RESEARCH ARTICLE

Association Between the XRCC3 T241M Polymorphism and Head and Neck Cancer Susceptibility: a Meta-analysis of Case-control Studies

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Abstract

Background: To evaluate the role of the X-ray repair cross complementing group 3 (XRCC3) T241M polymorphism in head and neck cancer susceptibility. Materials and Methods: We performed a meta-analysis of all available studies, which included 3,191 cases and 5,090 controls. Results: Overall, a significant risk effect of the T241M polymorphism was not found under homologous contrast (MM vs TT: OR=1.293, 95% CI=0.926-1.805; TM vs TT: OR=1.148 95% CI=0.930-1.418) and recessive models (MM vs TT+TM): OR=1.170, 95% CI=0.905-1.512, but a significantly increased risk was observed under a dominant model (MM+TM vs TT): OR=1.243, 95% CI=1.001-1.544. In stratified analyses, there were no significant associations for Asians or Caucasians. Conclusion: Our meta-analysis suggested the XRCC3 241M allele (MM+TM) might act as a head and neck cancer risk factor among all subjects, and the effect of T241M polymorphism on head and neck susceptibility should be studied with a larger, stratified population.

Keywords: Meta-analysis - head and neck cancer - XRCC3

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Introduction

Head and neck cancers (HNC) including oral, oropharynx, hypopharynx, pharyngeal and larynx are among the most common types of cancer and represent a major health problem, there are approximately 540,000 new cases and 271,000 deaths annually worldwide for a mortality of approximately 50% (Szymańska et al., 2010). Development of HNC is a multi-factorial process associated with a variety of risk factors. The principal risk factors for this disease include tobacco and alcohol use, exposure to the human papillomavirus (HPV) contributes to the development of at least 90% of squamous cell carcinoma of the head and neck (SCCHN) cases (Parkin et al., 2005) in a growing younger population. It has been reported that HNC is much more common in smokers than in non-smokers and most common in males over 50 years of age (Kamangar et al., 2006). In recent years, evidence has accumulated to support the hypothesis that diet may also play an important etiological role in development of the disease, and 10-15% of (SCCHN) cases in Europe are associated with a low intake of fruit and vegetables (Nicolotti et al., 2011; Chuang et al., 2012; Stott-Miller et al., 2012). Furthermore, candidate gene association studies also provide cumulative evidence that genetic factors including family history and polymorphisms in genes, such as DNA repair genes, play an important role in the development of HNC.

Many environmental factors, such as radiation, diet, smoking, and endogenous or exogenous estrogens, are associated with DNA damage (Schottenfeld et al.,2006). Unrepaired or misrepaired DNA results in gene mutations, chromosomal alterations and genomic instability. X-ray repair cross-complementing group 3 (XRCC3) belongs to the RAD51 gene family and encodes a protein that functions in the homologous recombination repair of DNA double strand break and participates in DNA double-strand break/recombination repair and likely participates in homologous recombination repair (HRR) (Tebbs et al., 1995; Brenneman et al., 2000). XRCC3 gene has been found polymorphic in the head and neck cancer; The Thr241Met substitution is the most thoroughly investigated polymorphism in XRCC3 due to a (C>T) transition at exon7 (XRCC3-18067C>T, rs861539), in this study, we called this SNP in the XRCC3 gene "T241M" for short. Another two polymorphisms investigated by a few studies is XRCC3-4541A>G (5'-UTR, rs1799794) and XRCC3 c.562-14 A>G (IVS5-14,rs1799796) (Werbrouck et al., 2008).

In the past decades, molecular epidemiological studies had investigated the relationship between the XRCC3 T241M polymorphism and predisposition to head and

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neck cancer. However, results of these studies were controversial, which might be caused by the limitation of individual studies. Therefore, the aim of this study was to assess the association of XRCC3 T241M polymorphism with the risk of head and neck cancer by conducting a meta-analysis from all eligible casecontrol studies published to date.

Materials and Methods

Study identification and selection

We searched for studies in the PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) electronic databases by using the terms "head and neck cancer", "oral cancer", "oropharyngeal cancer", "hypopharynx cancer" "laryngeal cancer", "pharyngeal cancer", "XRCC3", "excision repair cross-complementing group 3" and "polymorphism". The search was performed without any restrictions on language and was focused on studies that had been conducted in humans.

Inclusion criteria were defined as follows: (1) The articles evaluated the association between XRCC3 T241M polymorphisms and the risk of head and neck cancer; (2) The studies designed as case-control; (3) The sufficient data available to estimate an odds ratio (OR) with its 95% CI.

Data extraction

Information was carefully extracted from all eligible publications independently by two investigators according to the inclusion criteria listed above, discrepancies were adjudicated by a third reviewer until consensus was achieved on every item. The following information was extracted from each included publication: the first author's name, country or region, year of publication, source of publication, total numbers of cases and controls, and numbers of cases and controls who harbored the XRCC3 T241M polymorphism.

Statistical analysis

We assessed the strength of association between XRCC3 T241M polymorphism and head and neck cancer risk by using ORs with 95% CIs which were obtained from the data given in the eligible studies. Although fixed-effect model and random-effects model yielded similar conclusions, we chose to use the random-effects model with Mantel-Haenszel statistics (DerSimonian et al., 1986; Ades et al., 2005), which assumed that the true underlying effect varied among included individuals. Moreover, many investigators also consider that the random effects model to be a more natural choice than fixed effects model in medical decision-making contexts. First, the pooled ORs were performed for codominant model (MM vs TT, TM vs TT), dominant model (MM+TM vs TT), and recessive model (MM vs TT+TM) respectively. Subgroup analyses were done by ethnicity and source of controls. Heterogeneity assumptions among studies was checked by the Chi square-test based Q-statistic. A significant Q-statistic ($P < 0.05$) indicated heterogeneity across studies (Cochran WG., 1954). Meanwhile, we measured the effect of heterogeneity by another measure, $I^2 = 100\% \times (Q - df)/Q$ (Higgins et al., 2002). Publication bias was observed with the funnel plot and Egger's linear regression test (Egger et al., 1997).

Results

Characteristics of studies

Through searching and selection, a final list of 15 eligible studies were collected for meta-analysis (Shen et al., 2002; Benhamou et al., 2004; Huang et al., 2005; Majumder et al., 2005; Rydzanicz et al., 2005; Kietthubthew et al., 2006; Matullo et al., 2006; Wen et al., 2007; Werbrouck et al., 2008; Yen et al., 2008; Kietthubthew et al., 2010; Sliwinski et al., 2010; Gugatschka et al., 2011; Al-Hadyan et al., 2012; Kostrzewska-Poczekaj et al., 2012). In total, the 15 eligible studies provided 3,191 cases and 5,090 controls about the relationship between XRCC3 T241M polymorphism and head and neck cancer risk. The characteristics of selected studies are summarized in Table 1. Almost all of the cases were histologically confirmed. The controls were primarily healthy populations. There were 6 groups of Asians, 9 groups of Caucasians; 10 groups of

Table 1. Main Characteristics of All Studies Included in the Meta-analysis

First author	Year	Ethnicity	Area	Study Design	No. of Cases	No. of Control	HWE	Case (genotype)			Control (genotype)		
								TT	TM	MM	TT	TM	MM
Kostrzewska-Poczekaj M	2012	Caucasian	Poland	HB	293	160	0.037	35	138	120	22	58	80
Khaled S	2012	Asian	Saudi Arabia	HB	156	251	0.083	51	86	19	101	106	44
Gugatschka M	2011	Caucasian	Austria	HB	168	461	0.227	61	76	31	186	204	71
Sliwinski T	2010	Caucasian	Poland	PB	191	353	0.9	29	97	65	131	169	53
Kietthubthew S	2010	Asian	Thailand	HB	60	56	-	49	11		49	7	
Werbrouck J	2008	Caucasian	Belgium	PB	152	157	0.014	44	75	33	69	59	29
Yen CY	2008	Asian	China	HB	103	98	0.634	96	7	0	89	9	0
Wen SX	2007	Asian	China	HB	175	525	-	144	31		482	43	
Kietthubthew S	2006	Asian	Thailand	HB	106	164	0.958	83	22	1	140	23	1
Matullo G	2006	Caucasian	European	PB	82	1094	0.249	29	39	14	383	544	167
Majumder M	2005	Asian	India	HB	310	348	0.071	201	97	12	220	120	8
Rydzanicz M	2005	Caucasian	Poland	PB	266	143	0.247	31	112	123	14	71	58
Huang WY	2005	Caucasian	Maryland	PB	516	760	0.397	232	223	61	329	334	97
Benhamou S	2004	Caucasian	France	HB	246	166	0.281	86	116	44	47	89	30
Shen H	2002	Caucasian	USA	HB	367	354	0.45	150	159	58	141	170	43

HB hospital based; PB, population based; HWE Hardy–Weinberg equilibrium (>0.05 was considered representative of agreement with HWE in the controls)

Table 2. Results of Meta-analysis for XRCC3 Thr241Met Polymorphism and Head and Neck Cancer

Study group	Homozygous MM vs TT		Heterozygous TM vs TT		Dominant model (MM+TM vs TT)		Recessive model (MM vs TT+TM)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Total	1.293(0.926-1.805)	0	1.148(0.930-1.418)	0.001	1.243(1.001-1.544)	0	1.170(0.905-1.512)	0.001
Ethnicity								
Asian	1.074(0.643-1.793)	0.491	1.179(0.795-.1.749)	0.09	1.368(0.958-1.953)	0.034	0.991(0.472-2.081)	0.197
Caucasian	1.319(0.893-1.949)	0	1.139(0.874-1.485)	0.001	1.184(0.892-1.571)	0	1.205(0.911-1.594)	0
Source of controls								
HB	1.098(0.868-1.389)	0.715	1.057(0.851-1.312)	0.093	1.164(0.937-1.446)	0.028	1.002(0.763-1.317)	0.135
PB	1.567(0.768-3.200)	0	1.283(0.811-2.029)	0	1.376(0.821-2.380)	0	1.368(0.887-2.111)	0.001

P value of Q test for heterogeneity

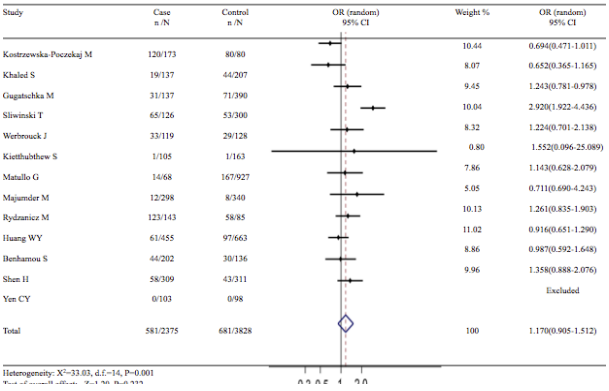

Figure 1. Forest Plot (random effects model) of Head and Neck Cancer Risk Associated with XRCC3 T241M Polymorphism for the MM Versus TT

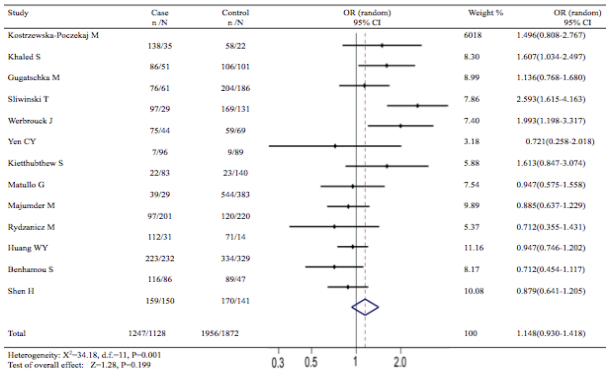

Figure 2. Forest Plot (random effects model) of Head and Neck Cancer Risk Associated with XRCC3 T241M Polymorphism for the TM Versus TT

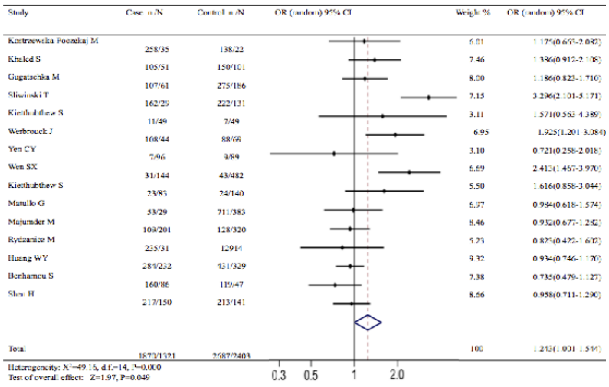

Figure 3. Forest plot (random effects model) of Head and Neck Cancer Risk Associated with XRCC3 T241M Polymorphism for (MM+TM) Versus TT

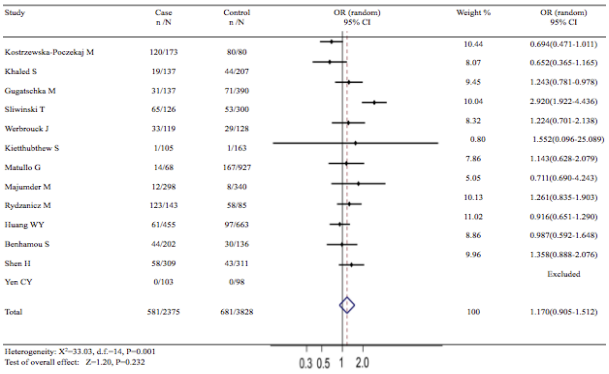

Figure 4. Forest Plot (random effects model) of Head and Neck Cancer Risk Associated with XRCC3 T241M Polymorphism for MM vs (TT+TM)

hospital-based and 5 groups of population-based. The polymorphisms in the control subjects were calculated in Hardy–Weinberg equilibrium.

Quantitative synthesis

Table 2 listed the main results of the meta-analysis for XRCC3 T241M polymorphisms. Overall, no significant associations were found between XRCC3 T241M polymorphism and head and neck cancer risk when all studies were pooled into the meta-analysis under homologous contrast (MM vs TT: OR=1.293, 95% CI=0.926-1.805, 95% CI=0.851–1.541, P=0.000 for heterogeneity; TM vs TT: OR=1.148 95% CI=0.930-1.418, P=0.001 for heterogeneity) (Figure 1,2) and recessive model (OR=1.170, 95% CI=0.905-1.512, P=0.001for heterogeneity) (Figure 4). However, as shown in Figure 3, significant associations were found for the dominant model (OR=1.243, 95% CI=1.001-1.544 P=0.000 for heterogeneity). In stratified analyses, as showed in Table 2, there was not significant association for Aians nor Caucasians, similarly, there was also not significant association for hospital-based nor pupolation-based subjects .

Heterogeneity and sensitivity analysis

There was substantial heterogeneity among these studies in overall comparisons. Therefore, we assessed the source of heterogeneity by source of controls and ethnicity. It was detected that the systemic results were not affected by these characteristics. The corresponding pooled ORs were not qualitatively altered with or without this study.

Publication bias test

We performed funnel plot and Egger's test to assess the publication bias of literatures. The shape of the funnel

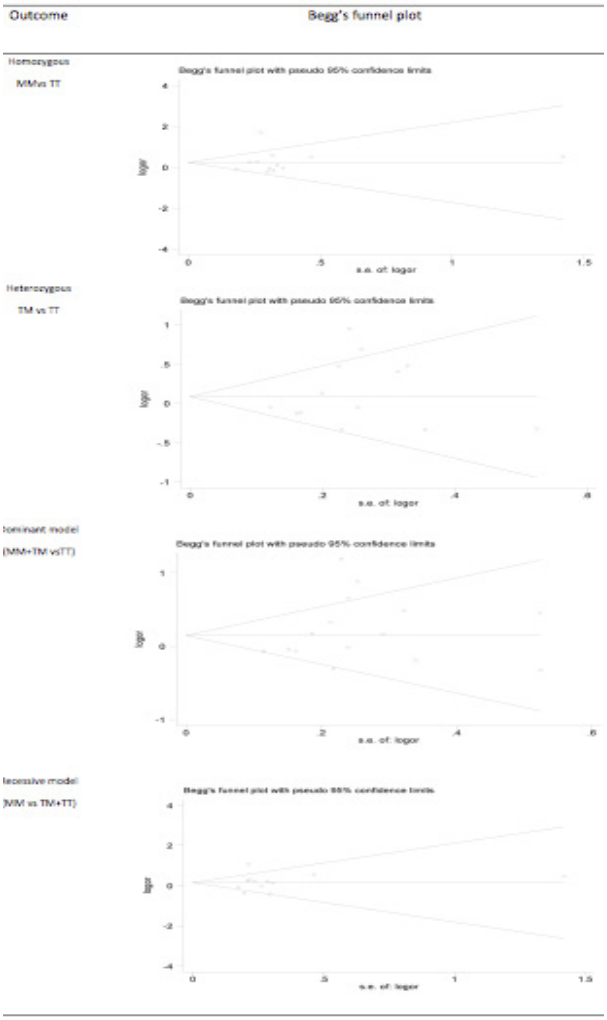

Figure 5. Begg's Funnel Plot of XRCC3 T241M Polymorphism and Head and Neck Cancer Risk

plots did not reveal any evidence of obvious asymmetry in each group (Figure 5) . The results of Egger's test did not suggest any evidence of publication bias.

Discussion

To clarify the controversial results from previous reports in the present studies, we identified all available studies and performed a meta-analysis to examine the association between XRCC3 T241M polymorphism and head and neck cancer risk. A total of 15 studies on the T241M genotype (8,281 subjects) were critically reviewed. Nevertheless, our analysis suggested that XRCC3 might play a small role in cancer susceptibility on homologous contrast (MM vs TT: OR=1.293, 95% CI = 0.926- 1.805; TM vs TT: OR=1.148 95% CI=0.930-1.418) and the XRCC3 241T allele (OR=1.170, 95% CI=0.905-1.512), which was consistent with the characteristics of low penetrance genes. However, the XRCC3 241M allele might act as a head and neck cancer risk factor among all subjects (OR=1.243, 95% CI=1.001-1.544). In the subgroup analysis, insignificant effects were found for any genetic contrast.

Assessment of effect modification might be particularly beneficial in studies of DNA-repair polymorphisms, because a single polymorphism with likely weak effects on the individual's phenotype might not be measurable except in the context of some supporting environmental factors, such as tobacco smoke or ionizing radiation. The double-strand break DNA repair pathway had been implicated in maintaining genomic stability and affecting cancer risk. Both biological and biochemical evidences indicated a direct role for XRCC3 in DSBs repair (Bishop et al., 1998; Pierce et al., 1999). Functional data also suggested that the XRCC3 Thr241Met polymorphism might be associated with slightly but not significantly decreased DNA repair capacity (Araujo et al., 2002). HRR was a major mechanism for double-strand break DNA repair. XRCC3 had a multiple function and acted both early and late in the HRR pathway (Tebbs et al., 1995).

The XRCC3 T241M variant has been shown to be functionally defective in suppressing duplication of the genome, which is thought to be important for maintaining genomic stability. Therefore, it seems much reasonable to take polymorphisms in XRCC3 as the low-penetrance variant candidate for cancer susceptibility.

There were still some limitations inherited from the published studies. First, there was the lack of of investigation about the detailed molecular mechanism of the association between XRCC3 T241M polymorphism and head and neck cancer risk. Second, the number of studies involved in the meta-analysis was relatively small, so the subgroup analysis was hard to perform. Third, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other co-variates including age, smoking status, environmental factors, and lifestyle. Therefore, in order to achieve a more convincible conclusion, further analysis using adjusted individual data and larger sample size was required, and further mechanism investigation should also be performed.

In conclusion, supported by a meta-analysis with a total of 3,191 cases and 5,090 controls, our study indicated that the XRCC3 241M allele might act as a head and neck cancer risk factor among all subjects. Although there were some limitations, our meta-analysis can still provided valuable information for studying the relationship between XRCC3 T241M polymorphism and head and neck cancer risk.

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The author(s) declare that they have no competing interests.

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