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ARTICLE

DNA repair gene XRCC3 polymorphisms and cancer risk: a meta-analysis of 48 case–control studies

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The X-ray repair cross-complementing group 3 (*XRCC3*) is a highly suspected candidate gene for cancer susceptibility. However, association studies on the *XRCC3* polymorphisms (4541A>G, *Thr*^{241}*Met*, 17893A>G) in cancer have shown conflicting results. Therefore, we performed a meta-analysis to better assess the purported associations. Forty eight eligible case–control studies including 24 975 cancer patients and 34 209 controls were selected for our meta-analysis. Overall, individuals carrying the *XRCC3 Met/Met* genotype showed a small cancer risk under a recessive genetic model. The subgroup and meta-regression analysis demonstrated different scenarios concerning the *XRCC3 Met/Met* genotype's role in cancer susceptibility for different subgroups. Specially, there was a significantly increased risk of breast cancer (OR, 1.14; $P=0.0004$; 95% CI, 1.06–1.23; $P=0.37$ for heterogeneity), elevated but not significant risk of cancer for head and neck, bladder, surprisingly, a significantly decreased risk of non-melanoma skin cancer (OR, 0.76; $P=0.007$; 95% CI, 0.62–0.93; $P=0.61$ for heterogeneity). A significantly elevated risk of cancer was observed in population-based case–control studies but not in nested or hospital based studies. Similarly, we found a significantly increased risk of cancer for A4541G and a decreased risk for A17893G under dominant genetic models. Our meta-analysis results support that the *XRCC3* might represent a low-penetrance susceptible gene especially for cancer of breast, bladder, head and neck, and non-melanoma skin cancer. A single larger study should be required to further evaluate gene–gene and gene–environment interactions on XRCC3 polymorphisms and tissue-specific cancer risk in an ethnicity specific population.

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Introduction

There is growing evidence that human cancer can be initiated by DNA damage caused by UV, ionizing radiation, and environmental chemical agents. Linkage analysis in multigenerational families affected with cancer has led to the identification of high penetrant cancer genes with roles in the repair of damaged DNA, such as *ATM*, *ERCC2*, *BRCA1*, *BRCA2*, etc. However, the individual high-risk alleles are generally rare and are estimated to account for only ~5% of the incidence of cancer in the population, so several to many other low-penetrant genes have been considered to be involved in the pathogenesis of cancer, each contributing a small effect to the total genetic component.[1]

The X-ray repair cross-complementing group 3 (*XRCC3*), one of the DNA repair genes, codes for a protein participating in homologous recombination repair (HRR)

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of DNA double-strand breaks (DSB). It is a member of an emerging family of Rad-51-related proteins that may take part in homologous recombination to repair DSB and maintain genome integrity.[2] *XRCC3*-deficient cells exhibited defects in Rad51 focus formation after radiation damage and demonstrated genetic instability and increased sensitivity to DNA damaging agents.[3] Carriers of the variant allele of XRCC3 *Thr*^{241}*Met* had relatively high DNA adduct levels in lymphocyte DNA, indicating that this polymorphism was associated with relatively low DNA repair capacity.[4] Therefore, *XRCC3* has been of considerable interest as a candidate susceptibility gene for cancer.

A large number of molecular epidemiologic studies have been preformed to evaluate the role of *XRCC3* polymorphisms on various neoplasm, such as cancer of breast, lung, bladder, head and neck, skin, etc.[5–61] The *Thr*^{241}*Met* substitution is the most thoroughly investigated polymorphism in *XRCC3* due to a (C->T) transition at exon7 (*XRCC3*-18067C>T, rs861539). Another two polymorphisms investigated by a few studies is *XRCC3*-4541A>G (5′-UTR, rs1799794) and *XRCC3*-17893A>G (IVS6-14, rs1799796). However, the results remain fairly conflicting rather than conclusive. One factor that would contribute to the discrepancy between different studies is that these polymorphisms might play a different role in different tumor sites. Also, even at the same tumor site, considering the possible small effect size of these genetic polymorphisms to cancer and the relatively small sample size in some studies, the discrepancy will become apparent since some single studies may have been underpowered to detect a small but real association.

Given the amount of accumulated data now available, it is important to perform a quantitative synthesis of the evidence using rigorous methods. The aim of this study was to assess the association of *XRCC3* polymorphisms with the risk of cancer by conducting a meta-analysis from all eligible case–control studies published to date. Our results suggest that *XRCC3* would not be a major risk factor for cancer but might represent a low-penetrance susceptible gene in cancer susceptibility.

Methods

Identification and eligibility of relevant studies

To identify all studies that examined the association of *XRCC3* polymorphisms with cancer, we conducted a computerized literature search of PubMed database (from January 1991 to April 2006) using the following keywords and subject terms: 'X-ray repair cross-complementing group 3', 'XRCC3', 'polymorphism', 'polymorphisms', and 'cancer'. References of retrieved articles were also screened. When a study reported results on different racial descent subpopulations or tumor sites, we treated each subpopulation or tumor as a separate comparison in our meta-analysis.

Studies included in the current meta-analysis have to meet all the following criteria: (1) use an unrelated case–control design, (2) have available genotype frequency, and (3) genotype distribution of control population must be in Hardy–Weinberg equilibrium (HWE).

Data extraction

Two investigators independently extracted the data and reached a consensus on all items. Data were collected on the authors, journal, years of publication, country of origin, demographics, selection and characteristics of cancer cases and controls, matched factors as well as adjusted factors, *XRCC3* polymorphisms genotyping information, interactions between environmental factors and genes, and racial descent (categorized as Asian, European, or mixed descent).

Statistical analysis

The strength of the association between *XRCC3* polymorphisms and cancer was measured by odds ratio (OR), which was calculated according to the method of Woolf.[62] We calculated the combined OR under dominant, recessive or additive genetic model for each polymorphism, respectively. A χ^2-based Q statistic test was performed to assess the between-study heterogeneity.[63] Owing to the low power of the statistic, heterogeneity was considered significant for $P<0.10$. A fixed effects model using the Mantel–Haenszel method or a random-effects model using the DerSimonian and Laird method were used to pool the results.[64] The significance of the pooled OR was determined by the *Z*-test.

For *Thr*^{241}*Met*, subgroup analysis was performed stratified by the study character of racial descent, study design and tumor site, respectively (If the tumor site contains less than three independent individual studies, it was categorized into the 'other sites' group.). Furthermore, the factors of racial descent, study design and tumor site were examined in a meta-regression model to explore the possible heterogeneity between different kinds of studies. A random-effects weighted linear regression model was used, whereby the study-specific log (OR) was regressed on the characters of each study.[65] The regression incorporated both the within-study variance as well as the between-study variance, and the weights were estimated using restricted maximum likelihood. Statistical significance was defined as a *P*-value less than 0.10 because of the relatively weak statistical power.

Publication bias was investigated by using a funnel plot, in which the standard error of log (OR) of each study was plotted against its OR. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test.[66] Hardy–Weinberg equilibrium was tested by the χ^2-test for goodness of fit or Fisher's exact probability test, where appropriate.

Analyses were performed using the software Stata version 7, ReviewManage 4.2 (Oxford, England, UK). All *P*-values were two-sided.

Results

Study inclusion

Through literature search and selection based on the inclusion criteria, 57 studies (69 comparisons) were found, but only 48 studies (57 comparisons) met our inclusion criteria, as listed in Table 1. For *Thr*^{241}*Met*, 12 comparisons of nine studies were not included for various reasons. Specifically, in two comparisons,[6,50] genotype distributions in control population significantly deviate from HWE. Three studies[20,23,51] did not contain genotype distribution information. Another four studies[38,39,47,49] investigated the same or a subset population of reported articles and the newest studies[39,47] were retained for the analysis. At last, three studies of *Thr*^{241}*Met*[7,11,27] and one comparison of 4541A>G,[44] in which the variant allele frequency was extremely higher than expected that might reflect a wrong allele counting or poor genotyping quality, were also excluded from our meta-analysis. Hence, the data for this analysis were available from 48 case–control studies, including 24 975 cancer cases and 34 209 controls for *Thr*^{241}*Met* from 48 studies (57 comparisons), 9284 cancer cases and 12 302 controls for 4541A>G from seven studies (8 comparisons), and 12 518 cancer cases and 19 526 controls for 17893A>G from seven studies (11 comparisons).

Meta-analysis database

We established a database according to the extracted information from each article. Table 1 lists the tumor site of the study, ethnicity of the population, study design, the genotype frequency of cases and controls, and the rare variant allele frequency in controls for each *XRCC3* polymorphisms. Overall, the quality of these included studies was good: methods of recruitment, total numbers, characters of participants and inclusion criteria were generally clearly stated; Tumors were all confirmed by histological or pathogenic analysis; most studies (74%) matched in age, sex, and ethnicity in frequency. A classic PCR-RFLP assay was performed in 50% of the studies, 58% randomly repeated a portion of samples while genotyping. However, only 25% of the studies described use of blindness of the case–control status of DNA samples while genotyping; not more than half of the studies (33%) investigated the interactions between *XRCC3* polymorphisms and environmental factors or other genes; few studies have been done to explore the role of *XRCC3* haplotype on cancer susceptibility (12%).

Quantitative synthesis

XRCC3 Thr*^{241}*Met There were significant differences in terms of the variant *Met*^{241} allele frequency between the two major ethnicities (European, 36.1%; 95% confidence interval (95% CI), 34.8–37.5; Asian, 8.22%; 95% CI, 3.00–13.4; $P<0.0001$). Overall, individuals carrying the XRCC3 *Met/Met* genotype have a small cancer risk compared with the individuals with the *Thr/Thr* or *Thr/Met* genotype (OR, 1.07; $P=0.008$; 95% CI, 1.02–1.13; $P=0.47$ for heterogeneity), and this positive association maintained in some subgroup meta-analysis stratified by cancer site, study design and ethnicity (Table 2). Notably, there was a significantly increased risk of breast cancer (OR, 1.14; $P=0.0004$; 95% CI, 1.06–1.23; $P=0.37$ for heterogeneity), however, a significantly decreased risk was confirmed with non-melanoma skin cancer (OR, 0.76; $P=0.007$; 95% CI, 0.62–0.93; $P=0.61$ for heterogeneity) under a recessive genetic model.

XRCC3 *A4541G and A17893G* As limited studies have investigated the *XRCC3* A4541G or A17893G polymorphism and cancer risk to date, we did not perform stratification analysis for the two polymorphisms. For A4541G, a significantly increased risk was associated with the variant genotypes (G/G + A/G), compared with the wild homozygote A/A genotype (OR, 1.09; $P=0.004$; 95% CI, 1.03–1.15) without between-study heterogeneity. For A17893G, individuals with the variant genotypes (G/G + A/G) had a significantly decreased cancer risk, compared with individuals with the A/A genotype under a dominant genetic model (OR, 0.92; $P=0.0004$; 95% CI, 0.87–0.96) without between-study heterogeneity.

Test of heterogeneity

There was no significant heterogeneity among the 57 comparisons that included the *XRCC3 Thr*^{241}*Met* polymorphism (*Met/Met versus Thr/Thr* + *Thr/Met*, $\chi^2=56.15$, df = 56, $P=0.47$). Similarly, no significant heterogeneity among the eight comparisons that included the A4541G polymorphism (G/G + A/G *versus* AA, $\chi^2=7.25$, df = 7, $P=0.40$) and 11 comparisons that included the A17893G polymorphism (G/G + A/G *versus* A/A, $\chi^2=12.63$, df = 10, $P=0.25$). However, for *XRCC3 Thr*^{241}*Met*, the subgroup meta-analysis demonstrated different scenarios concerning the *XRCC3 Met/Met* genotype's role in cancer susceptibility for different subgroups. Specially, elevated risk of cancer was observed in population-based case–control studies but not in nested or hospital-based studies; there was a significantly increased risk of breast cancer (OR, 1.14; $P=0.0004$; 95% CI, 1.06–1.23; $P=0.37$ for heterogeneity), elevated but not significant risk of cancer for head and neck, bladder, surprisingly, a significantly decreased risk of non-melanoma skin cancer (OR, 0.76; $P=0.007$; 95% CI, 0.62–0.93; $P=0.61$ for heterogeneity). Meta-regression analysis also supported our subgroup analysis. More details are shown in Table 2.

Table 1 Characteristics of studies that investigated the association between *XRCC3* polymorphisms and cancer risk

First author (year) (reference)	*Country (Racial descent)*	*Study design*	*Case*[†] *(A4541G) [A17893G] T241M*	*Control*[†] *(A4541G) [A17893G] T241M*	*Variant allele frequency (4541G) [17893G] 241T*
Breast cancer					
Montserrat[5]	US (European)	Pop c/c	(980/521/63)	(837/357/52)	(0.18)
			[775/648/159]	[602/525/133]	[0.31]
			1102/1419/457	973/1213/368	0.38
Montserrat[5]	Poland (European)	Pop c/c	(1210/632/78)	(1386/736/96)	(0.21)
			[882/847/254]	[920/1028/332]	[0.37]
			785/907/282	980/1039/266	0.34
Millikan[6]	US (European)	Pop c/c	505/578/171	435/555/142	0.37
Millikan[6]	US (African-American)	Pop c/c	482/222/41	421/211/44	0.22*
Zhang[7]	China (Asian)	Pop c/c	33/80/107	29/115/166	*0.72*
Webb[8]	Australia (European)	Pop c/c	500/612/184	248/321/91	0.38
Figueiredo[9]	Canada (European)	Pop c/c	139/186/77	146/200/56	0.39
Han[10]	US (mixed)	Nested c/c	(630/322/39)	(865/372/54)	(0.19)
			[439/430/95]	[603/544/118]	[0.31]
			388/429/135	468/607/170	0.38
Forsti[11]	Finland (European)	Pop c/c	32/80/111	27/110/161	*0.72*
Forsti[11]	Poland (European)	Pop c/c	15/85/72	25/88/89	*0.66*
Smith[12]	US (European)	Pop c/c	62/74/26	112/141/49	0.40
Smith[13]	US (European)	Pop c/c	96/105/51	104/129/35	0.37
Jacobsen[14]	Denmark (European)	Nested c/c	163/203/59	160/198/65	0.39
Kuschel[15]	US (European)	Pop c/c	(1176/581/71)	(1196/535/77)	(0.19)
			[846/730/165]	[816/856/205]	[0.34]
			790/1026/327	728/827/229	0.36
Lung cancer					
Matullo[16]	Muti-country (European)	Nested c/c	[53/54/9]	[554/447/91]	[0.29]
			44/56/16	383/544/167	0.40
Zienolddiny[17]	Norway (European)	Pop c/c	114/90/16	115/111/24	0.32
Harms[18]	US (European)	Pop c/c	61/37/12	61/49/9	0.28
Popanda[19]	Germany (European)	Hosp c/c	175/201/86	168/222/69	0.39
Wang[20]	US (mixed)	Pop c/c	NA	119/58/13	0.22
Misra[21]	Finland (European)	Nested c/c	160/124/29	149/134/23	0.29
David-Beabes[22]	US (African American)	Pop c/c	90/54/9	136/88/10	0.23
David-Beabes[22]	US (European)	Pop c/c	76/78/24	175/210/68	0.38
Butkiewicz[23]	Poland (European)	Pop c/c	NA	NA	0.33
Head and neck cancer					
Ye[24]	Sweden	Pop c/c	67/88/22	203/218/51	0.34
Kietthubthew[25]	Thailand (Asian)	Pop c/c	83/22/1	140/23/1	0.076
Huang[26]	US (European)	Pop c/c	159/181/54	267/309/90	0.37
Matullo[16]	Muti-country (European)	Nested c/c	[46/28/7]	[554/447/91]	[0.29]
			29/39/14	383/544/167	0.40
Rydzanicz[27]	Poland (European)	Pop c/c	31/122/123	14/71/58	*0.65*
Majumder[28]	India (Asian)	Hosp c/c	201/97/12	220/120/8	0.20
Casson[29]	Canada (unknown)	Nested c/c	22/26/8	38/43/14	0.37
Sturgis[30]	US (European)	Pop c/c	45/69/20	83/60/18	0.30
Benhamou[31]	France (European)	Hosp c/c	86/116/44	47/89/30	0.45
Shen[32]	US (European)	Pop c/c	150/159/58	141/170/43	0.36
Bladder cancer					
Matullo[16]	Muti-country (European)	Nested c/c	[60/47/17]	[554/447/91]	[0.29]
			46/61/17	383/544/167	0.40
Matullo[33]	Italy (European)	Hosp c/c	(207/98/11)	(201/102/12)	(0.20)
			[171/117/21]	[166/126/19]	[0.26]
			99/155/63	117/148/52	0.40
Sanyal[34]	Sweden (European)	Pop c/c	131/129/51	107/109/30	0.34
Shen[35]	Italy (European)	Hosp c/c	89/87/25	71/116/27	0.40
Stern[36]	US (mixed)	Hosp c/c	90/110/33	94/91/24	0.33
Matullo[37]	Italy (European)	Hosp c/c	33/64/27	19/14/5	0.32
Leukemia					
Matullo[16]	Muti-country (European)	Nested c/c	[92/66/11]	[554/447/91]	[0.29]
			61/90/18	383/544/167	0.40
Seedhouse[38]	UK (European)	Pop c/c	99/87/30	92/64/19	0.29

Table 1 (*Continued*)

First author (year) (reference)	*Country (Racial descent)*	*Study design*	*Case*[†] *(A4541G) [A17893G] T241M*	*Control*[†] *(A4541G) [A17893G] T241M*	*Variant allele frequency (4541G) [17893G] 241T*
Seedhouse[38]	UK (European)	Pop c/c	20/16/8	92/64/19	0.29
Seedhouse[39]	UK (European)	Pop c/c	53/53/17	92/64/19	0.29
Seedhouse[39]	UK (European)	Pop c/c	12/12/7	92/64/19	0.29
Non-Melanoma Skin cancer					
Thirumaran[40]	Hungary, Romania and Slovakia (European)	Hosp c/c	229/236/64	180/265/88	0.41
Festa[41]	Sweden and Finland (European)	Pop c/c	91/86/20	270/225/53	0.30
Han[42]	US (mixed)	Nested c/c	(483/262/42) 255/239/61	(564/266/31) 300/396/114	(0.19) 0.39
Jacobsen[14]	Denmark (European)	Nested c/c	129/158/31	146/129/43	0.34
Melanoma Skin cancer					
Han[42]	US (mixed)	Nested c/c	75/84/28	300/396/114	0.39
Duan[43]	US (unknown)	Hosp c/c	119/148/38	116/158/45	0.37
Winsey[44]	UK (European)	Pop c/c	(5/48/73) 39/65/21	(8/80/122) 110/78/23	(0.77) 0.29
Colorectal cancer					
Moreno[45]	Spain (European)	Hosp c/c	140/170/51	111/158/47	0.40
Skjelbred[46]	Norway (European)	Pop c/c	138/201/60	64/73/20	0.36
Yeh[47]	China (Asian)	Hosp c/c	660/60/1	658/74/2	0.053
Jin[48]	China (Asian)	Nested c/c	124/15/1	268/11/1	0.023
Yeh[49]	China (Asian)	Hosp c/c	660/60/1	658/74/2	0.053
Krupa[50]	Poland (European)	Pop c/c	1/27/23	11/81/8	0.49*
Mort[51]	UK (European)	Pop c/c	NA	NA	0.44
Gastric cancer					
Huang[53]	Poland (European)	Pop c/c	128/128/25	174/163/53	0.34
Shen[54]	China (Asian)	Pop c/c	169/18/1	150/16/0	0.048
Duarte[55]	Brazil (unknown)	Pop c/c	84/53/23	67/60/23	0.35
Other cancer sites					
Webb[8a]	Australia (European)	Pop c/c	189/192/67	362/460/130	0.38
Auranen[52a]	Muti-Center (European)	Pop c/c	(1060/550/48) [769/692/203] 676/762/227	(2551/1188/161) [1757/1776/433] 1712/1946/583	(0.19) [0.33] 0.37
Sadetzki[56c]	Israel (mixed)	Pop c/c	80/88/31	77/90/33	0.39
Wang[57d]	US (European)	Pop c/c	134/138/37	147/147/48	0.36
Han[58e]	US (unknown)	Nested c/c	(140/73/7) [100/97/23] 94/97/29	(438/200/25) [274/296/89] 280/306/79	(0.19) [0.36] 0.35
Ritchey[59f]	China (Asian)	Pop c/c	139/17/3	214/31/2	0.071
Smedby[60g]	Denmark and Sweden (European)	Pop c/c	159/163/74	216/270/102	0.40
Hirata[61h]	Japan (Asian)	Pop c/c	91/21/0	145/31/4	0.11

Mixed ethnicity: Han (2004),[10] mostly European; Wang (2003),[20] African American or Mexican American; Stern (2002),[36] black and white subjects; Han (2004),[42] Caucasian, Asian, Hispanic and others; Sadetzki (2005),[56] African, Asian, and European; Other cancer sites: [a]ovarian cancer; [c]meningiomas; [d]glioma; [e]endometrial cancer; [f]prostate cancer; [g]follicular lymphoma; [h]renal cell carcinoma.
NA: not available; c/c = case/control.
*Indicates a significant deviate from HWE in control ($P<0.05$).
[†]Wild-type homozygote/heterozygote/variant homozygote.

Publication bias

Funnel plot for the comparison of *Met/Met versus Thr/Thr + Thr/Met* in the OR analysis for *XRCC3 Thr*^{241}*Met* and Egger's test provided no evidence for funnel plot symmetry ($t=0.14$, $P=0.89$). Similarly, no publication bias was detected for A4541G and A17893G polymorphisms under dominant genetic models ($t=0.58$, $P=0.58$; $t=0.32$, $P=0.75$, respectively).

Table 2 Summary of ORs for XRCC3 *Thr*^{241}*Met* polymorphism and cancer risk and meta-regression results under different genetic models

Subgroup	*Comparison*	*Genetic models*		
		Dominant	*Recessive*	*Additive*
Racial descent				
Asian	7	1.08 (0.83–1.42)*	1.33 (0.70–2.53)	1.09 (0.85–1.40)*
European	40	1.01 (0.95–1.08)*	1.09 (1.03–1.15)	1.03 (0.98–1.07)*
Other	10	0.87 (0.79–0.96)	0.98 (0.85–1.13)	0.93 (0.86–0.99)
P-value†		0.090	0.14	0.097
Study design				
Pop c/c	33	1.04 (0.97–1.10)*	1.12 (1.05–1.19)	1.05 (1.00–1.10)*
Hosp c/c	11	0.92 (0.77–1.09)*	1.03 (0.89–1.20)	0.97 (0.85–1.09)*
Nested c/c	13	0.94 (0.83–1.05)*	0.93 (0.82–1.05)	0.94 (0.88–1.00)
P-value†		0.044	0.009	0.009
Tumor site				
Breast	10	1.04 (0.99–1.10)	1.14 (1.06–1.23)	1.06 (1.02–1.10)
Lung	7	0.89 (0.78–1.02)	1.09 (0.89–1.34)	0.96 (0.87–1.06)
Head and neck	9	1.05 (0.93–1.19)*	1.16 (0.96–1.40)	1.06 (0.97–1.17)
Bladder	6	1.11 (0.83–1.49)*	1.20 (0.97–1.49)	1.10 (0.92–1.32)*
Leukemia	3	1.12 (0.88–1.42)	1.09 (0.60–1.98)*	1.05 (0.88–1.26)
Non-melanoma Skin	4	0.88 (0.65–1.20)*	0.76 (0.62–0.93)	0.88 (0.73–1.06)*
Melanoma Skin	3	1.20 (0.69–2.12)*	1.08 (0.81–1.44)	1.14 (0.79–1.66)*
Colorectal	4	1.13 (0.76–1.70)*	1.03 (0.74–1.44)	1.10 (0.79–1.51)*
Gastric	3	0.90 (0.71–1.14)	0.74 (0.50–1.09)	0.88 (0.73–1.05)
Other sites	8	0.97 (0.87–1.03)	1.01 (0.90–1.14)	0.97 (0.92–1.04)
P-value†		0.39	0.008	0.099
Overall	57	0.99 (0.94–1.05)*	1.07 (1.02–1.13)	1.01 (0.97–1.05)*

*Random effect estimate.
†The *P*-value of meta-regression coefficient.

Discussion

This meta-analysis, involving a total of 24 975 cancer patients and 34 209 controls from 48 case–control studies, investigated the associations of the three DNA repair gene *XRCC3* polymorphisms with cancer risk. For *XRCC3 Thr*^{241}*Met* polymorphism, individuals carrying the *XRCC3 Met/Met* showed a small cancer risk compared with the individuals with the (*Thr/Thr* + *Thr/Met*) genotype. However, the subgroup and meta-regression analysis demonstrated different scenarios concerning the role of *Met*^{241} allele in cancer susceptibility for different subgroups. We identified two potential sources of between-study heterogeneity: tumor site and study design. Similarly, we found a significantly increased risk of cancer for *XRCC3* A4541G and a decreased risk for A17893G under dominant genetic models. However, considering the limited studies of the A4541G and A17893G polymorphisms, our results related to these two polymorphisms should always be treated as preliminary. In addition, we evaluated the linkage disequilibrium (LD) patterns among the three polymorphisms using the Hapmap data (EGP_SNPS-PDR90, CEU, HCB) and found that these polymorphisms are in tight LD, so associations found with one of these polymorphisms might be the result of LD with one of the other two polymorphisms. Nevertheless, our analysis suggested that *XRCC3* may play a small role in cancer susceptibility, which is consistent with the characteristics of low-penetrance genes.

Both biological and biochemical evidence indicate a direct role for *XRCC3* in DSBs repair.[67,68] Functional data also suggested that the *XRCC3 Thr*^{241}*Met* polymorphism may be associated with slightly but not significantly decreased DNA repair capacity.[69] Therefore, it seems much reasonable to take polymorphisms in *XRCC3* as the low-penetrance variant candidate for cancer susceptibility. As the first report, Winsey *et al*[44] found that the *Met*^{241} allele was significantly associated with increased risk of melanoma in the UK. Subsequently, Matullo *et al*[37] replicated this positive association in bladder cancer in an Italian population. Thereafter, more and more studies were conducted in order to further verify this purported association in different tumor sites across different nations. However, the results were fairly confusing rather than conclusive. Most studies cannot confirm a significantly

increased risk in cancer of the polymorphisms, and even, some studies documented a significant protective effect on cancer susceptibility.

Actually, it should be not uncommon for the same polymorphism playing a different role in cancer susceptibility across different populations since cancer is a complex disease. Our meta-analysis results revealed some reasons that might contribute to the inconsistent result across different studies. First, cancer is a complex disease and genetic heterogeneity exists in different tumor sites. The *XRCC3 Thr*^{241}*Met* polymorphism might be an increased risk factor for cancer of breast, head and neck, bladder but not for lung, leukemia, colorectal, gastric and melanoma skin cancer, and even a decreased risk factor for non-melanoma skin cancer. Our incomplete understanding of the biological function of the allele makes it difficult to further interpret potentially meaningful differences that may be tissue specific. Second, study design of prospective or retrospective study might make some differences between different studies (larger effects in population-based case–control studies compared with cohort studies, $P=0.009$). Third, different genetic background may also contribute to the discrepancy. There were significant differences in terms of the variant *Met*^{241} allele frequency between the two major ethnicities (European, 36.1%; 95%95% CI, 34.8–37.5; Asian, 8.22%; 95% CI, 3.00–13.4; $P<0.0001$). We suspect that a selection pressure might exist that play a role in maintaining the lower frequency of *Met*^{241} allele in Asians. Last but not the least; the difference may arise from chance. As we know that individual study in small sample size may have not enough statistical power to detect a small risk factor or give a fluctuated estimation.

Assessment of effect modification may be particularly beneficial in studies of DNA-repair polymorphisms, because a single polymorphism, with likely weak effects on the individual's phenotype, may not be measurable except in the context of some supporting environmental factors, such as tobacco smoke or ionizing radiation. Unfortunately, only 18% of studies investigated the interactions between *XRCC3* polymorphisms and environmental factors. We have tried to evaluate the effect of smoking on the susceptibility of *XRCC3 Thr*^{241}*Met* on cancer. Four studies[9,32,33,35] were recruited for combined analysis since their stratification data on smoking is available. We found that risk of cancer associated with variant *Met*/*Met* genotype was higher among smokers (OR, 3.21; $P<0.00001$; 95% CI, 2.32–4.43; $P=0.14$ for heterogeneity) than among non-smokers (OR, 1.55; $P=0.04$; 95% CI, 1.03–2.34; $P=0.83$ for heterogeneity). The result is consistent with the hypothesis that the effect of *Met*/*Met* genotype on risk of cancer may be more apparent in the presence of high level DNA damage caused by smoking than nonsmoking. Another lesson can be gleaned from this review is that few studies did haplotypic analysis of XRCC3 on cancer susceptibility, since the analysis of haplotype can increase power to detect disease associations**.** Similarly, very few studies investigated the gene–gene interactions or pathway analysis which would provide more comprehensive insight into the studied associations and should be considered in future genetic epidemiological studies.

As being often the case with meta-analysis, several factors limited the current study. First, the effect of *XRCC3* is perhaps best represented by its haplotype. However, most studies included in the meta-analysis restricted their analysis to *Thr*^{241}*Met* polymorphism of *XRCC3* only and few did the *XRCC3* haplotypic analysis on cancer susceptibility. It was difficult to study the role of a particular haplotype on cancer susceptibility in current meta-analysis. Second, although we attempted to evaluate the environmental modification effects such as smoking, alcohol, and food etc, only a few investigators reported the same environmental condition and the definition of each stratum varied among studies. Third, multiple testing problem is an inevitably threat for our meta-analysis. In the current analysis, a large number of comparisons have been considered since we analyzed the different cancer types, with three different polymorphisms, under three different genetic models. Finally, the study numbers included in the subgroup meta-analysis was small. Therefore, some subgroup analysis may not have enough statistical power to explore the association of these polymorphisms with cancer susceptibility.

In spite of this, our meta-analysis shares some key advantages in several aspects. First, substantial number of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Second, the quality of case–control studies included in current meta-analysis was good and met our inclusion criterion. Third, we did not detect any publication bias indicating that the whole pooled result should be unbiased.

In conclusion, our meta-analysis supports that the *XRCC3* could not be a major increased risk factor for cancer but it might represent a low-penetrance susceptible gene especially for cancer of breast, bladder, head and neck, and non-melanoma skin cancer. A single larger study should be required to further evaluate gene–gene and gene–environment interactions on *XRCC3* polymorphisms and tissue-specific cancer risk in an ethnicity specific population.

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