WITHDRAWN: Association between XRCC3 rs861539(Thr241Met) polymorphism and thyroid cancer risk (a Meta-analysis)

Yayun Wu
FuYang Cancer Hospital
Yun Ren
825269275@qq.com
TaiHe County People's Hospital
Zhimin Cao
FuYang Cancer Hospital
Kai Zhang
FuYang Cancer Hospital
Xiaoqiang Dong
TaiHe County People's Hospital
Qinjing Lv
TaiHe County People's Hospital
Bowen Wang
TaiHe County People's Hospital
Wei Yao
TaiHe County People's Hospital

Research Article

Keywords: Thyroid cancer, XRCC3, rs861539, polymorphism, meta-analysis

Posted Date: March 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-285788/v1

Additional Declarations: No competing interests reported.

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Objective To explore the association between single nucleotide polymorphism (SNP) in the XRCC3 rs861539(Thr241Met) locus and thyroid cancer risk.

Methods Studies investigating the association between SNP in the XRCC3 gene and thyroid cancer susceptibility were retrieved from the PubMed, Embase, Web of Science, CNKI (Chinese National Knowledge Infrastructure), WanFang, and CBM (China Biology Medicine) databases. Eligible studies were screened according to inclusion/exclusion criteria and principles of quality evaluation. Meta-analysis was performed using Stata 14.0 software. Odds ratios with their corresponding 95% confidence intervals were pooled to assess the association between SNP in the XRCC3 gene rs861539 locus and thyroid cancer susceptibility.

Results 10 articles(11 studies) were eligible for this meta-analysis. Meta-analysis results were shown as follows: No significant association was found between XRCC3 rs861539 polymorphism and thyroid cancer risk in Dominant and Overdominant models Dominant model: CT+TT vs CC, OR=1.231, 95% CI(0.998, 1.474); Overdominant model: CT vs TT+CC, OR=1.05, 95% CI(0.94, 1.18) . Significant associations were found in Recessive and Allelic models Recessive model: TT vs CC+CT, OR=1.632, 95% CI(1.349, 1.974); Allelic model: T vs C: OR=1.263, 95% CI(1.091, 1.462) .

Conclusion The results of this study suggest that the XRCC3 rs861539(Thr241Met) polymorphism may be associated with an increased thyroid cancer risk in overall population, and a tendency for significantly increased thyroid cancer risk in TT(Met/Met) genotype population.

Introduction

Thyroid cancer(TC) is one of the most common endocrine malignancies in human, which accounts for 3.1% of all new cancer cases and 0.4% of cancer deaths worldwide annually[1]. The incidence of thyroid cancer has been increasing rapidly in recent years, and the largest increase in incidence of all cancers was seen for thyroid cancer in China [2]. The reason might due to the rapid development of imaging detection technologies and increasing awareness of people's health [3], especially considering that thyroid cancer mortality remained stable at a rate of approximately 0.5 cases per 100000 persons [4]. Thyroid cancers are divided into four main sub-types(papillary, follicular, medullary, and undifferentiated cancers)[5].To date, the mechanism of thyroid carcinogenesis remains incompletely understood, and the only well-established risk factor for thyroid cancer might be exposure to ionizing radiation[6].

DNA damaging which caused by ionizing radiation may lead to mutations, genomic instability. The XRCC3(X-ray repair cross-complementing group 3) located on chromosome 14q32.3 is structurally and functionally related to the RAD51 gene[7], which encodes a member of the RecA/Rad51-related protein family involved in homologous recombination to preserve chromosome stability and repair DNA damage caused by endogenous and exogenous factors[8].Over the past decade, several studies have reported the association regarding XRCC3 rs861539 polymorphism and thyroid cancer risk[9-14], however, the results remained inconclusive due to some potential limitations, such as small sample size, different ethnicity, and phenotypic heterogeneity. Therefore, this meta-analysis was conducted to make this discrepancy clear and to create a comprehensive picture of the association between XRCC3 rs861539 polymorphism and thyroid cancer susceptibility.

1. Materials and Methods

1.1 Literature selection criteria

1.1.1 Inclusion criteria

(1)Case–control or cohort studies were conducted to investigate the association between XRCC3 rs861539(Thr241Met) polymorphism and thyroid carcinoma risk; (2)studies with full text articles;(3)English or Chinese articles;(4) providing available genotype data for at least one genetic model.(4)all thyroid cancer cases must be pathologically confirmed.

1.1.2 Exclusion criteria

(1) Meeting abstracts, reviews, and animal experiments; (2) only case population; (3) studies with overlapping data; (4) not for cancer research

1.2 Search strategy

A comprehensive computerized literature search of the PubMed, EmBase, Web of Science, China National Knowledge Infrastructure (CNKI), WanFang, and China Biology Medicine databases up to February 2021 was conducted. The search strategy used the following keywords: XRCC3 or rs861539 or X-ray repair cross-complementing group 3 or Thr241Met or C241T or T241M and thyroid carcinoma or thyroid cancer. Furthermore, to retrieve as many articles meeting our criteria as possible, we also investigated the reference literature listed in the articles we had found.

1.3 Data extraction

Literature selection was completed by two investigators independently. For conflicting evaluations, a third reviewer assessed the articles until an agreement was reached. The following information was recorded for each study: first author, year of publication, country, ethnicity, number of cases, number of controls, genotype distribution, genotyping methods(all of the data are shown in Table 1).

1.4 Assessment of the risk of bias in the included literature

The Newcastle–Ottawa quality assessment Scales (NOS) was used to assess all case-control studies included in our present meta-analysis. The NOS contains 8 items,and the possible scores is ranged from 0 up to 9, a study is considered high quality if it gets more than 5 scores. Finally, the quality of all the studies included in this meta-analysis was acceptable.

1.5 Statistical analysis

All statistical analysis were carried out using the STATA version 14.0 software(StataCorp, College Station, TX, USA).χ^2 analysis with a significance level of P<0.05 was used to evaluate whether rs861539(Thr241Met) polymorphism distribution of the XRCC3 gene in controls fits HWE (Hardy Weinberg equilibrium). Heterogeneity among the studies in each genetic model was assessed by using Cochran's *Q* and I^2 statistics. A *P* value of <0.05 or I^2 value of >50% was interpreted as having signifcant heterogeneity, Random effect model was used to summarize all the studies. Otherwise, the fixed effects model was chosen.We used odds ratios (*ORs*) and their corresponding 95% confidence intervals (*CIs*) to evaluate relationships between rs861539(Thr241Met) polymorphism and any predisposition to thyroid cancer. Publication bias was assessed by performing Peters' test. The significance of the intercept was determined by the t-test suggested by Peters, where *P*<0.05 was considered representative of statistically significant publication bias. For all analyses, statistically significance was assumed at *P*<0.05, unless otherwise stated.

2. Results

2.1 Retrieval of studies and their characteristics

The initial search strategy resulted in the identification of 96 records (PubMed, N = 19; Web of Science, N = 23; Embase, N = 20; CNKI, N = 23; CBM, N = 2; Wanfang, N = 9), of which 85 were excluded after reading the title, abstract, full text. One relevant article was excluded by reason of the low quality evaluation[15]. Finally, 10 articles (11 studies) met the inclusion criteria (the detailed selection process has been illustrated in Fig. 1), consisting of 1 mixed, 5 Asian and 5 Caucasian populations, and these included eligible studies published between 2005 and 2019. Extracted data of eligible studies are summarized in Table 1. The genotype frequency among cases and controls for rs861539 polymorphism are also shown in Table 1. The distributions of genotype in the control group were in HWE for most studies (P > 0.05).

Table 1 General information of the included studies

Author	Year	Ethnicity	Case/Control	Cases			Controls			HWE	NOS	Genotyping
				CC	CT	TT	CC	CT	TT			
Sturgis[16]	2005	Mixed	134/161	45	69	20	83	60	18	0.165	7	RFLP
Ni[12]	2006	Asians	191/201	179	12	0	181	20	0	0.458	7	RFLP
Siraj[14]	2008	Asians	37/227	18	12	7	97	105	25	0.667	7	RFLP
Akulevich1[13]	2009	Caucasians	120/198	53	51	16	82	89	27	0.716	7	TaqMan
Akulevich2[13]	2009	Caucasians	132/398	55	65	12	161	192	45	0.278	7	TaqMan
Bastos[17]	2009	Caucasians	109/214	39	44	26	71	114	29	0.114	7	RFLP
Fayaz[18]	2013	Caucasians	161/182	71	76	14	101	68	13	0.739	6	RFLP
Yuan[19]	2016	Asians	183/367	95	64	24	232	115	20	0.255	6	MassARRAY
Sarwar[20]	2017	Asians	456/400	277	109	70	273	85	42	<0.05	6	ARMS-PCR
Yan[21]	2016	Asians	275/403	143	97	35	255	126	22	0.223	6	MassARRAY
Santos[22]	2019	Caucasians	106/209	36	44	26	70	112	27	0.085	7	RFLP

RFLP Restriction fragment length polymorphism

ARMS-PCR: Allele-specific polymerase chain reaction

HWE = Hardy-Weinberg Equilibrium test

NOS: Newcastle–Ottawa quality assessment Scales

2.2 Quantitative synthesis and sensitivity analysis

The relationship between rs861539 polymorphism and thyroid cancer is summarized in Table 2. Significant associations were observed between rs861539 polymorphism and the risk of TC under recessive and allelic models (Recessive model : TT vs CT+CC, OR=1.632, 95% CI (1.349, 1.974); Allelic model : T vs C, OR=1.263, 95% CI(1.091, 1.462) . The aim of sensitivity analysis was to assess the effect of individual studies on the consistency of the pooled ORs by omitting a single study in each order under all genetic models (as is shown in Table 3). The results suggested that no individual study significantly affected the pooled ORs in all genetic models.

Table 2 Meta-analysis of the association between polymorphism (SNP) in the XRCC3 rs861539 locus and the thyroid cancer risk

Genetic models	Genotype Comparison	No. of included studies	Case	Control	Heterogeneity test		Selected models	Meta-analysis results		Peters test	
					I^2	*P*		*OR*(*95% CI*)	*P*	*t*	*P*
Dominant model	CT+TT vs CC	11	1904	2960	55.1%	0.014	Random	1.231(0.998,1.474)	0.053	-1.21	0.256
Recessive model	TT vs CT+CC	10	1713	2759	34.4%	0.133	Fixed	1.632(1.349, 1.974)	<0.001	-0.14	0.890
Allele model	T vs C	11	3808	5920	54.2%	0.016	Random	1.263(1.091, 1.462)	0.002	-1.08	0.308
Overdominant model	CT vs TT+CC	11	1904	2960	60.0%	0.005	Random	0.994(0.805, 1.227)	0.954	-1.37	0.203

Table 3 Sensitivity analysis

Genetic models	Genotype Comparison	No. of included studies	Meta-analysis results OR(95% CI)	Sensitivity analysis Assess the effect of each individual study on the pooled ORs
Dominant model	CT+TT vs CC	11	1.231(0.998,1.474)	Minimum OR=1.161/Fluctuation of 95%CI(0.942, 1.531)
Recessive model	TT vs CT+CC	10	1.632(1.349, 1.974)	Minimum OR=1.537/Fluctuation of 95%CI(1.255, 2.144)
Allelic model	T vs C	11	1.263(1.091, 1.462)	Minimum OR=1.223/Fluctuation of 95%CI(1.048, 1.517)
Overdominant model	CT vs TT+CC	11	0.994(0.805, 1.227)	Minimum OR=0.945/Fluctuation of 95%CI(0.761, 1.288)

2.3 Subgroup analysis

We conducted subgroup analyses by different ethnicities (Asians/Caucasians/Mixed)(as is shown in table 4), and grouping studies by Asians/Caucasians/Mixed populations could lead to heterogeneities decreased partly. Since we could not confirm that various ethnicities be the source of heterogeneity. To be specific, we found that rs861539 (Thr241Met) polymorphism may be significantly associated with an increased thyroid cancer risk in recessive genetic model among Asians/Caucasians populations (recessive model: TT vs CC+CT, Asians /OR=1.964, 95% CI(1.487, 2.595); Caucasians/ OR=1.373, 95% CI(1.032,1.827)), and significantly associated with an increased thyroid cancer risk in allelic genetic model among Asians and Mixed populations(Asians/OR=1.378, 95% CI(1.108,1.715);Mixed/OR=1.614, 95%CI (1.147,2.270)). However, no significant association between rs861539(Thr241Met) polymorphism and thyroid cancer risk was observed in Caucasians in allelic model(OR=1.107, 95%CI (0.959,1.279)). Lastly, no significant association between rs861539(Thr241Met) polymorphism and thyroid cancer risk was observed in other genetic models among Asians/Caucasians populations.

Table 4 Subgroup analysis of ethnicity

Genetic models	Ethnicity	No. of included studies	*OR(95% CI)*	*P* value	I^2/ *P* value	Model
Dominant model TT+ CT VS CC	Overall	11	1.231(0.998,1.474)	0.053	55.1%/0.014	Random
	Caucasians	5	1.045(0.856,1.277	0.664	15.8%/0.314	Fixed
	Asians	5	1.284(0.977,1.688)	0.073	53.4%/0.073	Random
	Mixed	1	2.105(1.311,3.379	0.002	/	/
Recessive model TT VS CT+ CC	Overall	10	1.632(1.349, 1.974)	<0.001	34.4%/0.133	Fixed
	Caucasians	5	1.373(1.032,1.827	0.03	47.8%/0.105	Fixed
	Asians	4	1.964(1.487,2.595)	<0.001	0.00%/0.403	Fixed
	Mixed	1	1.394(0.704,2.758	0.340	/	/
Allelic model T vs C	Overall	11	1.263(1.091, 1.462)	0.002	54.2%/0.016	Random
	Caucasians	5	1.107(0.959,1.279	0.166	13.6%/0.327	Fixed
	Asians	5	1.378(1.108,1.715)	0.004	52.9%/0.075	Random
	Mixed	1	1.614(1.147,2.270)	0.006	/	/
Overdominant model CT vs TT+ CC	Overall	11	0.994(0.805, 1.227)	0.954	60.0%/0.005	Random
	Caucasians	5	0.885(0.633,1.238)	0.477	65.0%/0.022	Random
	Asians	5	1.078(0.898,1.293)	0.421	35.6%/0.184	Fixed
	Mixed	1	1.787(1.122,2.847)	0.015	/	/

2.4 Publication bias

Publication bias was assessed using Harbord's tests for each genetic model, and there was no evidence of publication bias for all of the genetic models (as is shown in Table 2).

3. Discussion

The X-ray repair cross-complementing group 3 gene (XRCC3) belongs to a family of genes responsible for repairing DNA double-strand breaks [23], and it encodes a 346 amino acid polypeptide that participates in DNA double-strand break repair [24]. Among several SNPs identified in the XRCC3 gene, the most extensively studied is Thr241Met on exon 7(rs861539), which can influence the ability to repair DNA [25]. The rs861539(C>T) polymorphism is a nonsynonymous substitution (C→T) resulting in an amino acid change from threonine to methionine at position 241 (Thr241Met)[26, 27]. In the past decade, Numerous studies have investigated the potential biological significance of the XRCC-3 rs861539(Thr241Met)[28-31], and it has been implicated as a causative risk factor for the development of different types of malignancies. The malignancy types included breast cancer [7, 32, 33], lung cancer [34], osteosarcoma[35], melanoma[36], thyroid cancer[14, 16]. However, the correlation between XRCC3 rs861539 polymorphism and thyroid cancer risk still remained controversial [9, 13, 16, 17]. To derive a more precise estimation, we performed this meta-analysis to investigate the association between rs861539 polymorphism on XRCC3 gene and the risk of thyroid cancer.

In this study based on results of 11 studies containing 1904 thyroid cancer cases and 2960 controls, we observed an association of XRCC3 rs861539 polymorphism with thyroid cancer risk in the overall analysis under recessive and allelic genetic models, and this result was inconsistent with the previous meta-analysis by Wang [37]. The result indicated that the variant T(Met) allele was associated with increased risk of thyroid cancer(OR=1.263, 95%CI (1.091, 1.462) P=0.002). TT genotypes were associated with 1.632-fold (95% CI 1.349 to 1.974, P<0.001) higher risk compared to CC+CT genotypes. No significant association was found between rs861539 polymorphism and thyroid cancer risk, and these results mean that although T allele is the risk factor, CT (heterozygous) genotype is not sufficient for disease induction and development, compared to TT genotype. Since there were obvious heterogeneities among studies under dominant/allelic/overdominant genetic models, then we performed a stratified analysis by ethnicity. Heterogeneities under most genetic models were not reduced through subgroup analysis, which means that ethnicity may not contribute to substantial heterogeneity among the overall meta-analyses.

In the subgroup analysis our results with rs861539 polymorphism show a significant association with thyroid cancer risk among Asians in recessive model (OR=1.964, 95%CI (1.487, 2.595), P<0.001). Additionally, we did not observe an association of XRCC3 rs861539 (Thr241Met) polymorphism with thyroid cancer risk in Allelic model among Caucasians (OR=1.107, 95%CI(0.959,1.279), P=0.166). These findings above indicate that the effect of XRCC3 rs861539 polymorphism on the risk of thyroid cancer is ethnically different and the rs861539 polymorphism has its obvious effect on the development of thyroid cancer in Asians. However, these results above by subgroup analysis were inconsistent with the previous meta-analysis by Lu[11].

To sum up, our meta-analysis indicates that rs861539 polymorphism may be associated with an increased thyroid cancer risk in overall population, and a tendency for significantly increased thyroid cancer risk in TT(Met/Met) genotype population., and this association was obviously exists in Asians.

Individuals with polymorphisms in XRCC3 rs861539 locus have a potential risk of thyroid cancer, but the carcinogenesis of rs861539 polymorphism to thyroid is still not completely understood. It is largely accepted that ionizing radiation would stimulate DNA damage, which would then induct genomic instability, and previous study indicated that variant genotypes of XRCC3 codon241 are associated with increased DNA damage with increased sensitivity to DNA toxic agents [38].

To our best knowledge, this is the most comprehensive meta-analysis with the largest sample size tried to explore the association between single nucleotide polymorphism (SNP) in the XRCC3 rs861539(Thr241Met) locus and thyroid cancer risk. Our study had the advantage of including higher numbers of cases and controls and assessment of sensitivity analysis. However, there were still some limitations in this meta-analysis. First, these results are based on unadjusted estimates that lack original data from the included studies, and a more precise analysis should be conducted. Second, the controls were not uniformly defined, and not all the controls from included studies in consistent with Hardy Weinberg equilibrium. Third, Additional functional as well as association studies investigating gene-gene and gene-environment interactions are required to elucidate this issue. Lastly, lack of available data prevented us from performing additional subgroup analyses by age, gender, ionizing radiation and other risk factors. For these limitations, the results should be treated with caution. Certainly, our discovery warrant confirmation by further investigations with larger sample size.

4. Declarations

Abbreviations:

XRCC3 (X-ray repair cross-complementing group 3);TC (thyroid cancer); CBM (China Biology Medicine); CNKI (Chinese National Knowledge Infrastructure); HWE (Hardy Weinberg equilibrium); SNP(single nucleotide polymorphism); NOS(Newcastle–Ottawa quality assessment Scales); ORs(odds ratios); CIs(confidence intervals); RFLP Restriction fragment length polymorphism; ARMS-PCR: Allele-specific polymerase chain reaction; RecA/Rad51 (recombination protein A).

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and analysed during the current study available from the published articles (Ref. 12-14, 16-22).

Competing interests:

The authors have declared that no competing interest exists.

Funding:

There were no sources of financial support for this research.

Authors' contributions

Yayun Wu and Yun Ren conceived and designed the study. Zhimin Cao, Kai Zhang, and Xiaoqiang Dong were responsible for the literature selection, data extraction, and statistical analysis. Yayun Wu and Yun Ren wrote the first draft of the manuscript. Qinjing Lv, Bowen Wang, and Wei Yao performed the databases searching. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

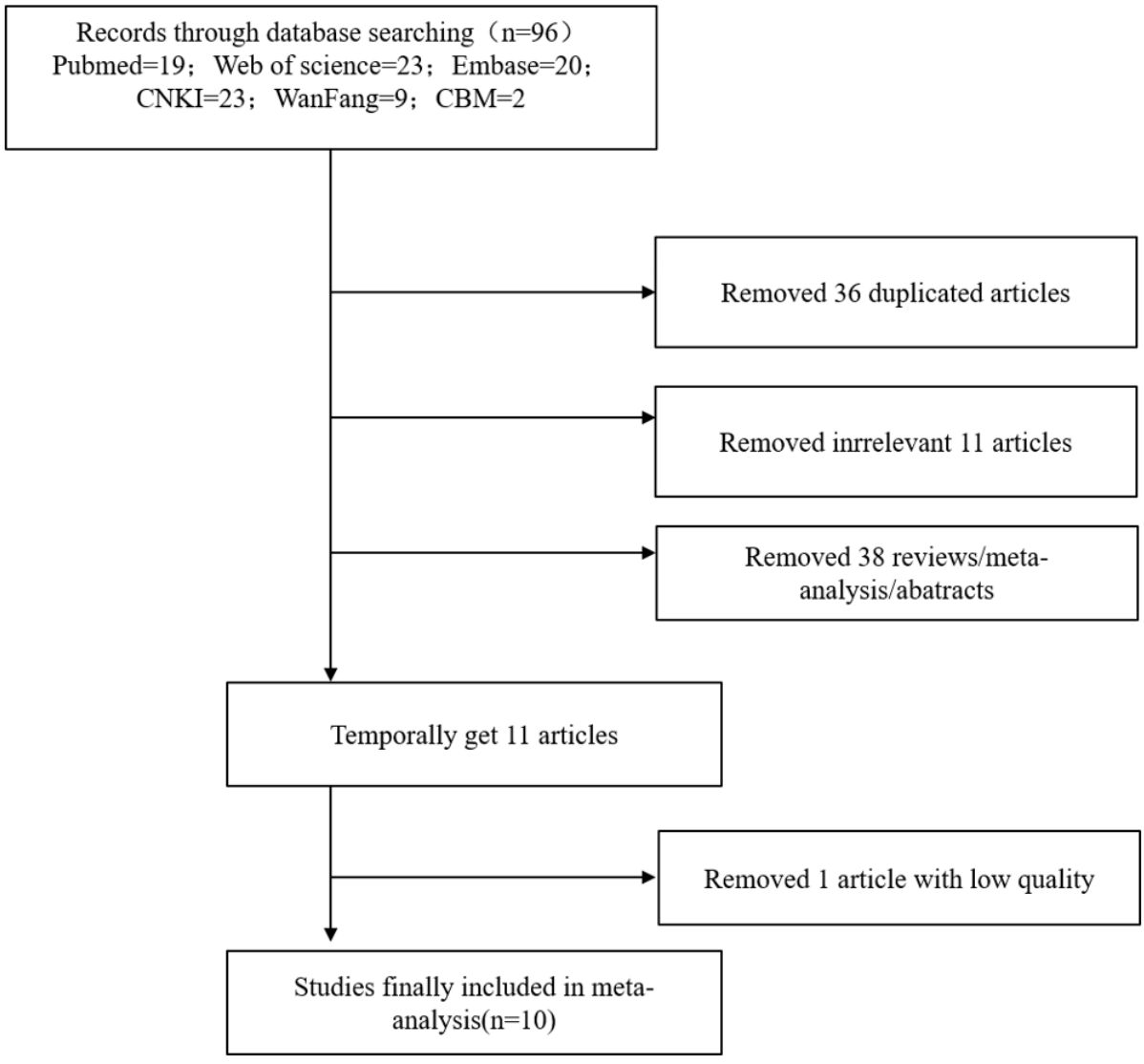

Figure 1

Literature screening process