RESEARCH ARTICLE

Genetic Association of XRCC1 Gene rs1799782, rs25487 and rs25489 Polymorphisms with Risk of Thyroid Cancer: a Systematic Review and Meta-Analysis

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Abstract

Background: A number of case-control studies have evaluated associations between the X-ray cross complementary group 1 protein (XRCC1) gene rs1799782 (Arg194Trp), rs25487 (Arg399Gln) and rs25489 (Arg280His) polymorphisms and thyroid cancer (TC) risk, but the results remain inconclusive. **Materials and Methods:** A systematic literature search was performed using PubMed and Google Scholar Search. According to defined criteria data were extracted and pooled odds ratios with 95% confidence intervals were calculated under five genetic models. **Results:** A total of 8 studies with 1,672 cases and 2,805 controls for the rs1799782 polymorphism, 14 studies with 2,506 cases and 5,180 controls for the rs25487 polymorphism, and 11 studies with 2,197 cases and 4,761 controls for the rs25489 polymorphism were included in this meta-analysis. Overall, there was a statistical association between XRCC1 rs1799782 polymorphism and TC risk with the homozygote genetic model (TT vs. CC: OR = 1.815, 95% CI = 1.115-2.953, p= 0.016) and the recessive genetic model (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 only in Asians under the recessive model (TT vs. TC+CC: OR = 1.816, 95% CI = 1.398-2.358, p= <0.001). In addition, there was no positive association between XRCC1 rs25487 and rs25489 polymorphisms and risk of TC. However, there was a significant association between XRCC1 rs25487 polymorphism risk of TC among Caucasians with 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). **Conclusions:** The results of our meta-analysis suggest an increased risk of TC with the XRCC1 rs1799782 and rs25487 polymorphisms. However, the XRCC1 rs25489 polymorphism appeared to be without influence.

Keywords: Thyroid cancer- XRCC1 gene- polymorphism- association- meta-analysis

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 (DeLellis, 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;

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Nagy and Ringel, 2015).

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), 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 ($P \geq 0.1$ or $I2 < 50\%$). Otherwise, the random effects model (the DerSimonian and Laird method) is used when they are heterogeneous ($P < 0.1$ or $I2 \geq 50\%$). 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 XRCC1 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 XRCC1 rs1799782 polymorphism (Table 1), 14 studies with a total of 2,506 cases and 5,180 controls for XRCC1 rs25487 polymorphism (Table 2), and 11 studies with a total of 2,197 cases and 4,761 controls for XRCC1 rs25489 polymorphism (Table 3). The article performed

Table 1. Characteristics of Studies Included in the Meta Analysis of XRCC1 rs1799782 Polymorphism and TC

First author	Country (Ethnicity)	Case/Control	Cases					Controls					HWE
			Genotype			Allele		Genotype			Allele		
			CC	CT	TT	C	T	CC	CT	TT	C	T	
Chiang et al. 2008	China (Asian)	283/469	127	119	37	373	193	254	119	36	627	191	0.002
Ho et al. 2009	USA (Caucasian)	251/503	203	45	3	451	51	433	69	1	935	71	0.306
Esfahani et al. 2011	Iran (Asian)	157/187	136	18	3	290	24	166	20	1	352	22	0.641
Ryu et al. 2011	Korea (Asian)	111/100	59	43	9	161	61	37	49	14	123	77	0.728
Santos et al. 2012	Portugal (Caucasian)	109/217	98	8	2	204	12	196	21	0	413	21	0.453
Yan et al. 2015	China (Asian)	276/403	124	112	40	360	192	202	173	28	577	229	0.267
Wang et al. 2015	China (Asian)	276/552	181	52	43	414	138	411	95	46	917	187	<0.001
Halkova et al. 2016	Czech (Caucasian)	209/374	178	31	0	387	31	314	59	1	687	61	0.304

Table 2. Characteristics of Studies Included in the Meta Analysis of XRCC1 rs25487 Polymorphism and TC

First author	Country (Ethnicity)	Case/Control	Cases					Controls					HWE
			Genotype			Allele		Genotype			Allele		
			GG	AG	AA	G	A	GG	AG	AA	G	A	
Zhu et al. 2004	China (Asian)	105/105	49	44	12	208	134	57	45	3	159	51	0.092
Chiang et al. 2008	China (Asian)	283/469	150	110	23	410	156	277	165	27	719	219	0.711
Siraj et al. 2008	Saudi Arabia (Asian)	50/299	35	13	2	83	17	142	72	15	356	102	0.164
Sigurdsson et al. 2009	Russia (Caucasian)	24/892	12	10	2	34	14	460	343	89	1,263	521	0.036
Akulevich et al. 2009	Russia (Caucasian)	132/398	65	53	14	183	81	158	193	47	509	287	0.302
Akulevich et al. 2009	Belarus (Caucasian)	123/199	55	50	18	160	86	75	100	22	250	144	0.185
Ho et al. 2009	USA (Caucasian)	251/503	133	99	19	365	137	220	216	67	656	350	0.229
Esfahani et al. 2011	Iran (Asian)	155/190	78	60	17	216	94	83	87	20	253	127	0.69
Ryu et al. 2011	Korea (Asian)	111/100	87	17	7	191	31	72	19	9	163	37	0.002
Garcia et al. 2011	Spain (Caucasian)	402/479	153	186	47	492	280	196	212	66	604	344	0.476
Santos et al. 2012	Portugal (Caucasian)	109/217	46	50	13	142	76	87	105	25	279	155	0.428
Wang et al. 2015	China (Asian)	276/552	138	105	32	381	169	290	206	56	786	318	0.034
Yan et al. 2015	China (Asian)	276/403	146	108	22	400	152	176	173	54	525	281	0.271
Halkova et al. 2016	Czech (Caucasian)	209/374	97	81	31	275	143	164	160	50	488	260	0.272

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

First author	Country (Ethnicity)	Case/Control	Cases					Controls					HWE
			Genotype			Allele		Genotype			Allele		
			GG	GA	AA	G	A	GG	GA	AA	G	A	
Chiang et al. 2008	China (Asian)	283/469	224	54	5	502	64	349	113	7	811	127	0.528
Siraj et al. 2008	Saudi Arabia (Asian)	50/299	33	12	5	78	22	129	79	21	337	121	0.088
Sigurdson et al. 2009	Russia (Caucasian)	25/896	24	1	0	49	1	800	96	0	1696	96	0.902
Akulevich et al. 2009	Russia (Caucasian)	132/398	117	15	0	249	15	366	32	0	764	32	0.403
Akulevich et al. 2009	Belarus (Caucasian)	123/195	113	10	0	236	10	176	19	0	371	19	0.474
Ho et al. 2009	USA (Caucasian)	251/503	229	22	0	480	22	453	50	0	956	50	0.24
Esfahani et al. 2011	Iran (Asian)	170/193	146	23	1	315	25	173	18	2	364	22	0.065
Garcia et al. 2011	Spain (Caucasian)	402/479	337	58	3	732	64	426	44	3	896	50	0.123
Wang et al. 2015	China (Asian)	276/552	153	91	32	397	155	322	174	56	818	286	<0.001
Yan et al. 2015	China (Asian)	276/403	218	52	6	488	64	298	97	8	693	113	0.974
Halkova et al. 2016	Czech (Caucasian)	209/374	188	19	2	395	23	338	36	0	712	36	0.328

by Akulevich et al. was separated as 2 studies for they evaluated 2 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)

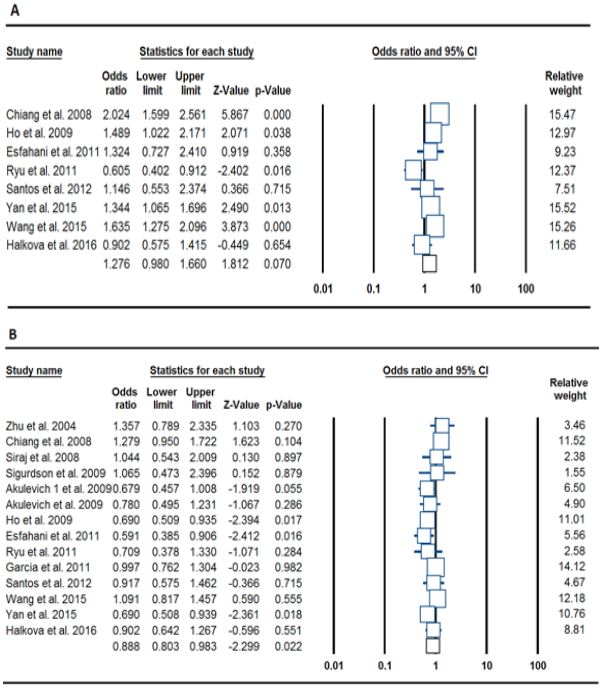

Figure 1. Forest Plots Showed Significant Association between XRCC1 Polymorphisms and TC Risk. A: XRCC1 rs1799782 polymorphism (Allele model: T vs. C) and B: XRCC1 rs25487 polymorphism (Homozygote model: AA vs. GG)

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

	Genetic model	Type of model	Heterogeneity		Odds ratio		
			I^2 (%)	P_H	OR	95% CI	P_{OR}
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

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 = .848-1.183, 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 (I^2=64.0%, P_H=0.007), homozygote (I^2=51.90%, P_H=0.042) and dominant (I^2=77.9%, P_H=0.007) genetic models (Table 4). After

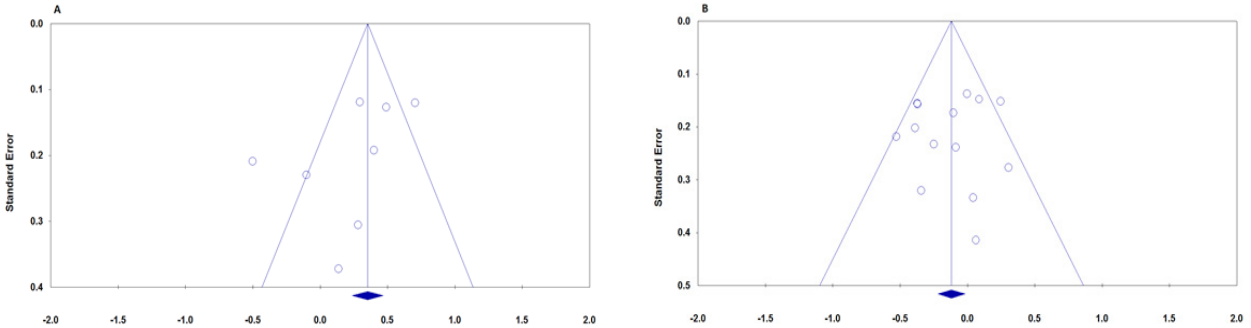

Figure 2. Begg's Funnel Plots of XRCC1 Gene Polymorphisms and TC Risk for Publication Bias Test. Each Point Represents a Separate Study for the Indicated Association. A: XRCC1 rs1799782 polymorphism (Allele model: T vs. C) and B: XRCC1 rs25487 polymorphism (Dominant model: AA+AG vs. GG)

Table 5. Meta-Analysis of the Association of XRCC1 rs25487 Polymorphism with TC

	Genetic model	Type of model	Heterogeneity		Odds ratio		
			I^2 (%)	P_H	OR	95% CI	P_{OR}
Overall							
	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							
Caucasian							
	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							
	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

subjects stratified by ethnicity, the heterogeneity obviously disappeared in the Caucasians (heterozygote: I2=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=0.019and 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

Table 6. Meta-Analysis of the Association of XRCC1 rs25489 Polymorphism with TC.

	Genetic model	Type of model	Heterogeneity		Odds ratio		
			I^2 (%)	P_H	OR	95% CI	P_{OR}
Overall							
	A vs. G	Fixed	23.4	0.22	1.044	0.920-1.183	0.507
	AG vs. GG	Fixed	42.4	0.067	0.984	0.848-1.141	0.836
	AA vs. GG	Fixed	0.0	0.891	1.154	0.803-1.658	0.439
	AA+AG vs. GG	Fixed	32.8	0.137	1.023	0.887-1.179	0.758
	AA vs. AG+GG	Fixed	0.0	0.894	1.206	0.846-1.719	0.3
Ethnicity							
Caucasian							
	A vs. G	Fixed	15.1	0.317	1.205	0.955-1.520	0.116
	AG vs. GG	Fixed	29.5	0.214	1.172	0.916-1.500	0.206
	AA vs. GG	Fixed	19.9	0.264	1.939	0.468-8.026	0.361
	AA+AG vs. GG	Fixed	24.9	0.248	1.194	0.936-1.521	0.153
	AA vs. AG+GG	Fixed	24.8	0.249	1.855	0.448-7.673	0.394
Asian							
	A vs. G	Fixed	21.5	0.278	0.983	0.847-1.142	0.825
	AG vs. GG	Fixed	44.5	0.125	0.89	0.738-1.073	0.222
	AA vs. GG	Fixed	0.0	0.974	1.113	0.765-1.619	0.575
	AA+AG vs. GG	Fixed	31.6	0.211	0.943	0.790-1.124	0.511
	AA vs. AG+GG	Fixed	0.0	0.968	1.172	0.813-1.690	0.395

1 study at a time, but the estimate of overall effect did not change noticeably. In addition, when we excluded the studies not in agreement with HWE, the statistical significance of the results not changed.

Publication Bias

We have used Begg's funnel plot and Egger's test to assess the publication bias. However, as show in Figure 2A, 2B, the funnel plots did not reveal any obvious asymmetry in all genotypes in overall population, and the results of Begg's test revealed no publication bias (P>0.05).

Discussion

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 XRCC1gene (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.

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