vs ArgArg: OR = 1.08, 95%CI = 0.88-1.33; dominant model: OR = 1.07, 95%CI = 0.75-1.54; recessive model: OR = 0.55, 95%CI = 0.22-1.38).

In a subgroup analysis based on ethnicity, in which the data were divided into Asian and Caucasian subsets, a significant association was found between the Arg194Trp polymorphism and TC risk among Caucasians (TrpTrp vs ArgArg: OR = 5.72, 95%CI = 1.39-23.54; ArgTrp vs ArgArg: OR = 1.20, 95%CI = 0.87-1.66; dominant model: OR = 1.31, 95%CI = 0.96-1.79; recessive model: OR = 0.18, 95%CI = 0.04-0.73), but not Asians (TrpTrp vs ArgArg: OR = 0.96, 95%CI = 0.19-4.71; ArgTrp vs ArgArg: OR = 0.84, 95%CI = 0.40-1.80; dominant model: OR = 0.85, 95%CI = 0.34-2.15; recessive model: OR = 0.93, 95%CI = 0.28-3.16).



**Figure 2.** Forest plot assessing the association between thyroid cancer and the *XRCCI* Arg194Trp polymorphism in Caucasian populations.



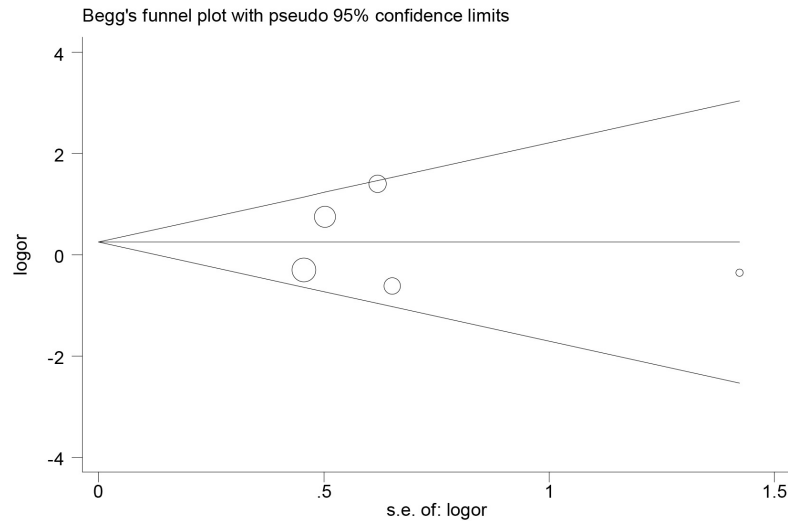
**Figure 3.** Forest plot assessing the association between thyroid cancer and the *XRCC1* Arg194Trp polymorphism in Asian populations.

**Table 2.** Summary of odds ratios and 95% confidence intervals relating to the association between the *XRCC1* Arg194Trp polymorphism and thyroid cancer risk.

Subgroup	Genetic model	Sample size		Model	Test of heterogeneity		Test of association	
		Cases	Controls		I <sup>2</sup> (%)	P	OR	95%CI
Overall	TrpTrp vs ArgArg	911	1476	Random	68.4	0.01	1.92	0.64-5.78
	Fixed			48.1	0.10	1.08	0.88-1.33	
	Random			62.2	0.03	1.07	0.75-1.54	
	Fixed			57.7	0.05	0.55	0.22-1.38	
Caucasians	TrpTrp vs ArgArg	517	907	Fixed	0.0	0.87	<b>5.72</b>	<b>1.39-23.54</b>
	Fixed			0.0	0.44	1.20	0.87-1.66	
	Fixed			0.0	0.62	1.31	0.96-1.79	
	Fixed			0.0	0.86	<b>0.18</b>	<b>0.04-0.73</b>	
Asians	TrpTrp vs ArgArg	394	569	Random	89.0	0.00	0.96	0.19-4.71
	Random			81.3	0.02	0.84	0.40-1.80	
	Random			88.6	0.00	0.85	0.34-2.15	
	Random			83.1	0.02	0.93	0.28-3.16	

### Sensitivity analysis and publication bias

Sensitivity analyses were performed by altering the statistical models. No single study was observed to substantially influence the pooled ORs. Therefore, the results of this meta-analysis were shown to be robust and credible. Visual inspection of the Begg’s funnel plot generated for this analysis revealed no evidence of publication bias (Figure 4).



**Figure 4.** Begg's funnel plot as a test of publication bias.

## DISCUSSION

Although TC currently accounts for less than 1% of human cancers, its incidence is increasing year after year. At present, the pathogenic mechanisms involved in the development and progression of TC are far from clear. Evidence is accumulating that this disease is a complex multifactorial disorder in which genetic factors play a key role. Genetic variations in genes controlling DNA repair and cell proliferation have an important influence on individual susceptibility to common cancers (Hunt et al., 2013). Previous studies of the interaction between the *XRCC1* Arg194Trp polymorphism and TC risk have produced contradictory results. Meta-analysis is a method of increasing the effective sample size under investigation by pooling data from individual association studies, thus enhancing the statistical power to estimate genetic effects (Munafò and Flint, 2004). We conducted the present meta-analysis to explore the relationship between the *XRCC1* gene Arg194Trp polymorphism and TC risk.

This meta-analysis included 911 TC cases and 1476 controls. The results failed to establish a significant relationship between the polymorphism of interest and TC risk in the overall dataset. However, such analyses may be affected by differences in the ethnicities of study populations; hence, we performed a stratified analysis based on ethnicity. From this, we established the *XRCC1* Arg194Trp polymorphism to be associated with TC risk among Caucasians, but not Asians. Three factors may explain this finding. First, the observed variation in the distribution of the Trp allele between Caucasians and Asians may be responsible for these contrasting results. Second, geographically separated populations tend to demonstrate different linkage disequilibrium patterns. A polymorphism may be in close linkage with another nearby causal polymorphism in one ethnic group, but not in another (Zhou et al., 2013). Third, other confounding factors, such as selection bias and different matching criteria, may also have caused this difference. In addition, as the number of studies included in this meta-analysis was limited, caution should be exercised when considering the conclusions reached.

In interpreting the results of our meta-analysis, some limitations should be addressed. First, as only articles written in English were included, relevant studies published in other languages may have been overlooked. Second, as our meta-analysis involved only case-control studies, the patient groups necessarily consisted of living individuals, therefore those having died previously were not recorded. As a result, selection/survival bias could not be avoided to some extent. Finally, the influence of gene-gene and gene-environment interactions was not evaluated in our meta-analysis owing to lack of relevant data.

In conclusion, this study demonstrated that the *XRCC1* Arg194Trp polymorphism is associated with TC risk in Caucasian populations. To achieve a more accurate conclusion, well-designed, unbiased, and large case-control studies should be performed.

### Conflicts of interest

The authors declare no conflict of interest.

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