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Original Article

Genetic Thr241Met polymorphism of XRCC3 gene and risk of cancer: a meta-analysis of 7845 cases and 9822 controls

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Abstract: *XRCC3* gene plays crucial roles in DNA damage repairing that is closely involved in pathogenesis of tumor. Studies have been conducted to identify the potential relationship between XRCC3 gene and Thr241Met polymorphism in patients with cancer. However, the results are still controversial up to now. In this study, we aim to investigate the pooled association based on the meta-analysis. Literature research was performed in the PubMed, EBSCO, and BIOSIS databases published in English before December 2015. The association was assessed by odds ratio (OR) with 95% confidence interval (CI). In total, 25 studies were included in this meta-analysis containing 7845 patients and 9822 controls. XRCC3 Thr241Met polymorphism was not correlated with the increased risks of developing cancer (CT vs. CC, OR: 1.08, 95% CI 0.92-1.28, P=0.34; TT vs. CC, OR: 1.04, 95% CI 0.93-1.17, P=0.46; recessive model TT vs. CC+CT, OR: 1.05, 95% CI 0.95-1.17, P=0.32; dominant genetic model CT+TT vs. CC, OR: 1.00, 95% CI 0.94-1.07, P=0.96). Besides, no obvious elevation was identified in the risk of developing cancer among Caucasians, mixed and Asians. Subgroup analysis involving different types of cancer also showed no significant associations in lung cancer, glioma, melanoma skin cancer, gastric cancer, and prostate cancer. Considering ethnicities and the limited sample size in this meta-analysis, further well-designed studies with a large sample size are needed to confirm our results.

Keywords: Meta-analysis, cancer, XRCC3, Thr241Met, polymorphism

Introduction

Cancer, one of the most common fatal diseases worldwide causing great public threats, is reported to be related to the complex interactions between genetic background and the environmental factors [1, 2]. Recently, genetic variation has been considered to lead to various consequences after the environmental exposure. Besides, it may be associated with the pathogenesis and progression of various types of cancer [1, 3, 4]. Up to now, DNA-repairing systems are regarded to play crucial roles in the maintenance of genomic variation and integrity of DNA-repairing genes. Cancer is apt to develop upon alternation of DNA repair capacity and accumulation of DNA damage [5] induced by various factors such as chemical exposure, radiation, as well as other factors that triggers the risk for malignancy [4, 6, 7].

The X-ray repair cross -complementing group 3 (XRCC3) is a member of gene family responsible for repairing DNA double strand breaks (DSB) induced by ionizing radiation exposure and/or normal metabolic processes [8]. As is known to all, XRCC3 gene coded a protein involved in homologous recombinational repair (HRR) for DSB of DNA and cross-link repair in mammalian cells [9]. During HRR process, XRCC3 could interact with Rad51 protein, which is crucial for the maintenance of chromosome stability. Up to now, one of the common polymorphisms in exon 7 of the XRCC3 gene is reported to trigger an amino acid substitution at codon 241 (Thr241Met), which may affect the enzyme function and/or its interaction with other proteins involved in DNA damage and repair [10]. The predominant homozygous allele, the heterozygous and the rare homozygous allele were wild-type genotype (C/C), the

Table 1. Characteristics of the studies included in the meta-analysis

Study	Year	Ethnicity	Case types	Sample size (case/control)	Cases			Controls			HWE
					CC	CT	TT	CC	CT	TT	P
Bertram [9]	2004	Caucasian	Melanoma skin cancer	140/335	50	68	22	135	160	40	0.48
David-Beabes [10]	2001	Caucasian	Lung cancer	178/453	76	78	24	175	210	68	0.70
David-Beabes [10]	2001	Mixed	Lung cancer	153/234	90	54	9	136	88	10	0.36
Duan [11]	2002	Mixed	Melanoma skin cancer	305/319	119	148	38	116	158	45	0.45
Figl [12]	2010	Caucasian	Melanoma skin cancer	1184/1274	451	541	192	436	645	193	0.07
Gonçalves [13]	2011	Mixed	Melanoma skin cancer	192/192	78	89	25	95	79	18	0.79
Han [14]	2004	Mixed	Melanoma skin cancer	187/810	75	84	28	300	396	114	0.36
Huang GP [15]	2006	Asian	Gastric cancer	309/188	149	135	25	112	66	10	0.95
Huang WY [16]	2005	Caucasian	Gastric cancer	281/390	128	128	25	174	163	53	0.14
Jacobsen [17]	2004	Caucasian	Lung cancer	246/269	95	123	28	113	113	43	0.11
Kiyohara C [18]	2012	Asian	Lung cancer	462/379	352	97	13	295	77	7	0.45
Liu [19]	2009	Caucasian	Glioma	371/360	132	179	60	151	165	44	0.92
Mandal [20]	2010	Asian	Prostate cancer	224/192	137	78	9	103	77	12	0.63
Misra [21]	2001	Caucasian	Lung cancer	313/306	160	124	29	149	134	23	0.34
Palli D [22]	2010	Caucasian	Gastric cancer	294/546	95	148	51	189	268	89	0.71
Popanda [23]	2004	Caucasian	Lung cancer	462/459	175	201	86	168	222	69	0.76
Qian B [24]	2011	Asian	Lung cancer	581/603	521	60	0	533	67	3	0.57
Ritchey [25]	2005	Caucasian	Prostate cancer	159/247	139	17	3	214	31	2	0.46
Ruzzo A [26]	2007	Caucasian	Gastric cancer	90/121	35	44	11	36	66	19	0.21
Wang [27]	2004	Caucasian	Glioma	309/342	134	138	37	147	147	48	0.25
Winsey [28]	2000	Caucasian	Melanoma skin cancer	125/211	39	65	21	110	78	23	0.11
Xia [29]	2008	Asian	Lung cancer	103/139	91	12	0	118	21	0	0.34
Ye W [30]	2006	Caucasian	Gastric cancer	126/472	52	63	11	203	218	51	0.51
Zhang [31]	2007	Asian	Lung cancer	291/273	259	30	2	244	28	1	0.84
Zhou [32]	2009	Asian	Glioma	760/708	677	80	3	629	75	4	0.29

homozygote (T/T), and the heterozygote (C/T), respectively.

To date, extensive molecular epidemiological studies are carried out to determine the correlation between the XRCC3, Thr241Met polymorphism and risk of cancers. Nevertheless, the results are still controversial. In this study, a meta-analysis was performed to identify the correlation between XRCC3, Thr241Met polymorphism and risk of various types of cancers that have been investigated.

Material and methods

Search strategy

Studies about the relationship between the XRCC3 Thr241Met polymorphism and risk of cancer published prior to December 2015 were identified by on-line search. Only the literatures in English were included in the meta-analysis. Literature research was conducted in the Medline, EB-SCO, and BIOSIS. Besides, hand search was carried out to identify the potential literatures that may not be included in the database research. Literature research was conducted using the following keywords, including "XRCC3" AND ("genetic variant*" or "genetic variation*" or "polymorphism*") AND ("lung cancer" or "prostate cancer" or "melanoma" or "Glioma" or "gastric cancer").

Inclusion criteria

The studies were reviewed by two investigators (Jian Song, Liang Liu) independently to determine the eligibility. Studies met with the following criteria were ascertain to the inclusion: (i) the XRCC3 Thr241Met polymorphism in cancer; (ii) case-control studies; (iii) availability of proper cancer diagnosis criteria; (iv) studies performed in human; (v) studies with a larger sample size in presence of multiple publications reported by the same study group. In presence of any disagreements, a consensus

Table 2. Odds ratios (ORs) of the XRCC3 Thr241Met polymorphism and cancer risk

Subgroup	Genetic model	Sample size		Heterogeneity		Test of association			Publication
		Cases	Controls	P	I^2 (%)	95% CI	Z	P	Bias *P*-value
Overall	CT vs. CC	6811	8899	<0.00001	81	1.08 [0.92, 1.28]	0.96	0.34	0.779
	TT vs. CC	5061	6070	0.13	25	1.04 [0.93, 1.17]	0.74	0.46	0.921
	CT+TT vs. CC	7845	9822	0.02	40	1.00 [0.94, 1.07]	0.06	0.96	0.852
	TT vs. CC+CT	7845	9822	0.39	5	1.05 [0.95, 1.17]	0.99	0.32	0.655
Ethnicities									
Caucasian	CT vs. CC	3678	5020	0.02	50	1.03 [0.90, 1.18]	0.42	0.67	
	TT vs. CC	2361	3165	0.08	37	1.04 [0.91, 1.18]	0.53	0.59	
	CT+TT vs. CC	4278	5785	0.02	50	1.00 [0.92, 1.09]	0.01	0.99	
	TT vs. CC+CT	4278	5785	0.20	24	1.05 [0.93, 1.18]	0.80	0.42	
Asian	CT vs. CC	2396	2511	<0.00001	92	1.24 [0.76, 2.03]	0.85	0.40	
	TT vs. CC	2238	2071	0.24	27	1.11 [0.72, 1.71]	0.46	0.64	
	CT+TT vs. CC	2730	2482	0.13	39	1.02 [0.88, 1.18]	0.21	0.84	
	TT vs. CC+CT	2730	2482	0.39	4	1.07 [0.69, 1.64]	0.29	0.77	
Mixed	CT vs. CC	737	1368	0.35	9	0.97 [0.80, 1.19]	0.27	0.79	
	TT vs. CC	462	834	0.37	6	1.06 [0.79, 1.42]	0.38	0.70	
	CT+TT vs. CC	837	1555	0.25	27	0.99 [0.83, 1.19]	0.09	0.93	
	TT vs. CC+CT	837	1555	0.58	0	1.08 [0.82, 1.42]	0.53	0.59	
Case types									
Melanoma skin cancer	CT vs. CC	1807	2708	0.001	75	1.10 [0.83, 1.46]	0.67	0.50	
	TT vs. CC	1138	1625	0.05	54	1.20 [0.89, 1.62]	1.21	0.23	
	CT+TT vs. CC	2133	3141	0.0004	78	1.14 [0.86, 1.51]	0.91	0.37	
	TT vs. CC+CT	2133	3141	0.57	0	1.12 [0.96, 1.32]	1.43	0.15	
Lung cancer	CT vs. CC	2598	2891	0.81	0	0.95 [0.83, 1.07]	0.85	0.40	
	TT vs. CC	2010	2155	0.59	0	1.04 [0.83, 1.30]	0.32	0.75	
	CT+TT vs. CC	2789	3115	0.93	0	0.96 [0.85, 1.09]	0.62	0.53	
	TT vs. CC+CT	2789	3115	0.33	12	1.07 [0.86, 1.32]	0.60	0.55	
Gastric cancer	CT vs. CC	977	1495	0.26	24	1.13 [0.95, 1.33]	1.39	0.17	
	TT vs. CC	582	936	0.13	43	0.95 [0.73, 1.23]	0.42	0.67	
	CT+TT vs. CC	1100	1717	0.12	46	1.09 [0.93, 1.28]	1.08	0.28	
	TT vs. CC+CT	1100	1717	0.25	26	0.91 [0.71, 1.16]	0.77	0.44	
Glioma	CT vs. CC	1340	1314	0.58	0	1.09 [0.90, 1.31]	0.87	0.38	
	TT vs. CC	1043	1023	0.16	46	1.15 [0.83, 1.58]	0.83	0.41	
	CT+TT vs. CC	1440	1410	0.32	13	1.09 [0.91, 1.30]	0.93	0.35	
	TT vs. CC+CT	1440	1410	0.23	31	1.08 [0.80, 1.46]	0.50	0.62	
Prostate cancer	CT vs. CC	371	425	0.79	0	0.79 [0.56, 1.10]	1.39	0.17	
	TT vs. CC	288	331	0.17	47	0.76 [0.34, 1.67]	0.70	0.49	
	CT+TT vs. CC	383	439	0.51	0	0.79 [0.57, 1.10]	1.41	0.16	
	TT vs. CC+CT	383	439	0.20	40	0.82 [0.37, 1.79]	0.50	0.62	

should be made after careful consideration of the investigators.

Exclusion criteria

Exclusion criteria: (i) the original article can not be downloaded; (ii) the raw data were not available; (iii) languages other than English; (iv) non-human researches; (v) case reports, editorials, meeting abstract, newsletter and review articles were excluded.

Data extraction

The data were independently extracted from the selected studies through a standardized protocol by two authors. The results were reviewed by a third investigator binded to the

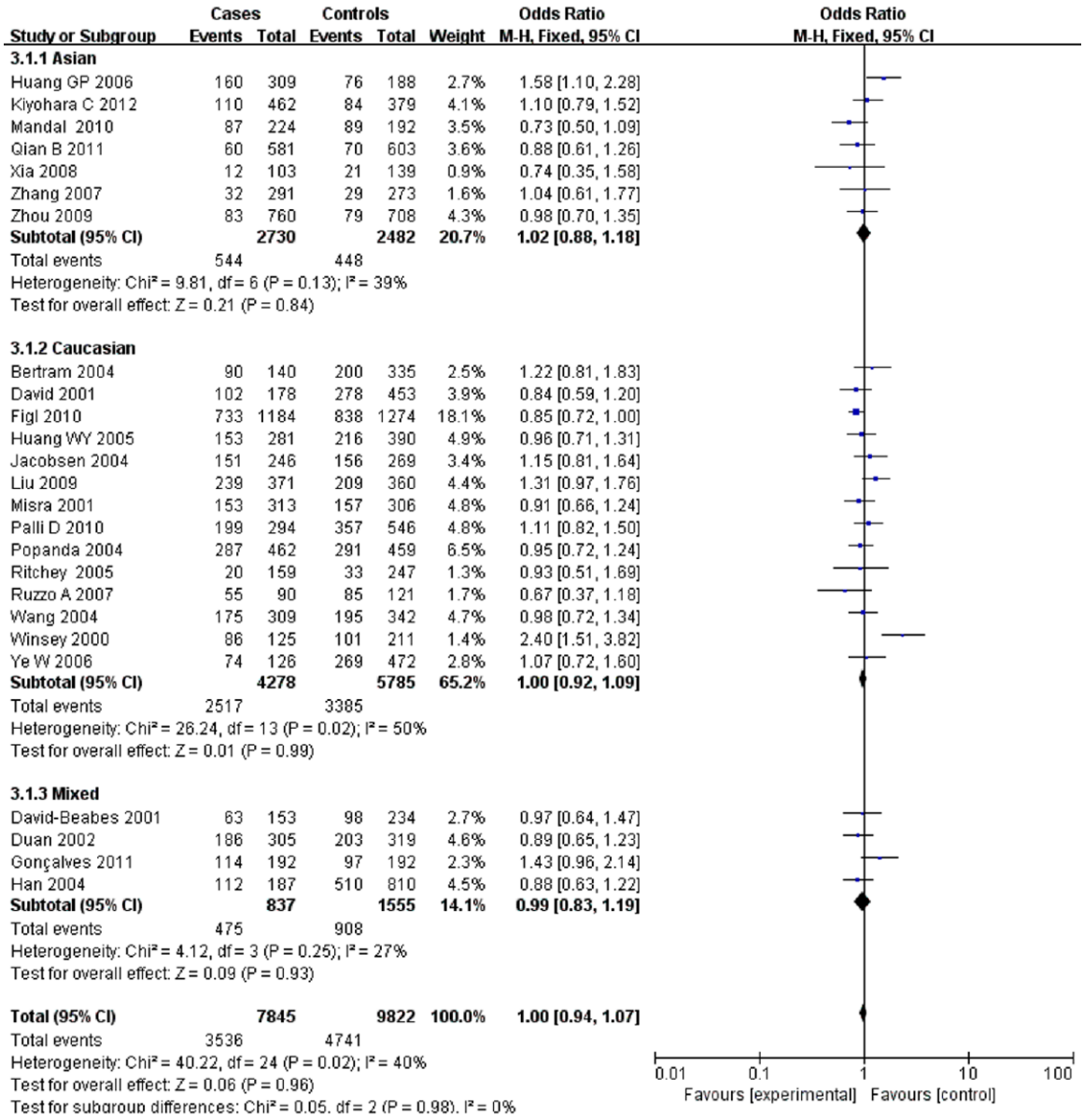

Figure 1. Forest plot for association of XRCC3 Thr241Met polymorphism and cancer risk (dominant genetic model, CT+TT vs. CC) in overall population.

analysis. The following information including first author, year of publication, types of cancer, study population such as country and ethnicity, as well as the genotype frequency and number of cases and controls was extracted from each study. Different ethnicities were divided as Caucasian, Asian and mixed (**Table 1**).

Statistical analysis

The deviation of the allele frequency from the Hardy-Weinberg Equilibrium (HWE) for distribution was analyzed by Fisher's exact test. Pooled estimates of the odds ratios (ORs) were obtained by calculating a weighted average of OR. We examined the contrast of CT vs. CC and TT vs. CC, and also examined the recessive genetic models (TT vs. CC+CT), as well as the dominant genetic models (CT+TT vs. CC). In addition, subgroup analyses were performed to determine the ethnicity and the disease conditions according to the subtype-specific effects. The relationship between the XRCC3 Thr241Met polymorphism and risk of cancer was determined by the ORs with 95% CIs. Z test was performed to evaluate the statistical significance

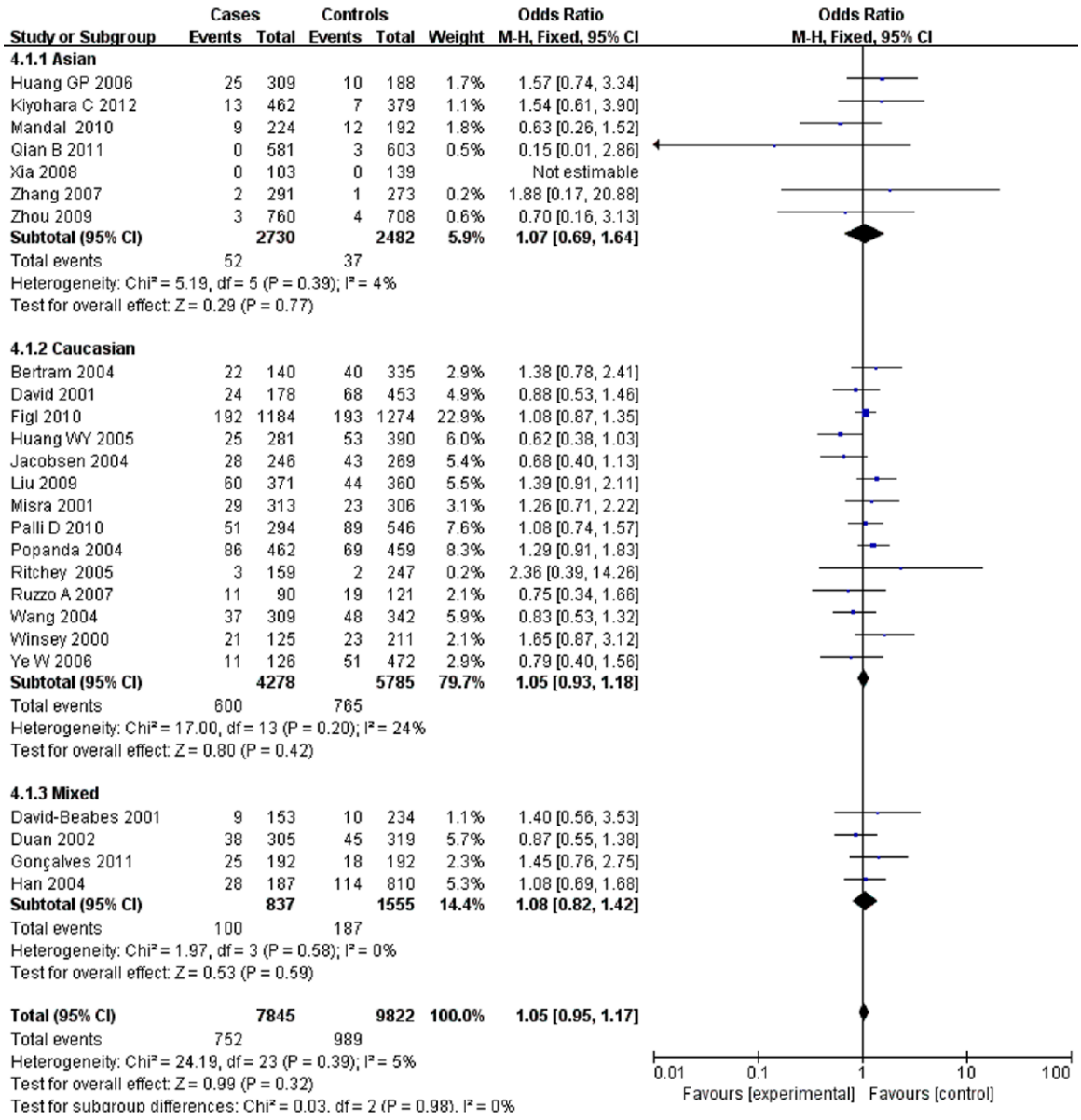

Figure 2. Forest plot for association of XRCC3 Thr241Met polymorphism and cancer risk (recessive genetic model, TT vs. CC+CT) in overall population.

of the summary OR. Chi square based Q test was performed to check the heterogeneity assumption. Also, I^2 metric (I^2 = (Q - df)/Q × 100%; I^2 < 25%, no heterogeneity; I^2=25-50%, moderate heterogeneity; I^2=50-75%, large heterogeneity; I^2 > 75%, extreme heterogeneity) was used to quantify the heterogeneity. Fixed effects model was applied in presence of effects assumed to be homogenous (P > 0.1, I^2 < 50%). Otherwise, the random-effects model was used. The results stability was evaluated by sensitivity analysis. The publication bias was evaluated by Begg's test if more than seven studies were included. Data analysis was conducted with STATA 12.0 software (Stata Corporation, College Station, TX, USA). P < 0.05 was considered as statistically significant (**Table 2**; **Figures 1**, **2**).

Sensitivity analysis

In this study, sensitivity analysis was performed to determine the stability of the results pooled with random-effects model. No substantial alternation was noticed in the pooled OR after

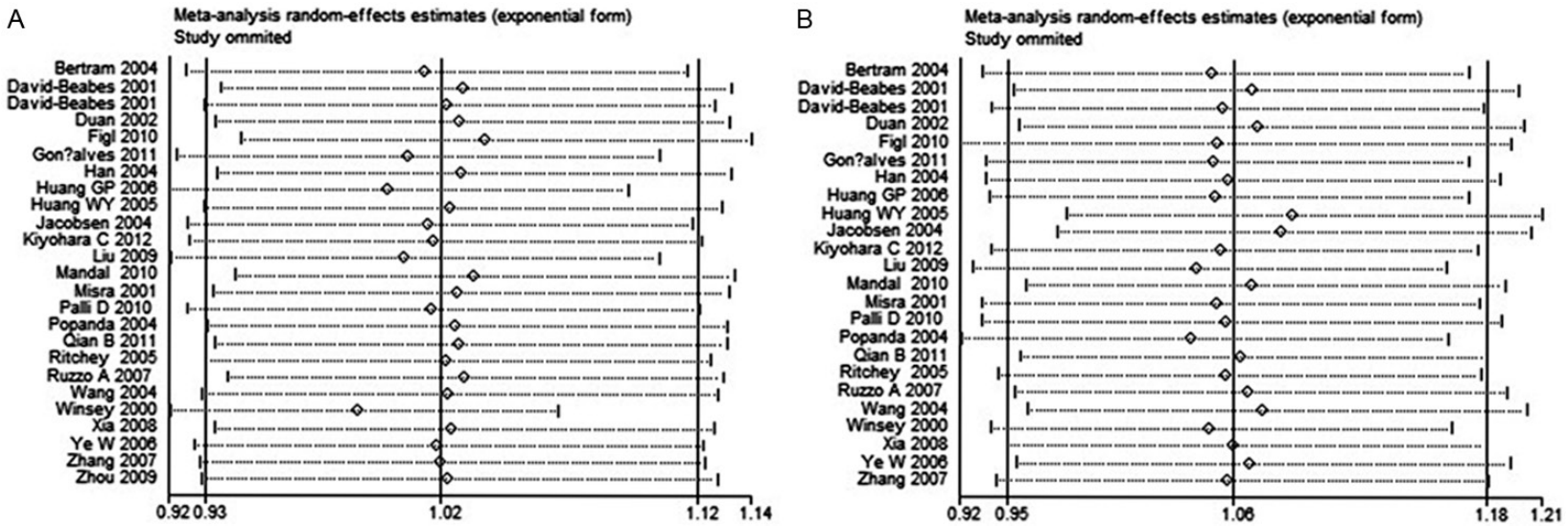

Figure 3. Sensitivity analysis of the association between the XRCC3 Thr241Met and cancer risk for the CT+TT vs. CC and TT vs. CC+CT model.

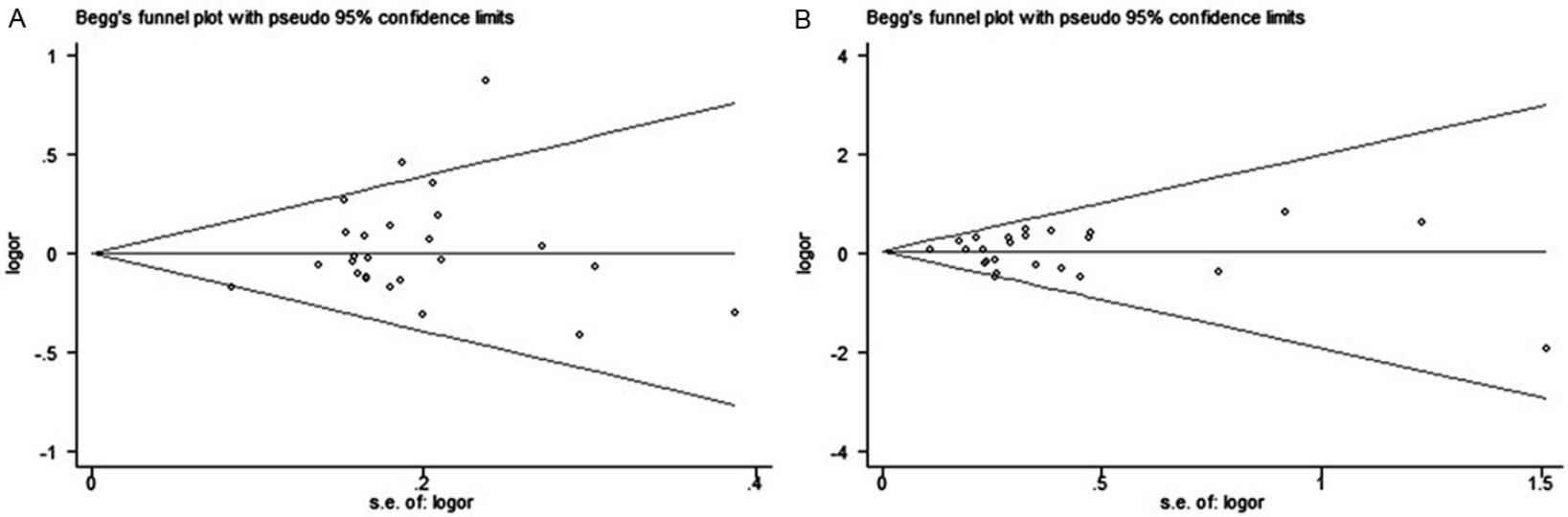

Figure 4. Begg's funnel plot of the association between the XRCC3 Thr241Met and cancer risk for the CT+TT vs. CC and TT vs. CC+CT model.

deletion of any single study. This confirmed the stability of the results of this meta-analysis (**Figure 3**).

Publication bias

In this study, a funnel plot was constructed to display the publication bias. The shape of the funnel plot was symmetrical in all the genetic models as revealed by the Begg's test (**Table 2**; **Figure 4**).

Results

Characteristics of studies

Twenty-five studies that met the inclusion concerning the association between XRCC3 Thr241Met polymorphism and risk of cancer were included in the meta-analysis [9-32]. Fourteen studies were performed in Caucasian population, 7 in Asian population, and 4 in mixed. A total of 7845 patients and 9822 controls were included, which was summed up by the 4278 patients and 5785 controls in Caucasian population, 2730 patients and 2482 controls in Asian population as well as 837 patients and 1555 controls in mixed population, respectively. Five (1100/1717) studies focused on gastric cancer, 3 (1440/1410) on Glioma, 9 (2789/3115) studies on lung cancer, 6 (2133/3141) on melanoma skin cancer, and 2 (383/439) on prostate cancer. Genotype distribution in the controls was in agreement with HWE. **Table 1** summarized the main characteristics of included studies.

Results of meta-analysis

We investigated the association between the XRCC3 Thr241Met polymorphism and risk of cancer in each selected study. Overall, no significant association was observed in the genetic models for CT versus CC (OR=1.08, 95% CI: 0.92-1.28, P=0.34), TT versus CC (OR=1.04, 95% CI: 0.93-1.17, P=0.46), CT+TT versus CC (OR=1.00, 95% CI: 0.94-1.07, P=0.96), and TT versus CC+CT (OR=1.05, 95% CI: 0.95-1.17, P=0.32). Significant difference was observed in the pooled Ors as revealed by Z-test. In stratified analyses in ethnicity, Caucasians showed no significant association in the model of CT versus CC (OR=1.03, 95% CI: 0.90-1.18, P=0.67), TT versus CC (OR=1.04, 95% CI: 0.91-1.18, P=0.59), CT+TT versus CC (OR=1.00, 95% CI: 0.92-1.09, P=0.99) and TT versus CC+CT (OR=1.05, 95% CI: 0.93-1.18, P=0.42), respectively. No significant association was found in Asian population (CT vs. CC, OR=1.24, 95% CI: 0.76-2.03, P=0.40; TT vs. CC, OR=1.11, 95% CI: 0.72-1.71, P=0.64; CT+TT vs. CC, OR=1.02, 95% CI: 0.88-1.18, P=0.84; TT vs. CC+CT, OR=1.07, 95% CI: 0.69-1.64, P=0.77).

In addition, no significant correlations were observed in the subtypes of cancer including the melanoma skin cancer (CT vs. CC, OR=1.10, 95% CI: 0.83-1.46, P=0.50; TT vs. CC, OR=1.20, 95% CI: 0.89-1.62, P=0.23; CT+TT vs. CC, OR=1.14, 95% CI: 0.86-1.51, P=0.37; TT vs. CC+CT, OR=1.12, 95% CI: 0.96-1.32, P=0.15), lung cancer (CT vs. CC, OR=0.95, 95% CI: 0.83-1.07, P=0.40; TT vs. CC, OR=1.04, 95% CI: 0.83-1.30, P=0.75; CT+TT vs. CC, OR=0.96, 95% CI: 0.85-1.09, P=0.53; TT vs. CC+CT, OR=1.07, 95% CI: 0.86-1.32, P=0.55), gastric cancer (CT vs. CC, OR=1.13, 95% CI: 0.95-1.33, P=0.17; TT vs. CC, OR=0.95, 95% CI: 0.73-1.23, P=0.67; CT+TT vs. CC, OR=1.09, 95% CI: 0.93-1.28, P=0.28; TT vs. CC+CT, OR=0.91, 95% CI: 0.71-1.16, P=0.44), glioma (CT vs. CC, OR=1.09, 95% CI: 0.90-1.31, P=0.38; TT vs. CC, OR=1.15 95% CI: 0.83-1.58, P=0.41; CT+TT vs. CC, OR=1.09, 95% CI: 0.91-1.30, P=0.35; TT vs. CC+CT, OR=1.08, 95% CI: 0.80-1.46, P=0.62), and prostate cancer (CT vs. CC, OR=0.79, 95% CI: 0.56-1.10, P=0.17; TT vs. CC, OR=0.76, 95% CI: 0.34-1.67, P=0.49; CT+TT vs. CC, OR=0.79, 95% CI: 0.57-1.10, P=0.16; TT vs. CC+CT, OR=0.82, 95% CI: 0.37-1.79, P=0.62). The detailed results were shown in **Table 2**.

Discussion

In this study, we aim to identify the relationship between the risk of developing cancer and the polymorphism of XRCC3 Thr241Met. Besides, we examined the contrast of the CT versus CC, TT versus CC, CT+TT versus CC and TT versus CC+CT genetic model. Moreover, subgroup analysis was carried out accordingly to evaluate the ethnicity and the disease based subtype-specific effects. Our results revealed no significant elevation was noticed in the cancer risk among Caucasians, Mixed and Asians. Also, no remarkable elevation was observed in subgroup analyses among melanoma, lung cancer, gastric cancer, glioma and prostate cancer.

SNPs are one of the most common sources for human genetic variation as they may contribute to patients' susceptibilities to cancer. To our knowledge, XRCC3 has been reported to play essential roles in maintenance of genomic integrity by repairing DSBs induced by various factors such as radiation and environmental factors [33]. Besides, the XRCC3 polymorphism may affect the DNA repair capacity of its encoded protein, which subsequently contributes to the development of cancers [34].

Up to now, extensive studies have been conducted to investigate the relationship between risk of cancer and XRCC3 Thr241Met polymorphism. However, the results were controversial considering the lower effects of the polymorphism on cancer risk, and/or low statistical power of the studies available [9-32]. Previously, several studies were carried out to assess the effect of XRCC3 Thr241Met polymorphism only on one or limited cancer types. Unlike the previous ones, our study is the most comprehensive one about the relationship between XRCC3 Thr241Met polymorphism and risk of all cancer types. Besides, the study results were more stable as those studies in which genotype distributions in the controls not concurrent with HWE were excluded in this analysis.

Indeed, there are still limitations for this study. Firstly, this meta-analysis only included articles in published English language, and we cannot exclude the bias that may induced by those reported in other languages although Begg's test revealed no publication bias in this study. Secondly, the current analysis could not include the eligible studies that were not published before this analysis. Thirdly, although environmental factors have been well acknowledged to closely be involved in the pathogenesis of cancer, it is still a challenge to determine the percentage of cancer types that were merely caused by environmental factors. Thus, the accuracy of the results may be affected by the existence of gene-environment and gene-gene interactions.

In conclusion, the relationship between risk of developing cancer and XRCC3, Thr241Met polymorphism is still controversial nowadays. In this meta-analysis, our results support the fact that the variant genotypes of XRCC3 Thr241Met polymorphism cause no contribution to the increased risk of cancer. In future, studies are needed to investigate the effect of the variants on the expression levels, the possible functional role of the XRCC3, Thr241Met variants in different types of cancer. Besides, the effects of gene-gene, gene-environment interaction should be addressed to illustrate their roles in the pathogenesis of cancer.

Disclosure of conflict of interest

None.

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