The association of XRCC3 Thr241Met genetic variant with risk of prostate cancer: a meta-analysis

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Abstract

Background: Previous studies suggest that the X-ray repair cross-complementing group 3 gene (XRCC3) Thr241Met genetic variant could be potentially associated with the risk of prostate cancer. However, results from these published studies were conflicting rather than conclusive.

Objectives: This meta-analysis aimed to conduct a better understanding of the effects of XRCC3 Thr241Met genetic variant on prostate cancer risk.

Methods: We identified three eligible studies, 499 prostate cancer cases and 571 controls.

Results: Overall, significant associations were detected in the heterozygote comparison genetic model (CT versus (vs.) CC: OR = 0.71, 95% CI 0.53-0.94, Z =2.38, p= 0.017), and the dominant genetic model (TT/CT vs. CC: OR = 0.74, 95% CI 0.57-0.98, Z = 2.11, p =0.035). In the subgroup analysis by ethnicities, we found that this genetic variant was significantly associated with the decrease risk of prostate cancer in Caucasians for heterozygote comparison genetic model (CT vs. CC: OR = 0.66, 95% CI 0.44-0.98, Z = 2.04, p = 0.042). No publication bias was found in this study.

Conclusions: Results from this meta-analysis indicate that the XRCC3 Thr241Met genetic variant is associated with prostate cancer risk.

Keywords: Prostate cancer; XRCC3 gene; Genetic variant; Meta-analysis

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Introduction

Prostate cancer is the most common malignancy of men in the world, accounting for 10% of men cancer-related mortality[1,2]. The etiology of prostate cancer is largely unknown, although genetic and environmental factors might increase risk of prostate cancer[2-6]. The X-ray repair cross-complementing group 3 (XRCC3) is one of the DNA repair genes, and is an important candidate gene for mediating the genetic influence on prostate cancer[7-13]. The C18067T genetic variant in XRCC3 gene at exon 7(C>T, rs861539), one of the most studied functional genetic variants, results from a C to T mutation and causes the substitution of Threonine (Thr) to Methionine (Met) at codons 241 (p.Thr241Met), has been potentially associated with the risk of prostate cancer [7-10]. However, results from published studies were conflicting rather than conclusive. Therefore, to clarify the effects of XRCC3 Thr241Met genetic variant on prostate cancer risk, we conducted a meta-analysis of all available published studies to date.

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Materials and methods

Publication search

Pubmed, Excerpta Medica Database (EMBASE), and Chinese National Knowledge Infrastructure (CNKI) databases were searched using the search terms: "prostate cancer/neoplasm", "XRCC3",m"Thr241Met", and "rs8761539" (the last search was updated on June 2014). Publication searching was utilized without limitation on language and publication date. Two investigators searched the publication literature and extracted data independently.

Inclusion, exclusion criteria and Data extraction

For inclusion criteria in the present meta-analysis, the selected eligible articles had to provide informa-

tion as follows:[1] using a case-control design;[2] evaluation of XRCC3 Thr241Met genetic variant with the risk of prostate cancer;[3] offering enough data for estimating the odds ratios (ORs) and 95% confidence intervals (CIs);[4] only full-text articles were included. The exclusion criteria of articles were as followed:[1] duplication; [2] no usable data was provided;[3] abstract, comment, letters, and review. For each eligible case-control articles, the following information was collected: the first author's name, publishing year, country, ethnicities, numbers of cases and controls, genotyping methods, numbers of allele and genotype.

Statistical analysis

The strength of the association of XRCC3 Thr241Met genetic variant with the risk of prostate cancer was assessed by the pooled ORs with their 95% CIs. Subgroup analyses were evaluated by ethnicities.

The significance of pooled ORs was determined by the Z-test. The heterogeneity assumption was evaluated by the chi-square-based Q-test[14,15] and the I2 index [16]. I2 index < 50% and/or P-value > 0.10 for Q-test indicated a lack of heterogeneity among the studies[17]. The fixed effect model (the Mantel-Haenszel method) was utilized to calculate the pooled ORs when the heterogeneity was not significant among the studies[18]. Otherwise, the random-effects model (the DerSimonian and Laird method) was employed[19]. The Begg's funnel plot and Egger's linear regression methods were used to assess the publication bias[20,21]. All analyses were analyzed by the STATA software (version 11.0; STATA Corporation, College Station, TX, USA). P-values < 0.05 were defined as statistically significant level.

Results

Eligible studies

According to the inclusion and exclusion criteria listed above for the association of XRCC3 Thr241Met genetic variant with the risk of prostate cancer, three eligible studies with 499 prostate cancer cases and 571 controls were finally included in this meta-analysis[7-9]. There were two studies of subjects of Caucasians decent[7-9], and one study of Asians decent[8]. The study characteristics were presented in Table 1. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF) methods were determined to investigate the genotypes of XRCC3 Thr241Met genetic variant in these included studies.

Table 1. The characteristics of eligible studies included in this meta-analysis.

First author	Year	Country	Ethnicity	Genotyping methods	No. (cases/controls)	Case (%)			Control (%)		
						CC	CT	TT	CC	CT	TT
Ritchey	2005	USA	Caucasians	MALDI-TOF	159/247	139	17	3	214	31	2
Mandal	2010	India	Asians	PCR-RFLP	224/192	137	78	9	103	77	12
Dhillon	2011	Australia	Caucasians	PCR-RFLP	116/132	60	44	12	54	72	6

MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR-RFLP, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism

Meta-analysis

Table 2 summarized the association strength between XRCC3 Thr241Met genetic variant and the risk of prostate cancer. In the overall, significant associations were detected in heterozygote comparison genetic model (CT versus (vs.) CC: OR = 0.71, 95% CI 0.53-0.94, Z =2.38, P = 0.017, Table 2, Figure 1), and dominant genetic model (TT/CT vs. CC: OR = 0.74, 95% CI 0.57-0.98, Z =2.11, P = 0.035, Table 2).

Table 2. The meta-analysis of *XRCC3* Thr241Met genetic variant and prostate cancer risk.

Comparisons	Population	Test of association					Test of Heterogeneity		
		N	OR (95% CI)	Z	P-value	Model	χ^2	P-value	I^2(%)
TT vs. CC	Overall	3	1.05(0.56-1.94)	0.14	0.887	F	3.58	0.167	44.1
	Asians	1	0.56(0.23-1.39)	1.25	0.213	F	-	-	-
	Caucasians	2	1.91(0.77-4.73)	1.40	0.161	F	0.05	0.815	0
CT vs. CC	Overall	3	0.71(0.53-0.94)	2.38	0.017	F	1.31	0.519	0
	Asians	1	0.76(0.51-1.14)	1.32	0.188	F	-	-	-
	Caucasians	2	0.66(0.44-0.98)	2.04	0.042	F	1.05	0.305	4.9
TT/CT vs. CC	Overall	3	0.74(0.57-0.98)	2.11	0.035	F	0.86	0.650	0
	Asians	1	0.74(0.50-1.09)	1.54	0.122	F	-	-	-
	Caucasians	2	0.75(0.51-1.11)	1.44	0.150	F	0.85	0.355	0
TT vs. CT/CC	Overall	3	1.37(0.51-3.73)	0.62	0.534	R	4.43	0.109	54.8
	Asians	1	0.63(0.26-1.52)	1.03	0.304	F	-	-	-
	Caucasians	2	2.41(1.00-5.82)	1.95	0.051	F	0	0.979	-
T vs. C	Overall	3	0.85(0.68-1.06)	1.47	0.142	F	0.91	0.634	0
	Asians	1	0.76(0.56-1.05)	1.65	0.100	F	-	-	-
	Caucasians	2	0.93(0.68-1.27)	0.45	0.653	F	0.17	0.680	0

N, number of comparisons; OR, odds ratio; CI, confidence interval; vs., versus; TT vs. CC: Homozygote comparison; CT vs. CC: Heterozygote comparison; TT/CT vs. CC: Dominant model; TT vs. CT/CC: Recessive model; T vs. C: Allele comparison; R, random effect model; F, fixed effect model; Random effect model was chosen when P-value < 0.10 and/or I^2 > 50% for heterogeneity test; otherwise fixed effect model was used.

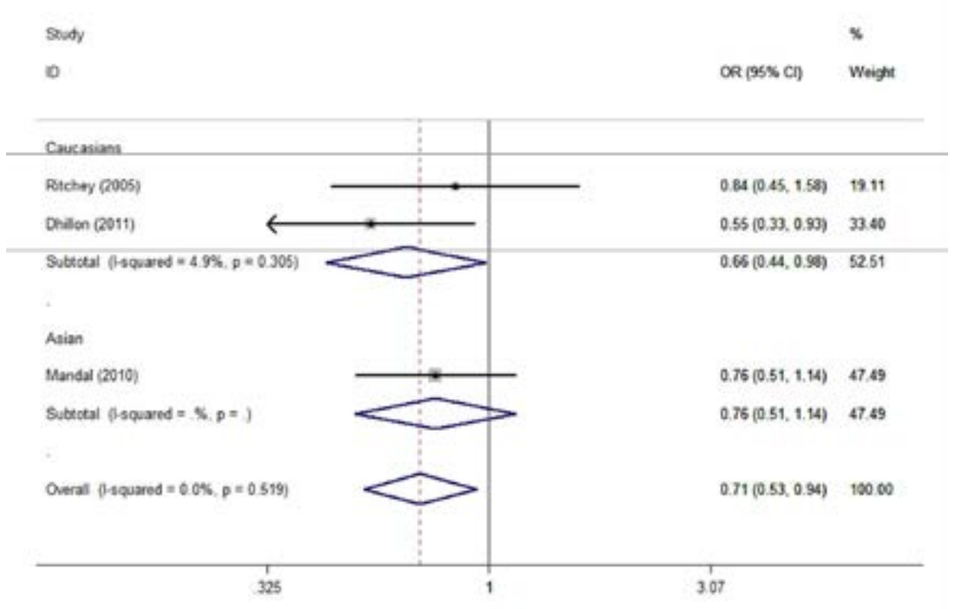
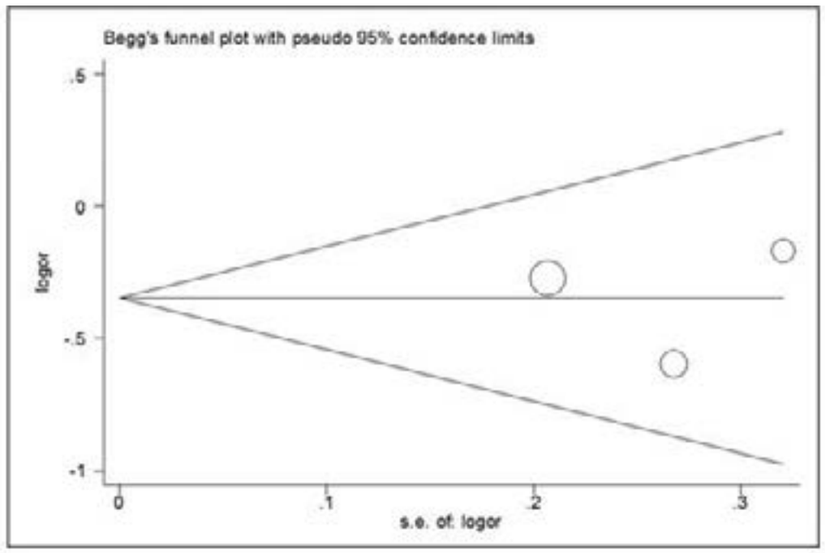


Figure 1. Forest plots of the association between *XRCC3* Thr241Met genetic variant and prostate cancer risk (Heterozygote comparison by ethnicities (CT versus. CC)).

In the subgroup analysis by ethnicities, we found that the XRCC3 Thr241Met genetic variant was significantly associated with the decrease risk of prostate cancer in Caucasians for heterozygote comparison genetic model (CT vs. CC: OR = 0.66, 95% CI 0.44-0.98, Z = 2.04, P = 0.042, Table 2). Our data indicated that there were no significant associations between XRCC3 Thr241Met genetic variant and prostate cancer risk in other genetic models (All P-values >0.05, Table 2). No evidence of publication bias was found in all comparison genetic models (All P-values > 0.05).

Figure 2. Begg's funnel plot for publication bias test (Heterozygote comparison (CT versus. CC)).



Discussion

Emerging evidence suggest that the XRCC3 is one of the most important candidate genes for influencing the risk of prostate cancer, and several studies have carried out to investigate the potential association of XRCC3 Thr241Met genetic variant with the risk of prostate cancer. Ritchey and colleagues reported that XRCC3 Thr241Met genetic variant showed no significant associations with the risk of prostate cancer, while a significant interaction was found for XRCC3 Thr241Met genetic variant and consumption of total preserved foods[7]. Mandal suggested that no significant association of XRCC3 Thr241Met genetic variant genotypes with the risk of prostate cancer was observed[8]. Dhillon demonstrated that there was no association between the XRCC3 Thr241Met genetic variant and prostate cancer risk [9]. The present meta-analysis, including 499 prostate cancer cases and 571 controls concerning the XRCC3 Thr241Met genetic variant, explored the more reliable association between Thr241Met genetic variant in XRCC3 gene and the risk of prostate cancer. Overall, we detected that this genetic variant were significantly associated with the risk of prostate cancer. Besides, in the subgroup analysis by ethnicities, we found that this genetic variant was significantly associated with the decrease risk of prostate cancer only in Caucasians population. Thus, results from this meta-analysis indicate that the XRCC3 Thr241Met genetic variant is associated with prostate cancer risk.

Some advantages of this meta-analysis should be addressed. First, a strict searching strategy to enroll all the possible eligible articles as much as possible was conducted. Second, all included articles had acceptable quality. Third, the whole pooled findings are unbiased. However, some limitations of this meta-analysis should be addressed. Firstly, only three eligible articles were eventually enrolled in this meta-analysis. Secondly, the enrolled articles only concerned about Asians and Caucasians, not mentioned about other ethnicities. Thirdly, only published articles were enrolled, unpublished articles were not enrolled in this study.

Conclusion

This meta-analysis provided evidence of the association of XRCC3 Thr241Met genetic variant with risk of prostate cancer. More well-designed studies in large populations should be carried out to confirm these findings.

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Conflict of Interest

None.

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