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XRCC3 Thr241Met polymorphism with lung cancer and bladder cancer: A meta-analysis

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Several studies have investigated the associations between X-ray repair cross-complementing group 3 (*XRCC3*) Thr241Met polymorphism and the susceptibility to lung cancer and bladder cancer, but results have been inconclusive. In order to derive a more precise estimation of the relationship, a meta-analysis was performed. A total of 22 case control studies, including 2976 cases and 4495 controls for lung cancer, and 3445 cases and 4599 controls for bladder cancer, met the inclusion criteria and were selected. Overall, there was no evidence showing a significant association between *XRCC3* Thr241Met polymorphism and lung cancer risk. Furthermore, the results for bladder cancer showed that significant decreased risk was found for the additive model (odds ratio [OR] = 0.959, 95% confidence interval [CI], 0.924–0.996) and dominant model (OR = 0.982, 95% CI, 0.963–1.000) but not for the recessive model (OR = 0.958, 95% CI, 0.905–1.014). In summary, our meta-analysis indicates that *XRCC3* Thr241Met polymorphism may be weakly associated with the risk of bladder cancer. (*Cancer Sci* 2010; 101: 1777–1782)

Lung cancer is one of the most common cancers worldwide, and it is the leading cause of cancer-related deaths in the world.[1] The role of genetic susceptibility in lung cancer has shown that the relatives of patients with lung cancer had an increased risk of the disease.[1,2] Only a fraction of smokers and a low number of non-smokers develop lung cancer, which implies influence of host factors in individual susceptibility. This inter-individual difference in susceptibility may be attributed to genetic polymorphisms in critical genes, including those involved in DNA repair.[3,4]

Bladder cancer is among the most frequent diagnosed cancer in the developed world.[5] Although development of bladder cancer is associated with exposure to tobacco and occupational exposure,[6] only a small proportion of exposed individuals will develop cancer, suggesting the involvement of genetic factors.

DNA repair systems play an critical role in maintaining genomic integrity.[3] If DNA damage is unrepaired, mutations are propagated during subsequent cellular replication and ultimately result in activation of oncogenes or inactivation of tumor suppressor genes. So mutations on these genes which alter the function of these proteins may predispose an individual to cancer. Increasing molecular epidemiologic evidence has shown that polymorphisms in various DNA repair genes are associated with an increased risk of cancer.[7,8]

The X-ray repair cross-complementing group 3 (*XRCC3*) belongs to a family of genes responsible for repairing DNA double strand breaks caused by normal metabolic processes and/or exposure to ionizing radiation. The XRCC3 is involved in homologous recombination repair (HRR) and chromosomal double-strand breaks repair processes, and it is necessary to maintain genomic integrity. It was demonstrated that cell lines defective in *XRCC3* had a 25-fold decrease in homology directed repair of DNA double-strand breaks.[9] Shen *et al.*[10] identified a C to T substitution in exon 7 at position 18067 of *XRCC3*, which results in a amino acid substitution (threonine to methionine) at codon 241. Carriers of the variant allele of *XRCC3* Thr241Met had different DNA adduct levels in lymphocyte DNA; and the Met variant was significantly associated with higher DNA adduct levels, indicating that this polymorphism was associated with the DNA repair capacity.[11] For this reason, we thought that the Met allele of the polymorphism should increase the risk of cancer.

Although the association between the risk of lung and bladder cancer and *XRCC3* Thr241Met polymorphism had been widely investigated, the results were inconsistent; and most studies included only small numbers of cases and controls. To determine the effects of this polymorphism on the risk of lung and bladder cancer, we have undertaken a meta-analysis.

Materials and Methods

Identification of studies. To identify all studies that examined the association of *XRCC3* Thr241Met polymorphisms with lung and bladder cancer, we conducted a literature search of the PubMed database, without a language limitation, covering all papers published up to March 2010, using the following keywords and subject terms: X-ray repair cross-complementing group 3, XRCC3, polymorphism, lung neoplasms, lung, neoplasms, and cancer; or X-ray repair cross-complementing group 3, XRCC3, polymorphism, urinary bladder neoplasms, bladder, neoplasms, and cancer. We evaluated potentially relevant publications by checking their titles and abstracts and then obtained the most relevant publications for a detailed examination. Moreover, the reference lists of the selected papers were also screened for other potential articles that may have been missed in the initial search.

Selection criteria. The following criteria were used for selection of reports for the meta-analysis: (i) studies concerning the association of the *XRCC3* Thr241Met polymorphism with lung cancer or bladder cancer; (ii) case-control studies; and (iii) studies with available genotype frequency, and genotype distribution of control population had to be in Hardy–Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: (i) the design and the definition of the experiments were obviously different from those of the selected papers; (ii) the source of cases and controls and other essential information were not provided; and (iii) reviews and duplicated publications. After searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

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Data extraction. Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. The following information was extracted from each article: first author, year of publication, country of origin, genotyping methods, genotype frequency, and the design of experiment for *XRCC3* Thr241Met polymorphism genotyping information. For conflicting evaluations, a final consensus was obtained following a discussion.

Statistical analysis. The odds ratio (OR) of *XRCC3* Thr241Met polymorphisms and lung cancer or bladder cancer risk was estimated for each study. The effect of association was indicated as OR with the corresponding 95% confidence interval (CI). The pooled ORs were performed for an additive model (C/C *vs* T/T), a dominant model (C/C+C/T *vs* T/T), and a recessive model (C/C *vs* C/T+T/T). The chi square-based Q statistical test was performed to assess heterogeneity among studies.[12] A *P*-value >0.05 for the Q-test indicated a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (Mantel–Haenszel method.[13]) Otherwise, the random-effects model (DerSimonian and Laird method[14]) was used. Subgroup analyses were performed by ethnicity, study design, and smoking habits. Sensitivity analysis was performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. An estimate of potential publication bias was assessed by visual inspection of funnel plots,[15] in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicates a possible publication bias. The symmetry of the funnel plot was further evaluated by Egger's linear regression test ($P < 0.05$ was considered indicative of significant publication bias).[16] To test for population stratification, the distribution of genotypes in control subjects of each individual population was tested for departure from the Hardy–Weinberg equilibrium using the chi square-test. Statistical analysis was performed using STATA version 10.1 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics. Through literature search and selection based on the inclusion criteria, 39 studies were found, but only 22 studies met our inclusion criteria, as listed in Table 1. Seventeen studies were excluded for the following reasons: five studies did not contain exact genotype distribution information;[17–21] four studies were reviews;[22–25] four studies were not case-control studies;[26–29] and in three studies,[30–32] genotype distributions in control population deviated from the Hardy–Weinberg equilibrium. Furthermore, one study of bladder cancer[33] in which the variant allele frequency was extremely lower than expected, which may reflect wrong allele counting or poor genotyping quality, was also excluded from our meta-analysis. Among the 22 studies, two populations (Caucasians and African) were included in one study,[34] so we divided the relevant data into two studies; and two studies[35,36] were just included in the recessive model because they provided the genotype of C/T+T/T as a whole. The data for this analysis were derived from 22 studies, including 2976 cases and 4495 controls for lung cancer from 13 studies, and 3445 cases and 4599 controls for bladder cancer from nine studies. Table 1 lists the identified studies and their main characteristics.

Meta-analysis results. To summarize the published data, we did a comprehensive meta-analysis. The overall data showed that the individuals who carried the C/C genotype did not have significantly increased lung cancer risk compared with those who carried T/T genotype (additive model: OR = 0.888, 95% CI, 0.646–1.222; Fig. 1); and no significant association was found in the dominant model (OR = 0.871, 95% CI,

Table 1. Main characteristics of all studies included in the meta-analysis

Author	Year	Country (Racial descent)	Design	Methods	Case	Control	Case			Control			HWE (*P*)
							C/C	C/T	T/T	C/C	C/T	T/T	
Lung cancer													
Matullo[42]	2006	Europe (Caucasian)	PB	TaqMan	116	1094	44	56	16	383	544	167	0.249
David-Beabes[34]	2001	USA (Caucasian)	PB	PCR-RFLP	178	453	76	78	24	175	210	68	0.701
David-Beabes[34]	2001	USA (African)	PB	PCR-RFLP	153	234	90	54	9	136	88	10	0.365
Misra[43]	2003	Finland (Caucasian)	PB	TaqMan	313	306	160	124	29	149	134	23	0.339
López-Cima[44]	2007	Spain (Caucasian)	HB	PCR-RFLP	403	434	168	185	50	178	196	60	0.607
Zienolddiny[45]	2006	Norway (Caucasian)	PB	TaqMan	220	250	114	90	16	115	111	24	0.709
Improta[46]	2008	Italy (Caucasian)	HB	PCR-RFLP	94	121	31	33	30	67	46	8	0.978
Zhang[47]	2007	China (Asian)	HB	TaqMan	291	273	259	30	2	244	28	1	0.837
Popanda[48]	2004	Germany (Caucasian)	HB	PCR-RFLP	462	459	175	201	86	168	222	69	0.756
Jacobsen[49]	2004	Denmark (Caucasian)	Cohort	TaqMan	246	269	95	123	28	113	113	43	0.105
Xia[50]	2008	China (Asian)	PB	TaqMan	103	139	91	12	0	118	21	0	0.335
Harms[51]	2004	USA (Caucasian)	HB	PCR-RFLP	110	119	61	37	12	61	49	9	0.845
Rky[35]	2006	Sweden (Caucasian)	PB	TaqMan	175	154	79	96		56	98		NA
Wang[36]	2003	USA (Mixed)	PB	PCR-RFLP	112	190	69	43		119	71		NA
Bladder cancer													
Figueroa[52]	2007	Spain (Caucasian)	HB	TaqMan	1083	1010	392	524	167	398	468	144	0.733
Stern[53]	2002	USA (Caucasian)	HB	PCR-RFLP	233	209	90	110	33	94	91	24	0.781
Broberg[54]	2005	Sweden (Caucasian)	PB	MALDI-TOF	61	153	23	33	5	60	72	21	0.935
Matullo[42]	2006	Europe (Caucasian)	PB	TaqMan	131	1094	46	61	17	383	544	167	0.248
Matullo[55]	2005	Italy (Caucasian)	HB	TaqMan/PCR-RFLP	317	317	99	155	63	117	148	52	0.652
Sanyal[56]	2004	Sweden (Caucasian)	PB	PCR-RFLP	311	246	131	129	51	107	109	30	0.782
Andrew[57]	2008	USA and Italy (Caucasian)	PB	TaqMan/PCR-RFLP	1046	1275	397	477	172	482	617	176	0.335
Gangwar[58]	2009	India (Asian)	HB	PCR-RFLP	212	250	135	68	9	159	80	11	0.816
Fontana[59]	2008	France (Caucasian)	HB	TaqMan	51	45	8	28	15	4	23	18	0.376

HB, hospital-based study; HWE, Hardy–Weinberg equilibrium; NA, not available; PB, population-based study.

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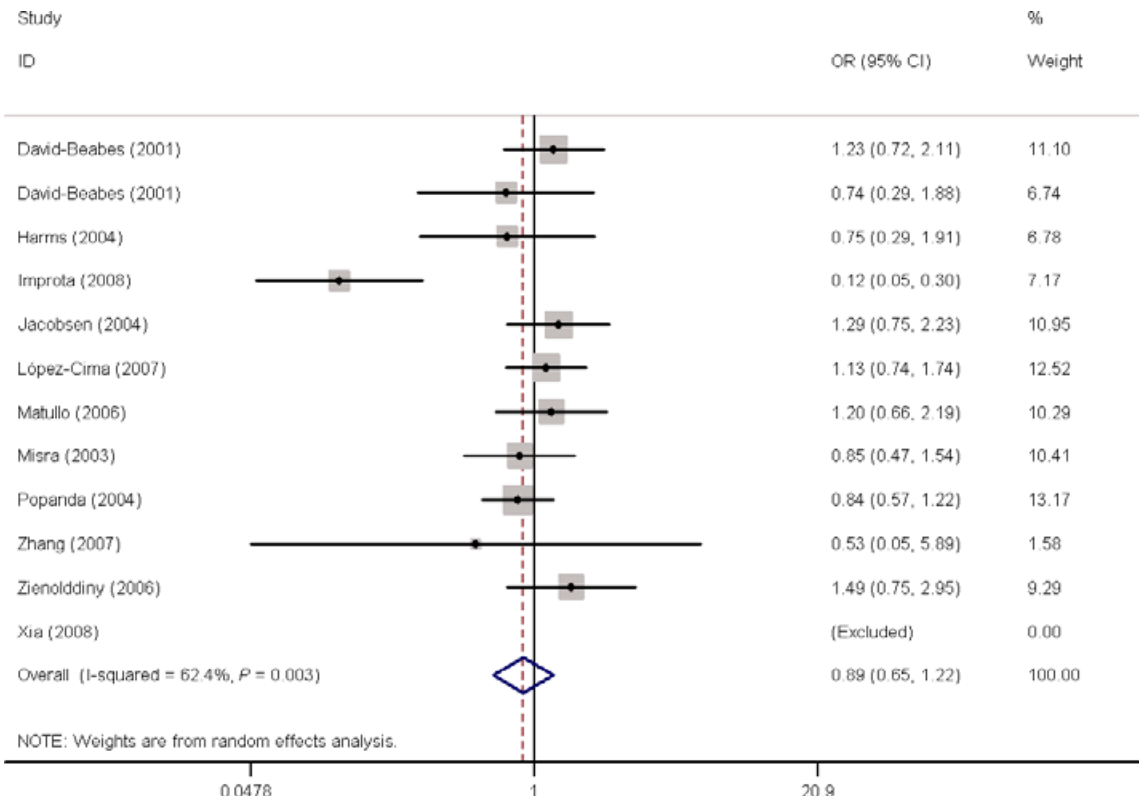

Fig. 1. Forest plot of OR of lung cancer risk associated with X-ray repair cross-complementing group 3 (*XRCC3*) Thr241Met polymorphism by additive model. Studies are plotted according to the first author's last name. Horizontal lines represent 95% CI. Each square represents the OR point estimate and its size is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with confidence interval given by its width. The unbroken vertical line is at the null value (RR = 1.0).

0.644–1.178) or recessive model (OR = 1.016, 95% CI, 0.968–1.066). Then, the 13 studies were analyzed by stratification based on ethnicity, study design, and smoking habits. In the subgroup analysis of ethnicity and smoking habits, there was no significant association between polymorphism and lung cancer risk. In the stratified analysis of study design, significant increased risk was found in population-based study for the dominant model (OR = 1.071, 95% CI, 1.003–1.144). The details are listed in Table 2.

For bladder cancer, the results showed that significant decreased risk was found for the additive model (OR = 0.959, 95% CI, 0.924–0.996; Fig. 2) and dominant model (OR = 0.982, 95% CI, 0.963–1.000), but not for the recessive model (OR = 0.958, 95% CI, 0.905–1.014). In the subgroup analysis by ethnicity, statistically significant decreased risk was found in Caucasians (additive model: OR = 0.954, 95% CI, 0.916–0.995 and dominant model: OR = 0.980, 95% CI, 0.960–1.000). When stratified by study design, statistically significant decreased risk was found in hospital-based study (recessive model: OR = 0.920 95% CI, 0.852–0.994). The details are listed in Table 3.

Sensitivity analysis. Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. These were carried out by limiting the meta-analysis to studies conforming to HWE and altering corresponding statistic variables and

Table 2. Summary of OR for *XRCC3* Thr241Met polymorphism and lung cancer risk

Subgroup	Number of comparisons	C/C *vs* T/T	(C/C+C/T) *vs* T/T	C/C *vs* (C/T+T/T)
Ethnicity				
Caucasian	10	0.904 (0638–1.282)*	0.886 (0.637–1.232)*	1.031 (0.968–1.099)
Asian	2	0.996 (0.983–1.010)	0.997 (0.985–1.009)	1.009 (0.960–1.060)
Design				
Hospital case-control	5	0.587 (0.291–1.181)*	0.590 (0.313–1.112)*	0.907 (0.676–1.218)*
Population case-control	8	1.018 (0.970–1.068)	1.004 (0.977–1.031)	**1.071 (1.003–1.144)****
Smoking habits				
Never	2	NA	NA	0.952 (0.851–1.065)
Heavy smokers	4	0.975 (0.902–1.054)	0.980 (0.938–1.024)	0.835 (0.44–1.584)
Light smokers	3	NA	NA	1.006 (0.854–1.186)
Overall	12	0.888 (0.646–1.222)*	0.871 (0.644–1.178)*	1.016 (0.968–1.066)

*Random effect estimate. ***P* = 0.041. OR, odds ratio; XRCC3, X-ray repair cross-complementing group 3.

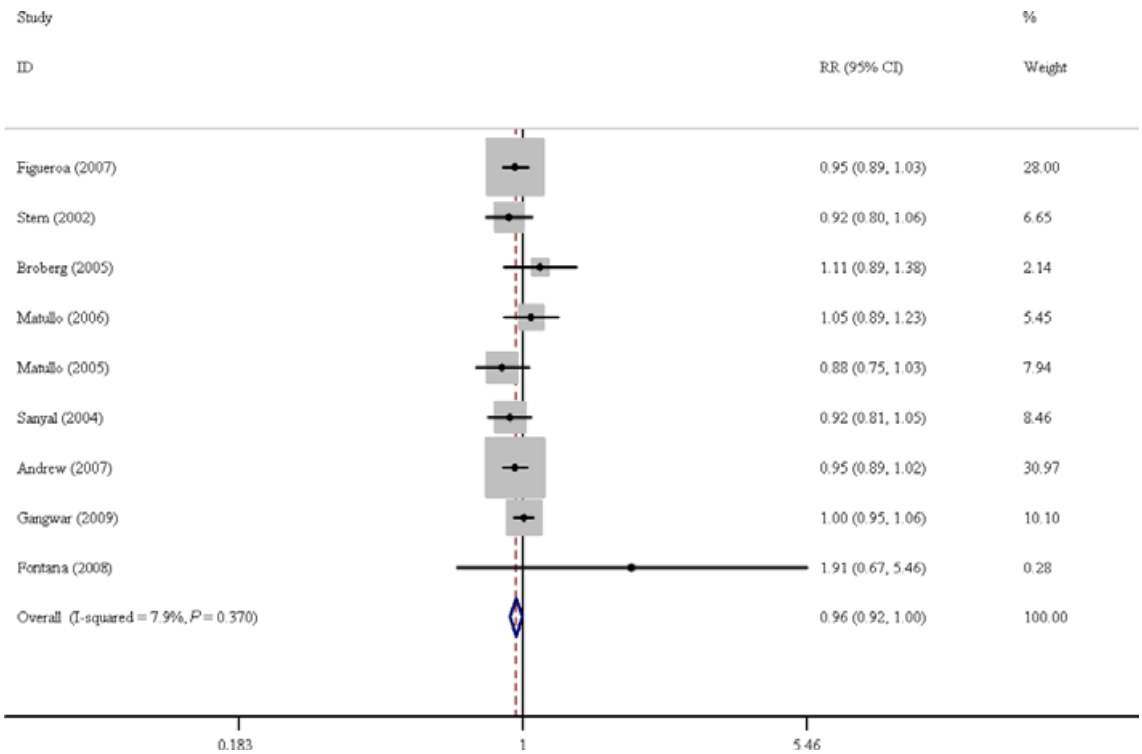

Fig. 2. Forest plot of OR of bladder cancer risk associated with X-ray repair cross-complementing group 3 (*XRCC3*) Thr241Met polymorphism by additive model. CI, confidence interval.

Table 3. Summary of OR for *XRCC3* Thr241Met polymorphism and bladder cancer risk

Subgroup	Number of comparisons	C/C *vs* T/T	(C/C+C/T) *vs* T/T	C/C *vs* (C/T+T/T)
Ethnicity				
Caucasian	8	**0.954 (0.916–0.995)***	**0.980 (0.960–1.000)****	0.953 (0.895–1.013)
Design				
Hospital-based study	5	0.954 (0.907–1.003)	0.985 (0.960–1.011)	**0.920 (0.852–0.994)*****
Population-based study	4	0.965 (0.913–1.021)	0.978 (0.951–1.005)	1.002 (0.921–1.090)
Overall	9	**0.959 (0.924–0.996)******	**0.982 (0.963–1.000)*******	0.958 (0.905–1.014)

**P* = 0.027; ***P* = 0.050; ****P* = 0.034; *****P* = 0.029; ******P* = 0.050. OR, odds ratio; XRCC3, X-ray repair cross-complementing group 3.

analysis models. No results were materially altered (data not shown).

Publication bias. Begg's funnel plots and Egger's tests were performed to assess publication bias. The shapes of the funnel plots revealed no obvious asymmetry. Egger's test was then used to statistically assess funnel plot symmetry. The results suggested no evidence of publication bias (lung cancer: $P = 0.283$ for additive model, $P = 0.322$ for dominant model, and $P = 0.846$ for recessive model; bladder cancer: $P = 0.591$ for additive model, $P = 0.723$ for dominant model, and $P = 0.264$ for recessive model). The results indicated that the results of these meta-analyses are relatively stable and that publication bias is unlikely to affect the results of the meta-analyses.

Discussion

Biological evidence has indicated that *XRCC3* takes part in the homologous recombination repairs of DNA damage.[9] Functional data had validated that *XRCC3* Thr241Met polymorphism was associated with the capacity of DNA repair.[11] Increasing molecular epidemiologic evidence has shown that this polymorphism was associated with an increased risk of different kinds of cancer.[37–40]

As it is known that individual studies with a small sample size may have not enough statistical power to detect a small risk factor, in this meta-analysis, we involved a total of 2976 cases and 4495 controls for lung cancer and 3445 cases and 4599 controls for bladder cancer, and investigated the associations of the *XRCC3* Thr241Met polymorphism with lung and bladder cancer risk.

We found that there were no significant associations between the *XRCC3* Thr241Met polymorphism and lung cancer risk. However, in the subgroup analysis of study design, the individuals carrying the C/C genotype showed a higher lung cancer risk compared with those with the (C/T+T/T) genotype for population-based study, but not for the hospital-based studies. This may be due to the fact that the hospital-based studies may have some biases when controls represent an ill-defined reference population sample and are not truly representative of the general population, particularly when the genotypes under investigation are associated with the disease conditions that the hospital-based

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controls may have. Therefore, using a proper and representative population-based study is very important to reduce biases in such genetic association studies.

For bladder cancer, individuals who carried the C/C or C/T genotype had a significant smaller cancer risk compared with the T/T carriers. But in the subgroup of hospital-based study, the C/C carriers had a decreased cancer risk compared with the individuals who carried the (C/T+T/T) genotype. This result is contradictory with the overall results and results from Caucasian patients. For the above-mentioned reason, we thought that the association may be a false positive result. So it is necessary to take into account case-control study design, especially for hospital-based case control studies.[41]

The results showed that *XRCC3* Thr241Met polymorphism plays different role in lung cancer and bladder cancer. It may not be uncommon for the same polymorphism to play different roles in cancer susceptibility across different tumor locations, because cancer is a complicated multi-genetic disease and genetic heterogeneity exists in different tumor sites.

There are some limitations to this meta-analysis. First, only published studies were included in the meta-analysis. It is possible that some related unpublished studies that might meet the inclusion criteria were missed; therefore, publication bias may have been present, even though statistical analysis indicated this not to be the case. Second, our results were based on unadjusted estimates and a more precise analysis could have been conducted if individual data were available; this would allow for adjustment by other covariates such as age, ethnicity, environmental factors, and lifestyle. Third, in the subgroup analyses, the number of Asians was relatively small for lung cancer and there was no Asian study on bladder cancer with enough statistical power to explore the association of the polymorphism with cancer susceptibility. However, our meta-analysis also had some advantages. First, a substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias was detected, indicating that the pooled result should be reliable.

In summary, our meta-analysis indicates that *XRCC3* Thr241Met polymorphism is weakly associated with the risk of lung and bladder cancer. However, it is necessary to conduct large sample studies using standardized unbiased genotyping methods and well-matched controls.

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