Original Research

XRCC1 Arg399Gln polymorphism and bladder cancer risk: updated meta-analyses based on 5767 cases and 6919 controls

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Abstract

Previous reports implicate XRCC1 Arg399Gln polymorphism as a possible risk factor for several cancers. Published meta-analyses have been conducted on the association of XRCC1 Arg399Gln polymorphism with susceptibility to bladder cancer, and have generated conflicting results. The present study aimed to derive a more precise estimation of the relationship. Updated meta-analyses assessing the association of XRCC1 Arg399Gln polymorphism with bladder cancer were conducted and subgroup analyses on ethnicity, smoking status and source of controls were further performed. Eligible studies were identified for the period up to May 2012. A total of 19 case-control studies comprising 5767 cases and 6919 controls were lastly selected for analysis. The overall data failed to indicate significant associations between XRCC1 Arg399Gln polymorphism and bladder cancer risk (Gln/Gln versus Arg/Arg: odds ratio (OR) = 0.97; 95% CI = 0.85–1.10; dominant model: OR = 1.02; 95% CI = 0.94–1.09; recessive model: OR = 0.95; 95% CI = 0.84–1.07). In subgroup analyses stratified by ethnicity, smoking status and source of controls, respectively, similar results were obtained. In conclusion, the results of the present study suggest that XRCC1 Arg399Gln polymorphism might not modify the susceptibility to bladder cancer. Further large and well-designed studies are needed to confirm this conclusion.

Keywords: XRCC1 Arg399Gln, bladder cancer, malignancy, susceptibility, meta-analysis, polymorphism

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Introduction

Bladder cancer is one of the most common cancers of the urinary tract worldwide. The majority of bladder cancers occur in men and there is a 14-fold polymorphism in the incidence internationally.[1] Previously, several environmental factors such as cigarette smoking, aromatic amines contained in dyes, chronic inflammation due to infection, anticancer drugs and radiation are thought to be risk factors for bladder cancer.[2] Nevertheless, the mechanisms of bladder carcinogenesis are still unclear. Notably, even in individuals exposed to these environmental factors, bladder cancer only develops in a small proportion of them, indicating that the host genetic factors might play a critical role in the tumorigenesis of bladder cancer.

Interaction of genetic factors with environmental factors may contribute to increased bladder carcinoma susceptibility. Several genetic polymorphisms have been considered as possible risk factors for bladder cancer by meta-analyses. Polymorphisms of GSTM1, GSTT1 and MTHFR have been indicated to increase bladder cancer risk.[3–5] However, polymorphism of hOGG1 has been suggested to have little influence on bladder cancer susceptibility.[6] Hence, different genetic polymorphisms might exert different effects on bladder cancer risk. So far, only a few gene polymorphisms have been identified that are associated with bladder cancer susceptibility.

Carcinogen exposure could induce DNA damage and cell injury in bladder tissues.[7,8] The consequences to the cell can range from single gene mutations to massive chromosomal breakdown and re-arrangements. The instabilities may result in severe human disorders such as Alzheimer's disease, Parkinson's disease and cancer.[9–11] The repairing of various types of DNA damages is important for maintenance of genomic stability and cell survival. Base excision repair pathways are critical in this process. X-ray repair cross-complementing gene 1 (XRCC1) is one of the most important DNA repair genes that plays a key role in the process of base excision repair. The XRCC1 gene is located on chromosome 19q13.2–13.3 and is 33 kb in length, comprising 17 exons and encoding a 70 kDa protein.[12] A widely studied XRCC1 single-nucleotide polymorphism at the codon 399, with an Arg to Gln change (rs25487), could

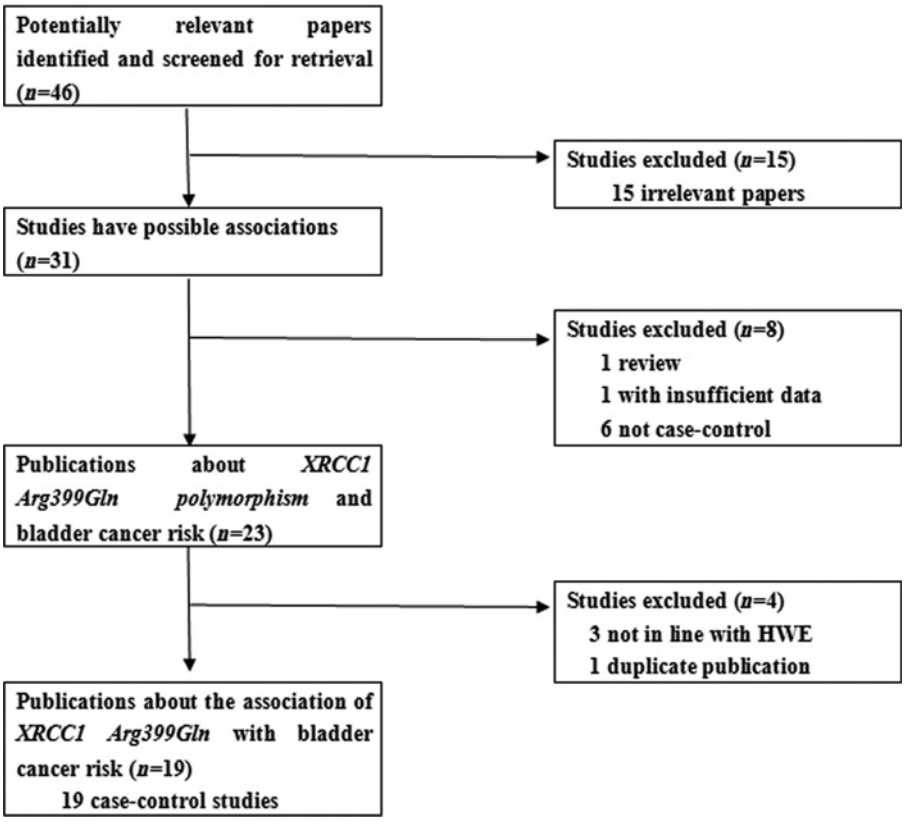

Figure 1 Flow diagram of included/excluded studies

have a diminished capacity to remove DNA adducts and oxidized DNA damage.[13] Hence, Arg399Gln polymorphism has been reported to have a correlation with increased cancer susceptibility.[14]

Published data on the possible association of XRCC1 Arg399Gln polymorphism with bladder cancer have yielded conflicting results. Previous two meta-analyses on this issue involved data published prior to 2008[15,16] and generated conflicting results. A number of studies regarding the association of XRCC1 Arg399Gln polymorphism with bladder cancer have been recently published. Thus, in this study, we conducted a quantitative updated meta-analysis including data up to May 2012, increasing statistical power to derive a more precise estimation of the relationship.

Materials and methods

Literature search strategy

A search without a language limitation in the Medline, EMBASE, OVID, Sciencedirect and Chinese National Knowledge Infrastructure (CNKI) was conducted, covering published papers prior to May 2012. A combination of the following keywords was used: *XRCC1*, *X-ray repair cross-complementing gene 1*, *genome-wide association studies*, *bladder*, *neoplasm*, *cancer*, *variation* and *polymorphism*. All searched publications were retrieved and the corresponding bibliographies were checked for other possible relevant papers. Review articles and bibliographies of the relevant articles identified were hand searched to find other potential eligible studies.

Inclusion criteria

We used the following criteria for the literature selection: firstly, studies should concern the association between XRCC1 Arg399Gln polymorphism and bladder cancer risk; secondly, studies must be case-control designed; thirdly, papers should offer the sample sizes, odds ratios (ORs) and their 95% confidence intervals (CIs), the genetic distribution or the information that can help infer the results. Then, we carefully reviewed all possible publications according to the criteria for further analysis.

Data extraction

Necessary information were carefully extracted from all eligible articles by two of the authors (WZ and LZ) independently according to the inclusion criteria. If their evaluations were conflicting, an agreement was reached after a discussion. If a consensus was not reached, another author was consulted to resolve the dispute; then, a final decision was made by the majority of the votes. Essential information from the literature was entered into a database. For any data not provided in the primary articles, the relevant information was obtained by contacting the corresponding authors, wherever possible.

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

First author	Publication year	Number of cases (male/female)	Number of controls (male/female)	Type of controls	Median (or mean) age, (range) year (cases/controls)	Racial decent	Country
Stern	2001	235 (183/53)	213 (173/40)	Non-cancer controls (age-, sex-, ethnicity-matched; HB)	65.6 (NA)/63.3 (NA)	Caucasian	USA
Matullo	2001	124 (124/0)	85 (85/0)	Non-cancer controls (HB)	NA (45–74)/NA (40–74)	Caucasian	Italy
Shen	2003	201 (201/0)	214 (214/0)	Non-cancer controls (age, period of recruitment admission hospital-matched; HB)	63 (20–80)/63 (NA)	Caucasian	Italy
Sanyal	2004	327 (NA/NA)	246 (NA/NA)	Healthy controls (age-, area-, ethnicity-matched; PB)	70 (33–96)/NA (NA)	Caucasian	Germany
Broberg	2005	63 (54/9)	158 (121/37)	Healthy controls (age-, gender-, enrolment year, living country-matched; PB)	69 (35–85)/69 (21–90)	Caucasian	Sweden
Matullo	2005	317 (317/0)	317 (317/0)	Non-cancer controls (HB)	63.6 (34–76)/57.1 (34–76)	Caucasian	UK
Matullo	2006	227 (NA/NA)	1094 (565/526)	Healthy controls (age-, gender-, smoking status-matched; PB)	NA (35–74)/61.2 (35–74)	Caucasian	Eight countries in Europe
Karahalil	2006	100 (NA/NA)	100 (NA/NA)	Healthy controls (age-matched; PB)	59.87 (25–87)/59.33 (23–79)	Mixed	Turkey
Wu	2006	613 (NA/NA)	596 (NA/NA)	Healthy controls (age-, sex-, ethnicity-matched; PB)	63.91 (NA)/62.77 (NA)	Mixed	USA
Figueroa	2007	1150 (1004/146)	1149 (1002/147)	Non-cancer controls (age-, gender-, ethnicity-, region-matched; HB)	66 (21–80)/65 (NA)	Caucasian	USA
Sak	2007	532 (377/155)	560 (367/193)	Healthy controls (HB)	72.8 (NA)/71.9 (NA)	Caucasian	UK
Huang	2007	613 (NA/NA)	596 (NA/NA)	Healthy controls (age-, sex-, ethnicity-matched; PB)	NA/NA	Caucasian	USA
Arizono	2008	251 (187/64)	251 (187/64)	Healthy controls (age-, sex-, matched; PB)	68.2 (31–90)/68.1 (34–94)	Asian	Japan
Fontana	2008	51 (51/0)	45 (45/0)	Non-cancer controls (HB)	NA/NA	Caucasian	France
Wen	2009	130 (104/26)	304 (218/86)	Non-cancer controls (HB)	64.86 (NA)/62.84 (NA)	Asian	China
Gao	2010	194 (154/40)	313 (152/161)	Clinic healthy subjects (HB)	71.2 (39–100)/58.9 (27–85)	Caucasian	UK
Ricceri	2010	456 (456/0)	376 (376/0)	Non-cancer controls (HB)	63.78 (40–75)/60.55 (NA)	Caucasian	Italy
Wang	2010	234 (191/43)	253 (197/56)	Non-cancer controls (age-,sex-matched; HB)	63.5 (NA)/62.9 (NA)	Asian	China
Mittal	2011	212 (187/25)	250 (215/35)	Healthy individuals (age-, sex-matched; PB)	59.6 (NA)/58.8 (NA)	Mixed	India

NA, not available; PB, population-based; HB, hospital-based

Statistical analysis

The OR of XRCC1 Arg399Gln polymorphisms and bladder cancer risk was estimated for each study. The pooled ORs for three genetic models were assessed, namely, a homozygote comparison model (Gln/Gln versus Arg/Arg), a dominant model (Gln/Gln + Gln/Arg versus Arg/Arg) and a recessive model (Gln/Gln versus Gln/Arg + Arg/Arg). To detect any possible sample size bias, the OR and its 95% CI in each study was plotted against the number of participants. To assess heterogeneity between the studies, a Chi-square based Q statistic test was conducted. If the Q statistic P value was >0.1, the ORs were pooled according to a fixed-effect model (Mantel-Haenszel); otherwise, a random-effect model (DerSimonian and Laird) was selected. The significance of the pooled ORs was evaluated by Z-test. The Hardy–Weinberg equilibrium (HWE) was assessed by Fisher's exact test. Possible publication bias was evaluated by visual inspection of funnel plots,[17] in which the standard error of log (OR) of each study was plotted against its log (OR). If the plot was asymmetric, a possible publication bias might exist. Moreover, Egger's linear regression test was also used to assess the symmetry of the funnel plot.[18] If the P value of Egger's linear regression test was <0.05, the funnel plot was regarded as asymmetric, indicating the existence of the publication bias. All statistical analyses were performed using the program STATA 11.0 software (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

Relevant original publications were retrieved and screened. A total of 46 publications were identified, of which 15 irrelevant papers were excluded. As shown in Figure 1, 31 publications were preliminary eligible, of which one review article was excluded.[19] Next, six publications not being case-control studies[20–25] and one study without sufficient data were also excluded.[26] As a result, 23 publications

Table 2 Distribution of XRCC1 Arg399Gln genotypes among bladder cancer cases and controls included in the present meta-analysis

First author	Year	Genotyping method	Cases			Controls			HWE (control)	
			Gln/Gln	Gln/Arg	Arg/Arg	Gln/Gln	Gln/Arg	Arg/Arg	Chi-square	*P*
Stern	2001	PCR-RFLP	21	106	87	26	92	79	0.009	>0.05
Matullo	2001	PCR-RFLP	13	58	53	12	41	31	0.070	>0.05
Shen	2003	PCR-RFLP	21	87	93	24	98	92	0.075	>0.05
Sanyal	2004	PCR-RFLP	32	155	124	23	110	113	0.260	>0.05
Broberg	2005	TaqMan	4	31	26	13	62	80	0.041	>0.05
Matullo	2005	PCR-RFLP	40	135	136	47	145	120	0.087	>0.05
Matullo	2006	TaqMan	17	53	54	128	482	484	0.229	>0.05
Karahalil	2006	PCR-RFLP	13	38	49	17	42	41	1.181	>0.05
Wu	2006	TaqMan	70	277	266	73	256	267	0.913	>0.05
Figueroa	2007	TaqMan	133	494	434	110	453	433	0.273	>0.05
Sak	2007	TaqMan	66	248	218	75	259	226	0.003	>0.05
Huang	2007	TaqMan	347*	–	266	329*	–	267	–	–
Arizono	2008	PCR-RFLP	10	102	139	21	90	140	1.410	>0.05
Fontana	2008	TaqMan	5	25	21	7	18	18	0.467	>0.05
Wen	2009	TaqMan	9	40	67	19	119	153	0.419	>0.05
Gao	2010	PCR-SSCP	107*	–	85	177*	–	136	–	–
Ricceri	2010	PCR-RFLP	54	206	186	50	165	153	0.269	>0.05
Wang	2010	PCR-RFLP	19	102	113	22	126	105	3.415	>0.05
Mittal	2011	PCR	39	106	67	39	109	102	0.011	>0.05

PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction-single-strand conformation polymorphisms
*Gln/Gln + Gln/Arg

Table 3 Distribution of XRCC1 Arg399Gln genotypes among ever-smokers and never-smokers bearing bladder cancers in the present meta-analysis

First author	Year	Cases			Controls		
		Gln/Gln	Gln/Arg	Arg/Arg	Gln/Gln	Gln/Arg	Arg/Arg
Ever smoking							
Matullo	2001	64*	–	45	34*	–	12
Shen	2003	17	81	86	19	77	65
Matullo	2005	35	123	123	31	102	81
Karahalil	2006	5	18	12	8	16	19
Sak	2007	45*	–	352	28*	–	342
Huang	2007	265*	–	190	181*	–	138
Arizono	2008	6	63	96	15	55	88
Wen	2009	6	27	38	6	46	52
Never smoking							
Matullo	2001	7*	–	6	19*	–	19
Shen	2003	4	6	7	5	21	27
Matullo	2005	5	12	13	16	43	39
Karahalil	2006	2	2	9	9	26	22
Sak	2007	12*	–	103	16*	–	174
Huang	2007	82*	–	76	148*	–	129
Arizono	2008	4	39	43	6	35	52
Wen	2009	3	13	29	13	63	101

*Gln/Gln+ Gln/Arg

were selected for data extraction and assessment.[27–49] Then, one duplicate publication[49] and three studies whose genetic distributions of controls markedly deviated from the HWE were discarded.[27,28,36] Lastly, 19 case-control studies were included for meta-analyses.

All the selected publications were in English language. Table 1 lists the author, case/control numbers and other relevant information on the studies reported in these publications. According to Table 1, the first author and the number and characteristics of cases and controls for each study as well as other necessary information were presented. In the selected articles, there were 13 groups of Caucasians,[30–34,37–39,41–45] three of Asians[29,46,47] and three of mixed ethnicities.[35,40,48]

The distribution of XRCC1 Arg399Gln genotypes as well as the genotyping methods of the included studies is presented in Table 2. The genetic distributions of the control groups in all studies were consistent with the HWE. Genetic distributions of Gln/Gln and Gln/Arg in four studies were combined as Gln/Gln + Gln/Arg.[33,34,41,47] Detailed genetic distributions were not available from the primary literature. However, for the study by Wen *et al.*,[47] the relevant dissertation was found in the CNKI database through our searching and, thus, detailed genetic distributions with larger sample sizes were extracted for further analysis. For the study by Ricceri *et al.*,[41] the detailed genetic distributions were provided by the corresponding author through a correspondence enquiry.

Table 4 Main results of the pooled data in the present meta-analysis

	No. (cases/controls)	Gln/Gln versus Arg/Arg			(Gln/Gln + Gln/Arg) versus Arg/Arg			Gln/Gln versus (Gln/Arg + Arg/Arg)		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	5767/6919	0.97 (0.85–1.10)	0.598	0.596	1.02 (0.94–1.09)	0.671	0.534	0.95 (0.84–1.07)	0.423	0.810
Ethnicity										
Asian	601/795	0.74 (0.48–1.14)	0.167	0.368	0.86 (0.69–1.07)	0.183	0.498	0.79 (0.52–1.21)	0.275	0.201
Caucasian	4241/5178	0.98 (0.84–1.14)	0.779	0.729	1.02 (0.94–1.12)	0.581	0.796	0.97 (0.83–1.12)	0.635	0.843
Mixed	925/946	0.98 (0.84–1.14)	0.777	0.729	1.10 (0.91–1.32)	0.311	0.096	0.98 (0.75–1.27)	0.860	0.489
Smoking status										
Ever smoking	1697/1415	0.71 (0.49–1.02)	0.061	0.536	0.94 (0.81–1.10)	0.464	0.173	0.76 (0.54–1.07)	0.112	0.445
Never smoking	477/983	0.97 (0.53–1.78)	0.915	0.606	0.96 (0.75–1.23)	0.754	0.516	1.08 (0.60–1.93)	0.808	0.671
Source of controls										
PB	2285/3288	1.02 (0.82–1.27)	0.871	0.258	1.10 (0.98–1.24)	0.094	0.465	0.96 (0.78–1.18)	0.667	0.414
HB	3482/3631	0.94 (0.80–1.10)	0.441	0.748	0.96 (0.87–1.06)	0.404	0.735	0.95 (0.82–1.10)	0.498	0.843

PB, population-based; HB, hospital-based

As shown in Table 3, information regarding smoking status could be extracted from eight studies,[29,34,35,38,39,42,44,47] of which three studies provided combined genetic distributions (Gln/Gln + Gln/Arg).[34,38,42]

Test of heterogeneity

As shown in Table 3, we analyzed the heterogeneity of the homozygote comparison (Gln/Gln versus Arg/Arg) and dominant model (Gln/Gln + Gln/Arg versus Arg/Arg) as well as recessive model (Gln/Gln versus Gln/Arg + Arg/Arg). Studies providing combined genetic distributions (Gln/Gln + Gln/Arg) rather than detailed distributions were only included in the dominant model evaluation.

The absence of heterogeneity was shown for overall data in the homozygote comparison ($P = 0.596$ for Q-test), dominant ($P = 0.534$ for Q-test) and recessive models ($P = 0.810$ for Q-test). Moreover, no heterogeneities were observed in the subgroup analyses.

Meta-analysis results

The main results of the meta-analysis are listed in Table 4. For the overall data including 5767 cases and 6919 controls, no significant associations of XRCC1 Arg399Gln polymorphism with bladder cancer risk were shown in the homozygote comparison (OR = 0.97; 95% CI = 0.85–1.10; $P = 0.596$ for heterogeneity), dominant (OR = 1.02; 95% CI = 0.94–1.09; $P = 0.534$ for heterogeneity) or recessive models (OR = 0.95; 95% CI = 0.84–1.07; $P = 0.810$ for heterogeneity), indicating that XRCC1 Arg399Gln polymorphisms might not have a correlation with bladder carcinoma risk (Figure 2).

In subgroup analysis with respect to ethnicity, no significant associations were shown in Asian, Caucasian or mixed ethnicities subgroups (Figure 3). Similarly, in subgroup analysis with respect to smoking status, no significant associations were found in either ever-smokers or never-smokers (Figure 4). Likewise, when the data were divided by source of controls, significant associations were observed in neither the hospital-based nor the population-based subgroups, under the three genetic comparisons (Figure 5).

Sensitivity analysis

When the effect-models were changed, the significance of the overall data for the three comparisons, respectively, was not altered (data not shown). One-way sensitivity analysis[50] was carried out to assess the stability of the meta-analysis. The statistical significance of the results was not changed when any single study was omitted (data not shown), indicating the robustness and credibility of the results.

Bias diagnostics

Funnel plots were created for assessment of possible publication biases. Further, Egger's linear regression tests were used to assess the symmetries of the plots. The funnel

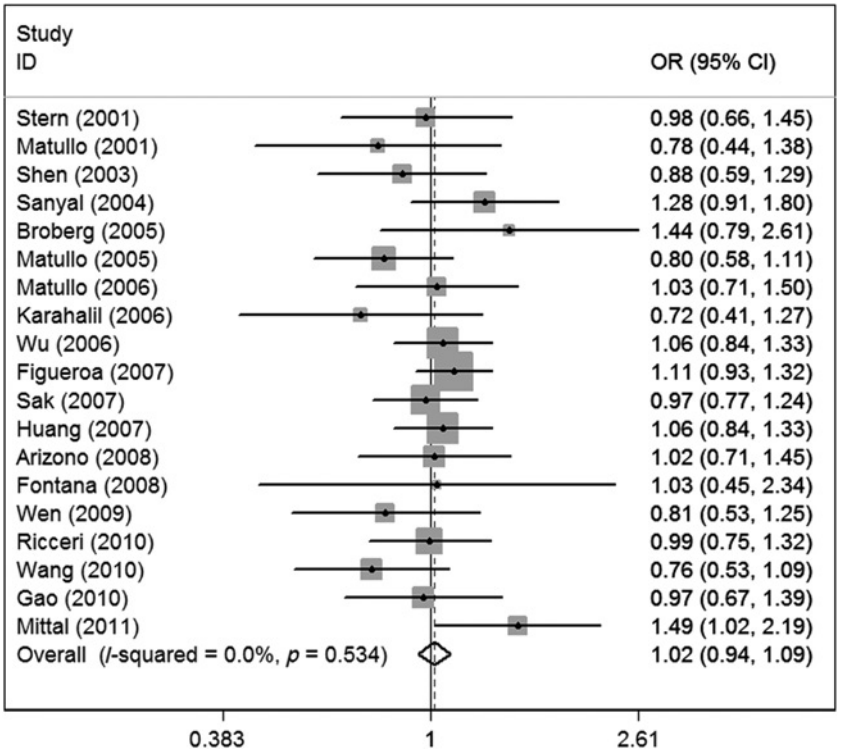

Figure 2 Meta-analysis for the association of bladder cancer risk with XRCC1 Arg399Gln polymorphism (Gln/Gln + Gln/Arg versus Arg/Arg; overall data)

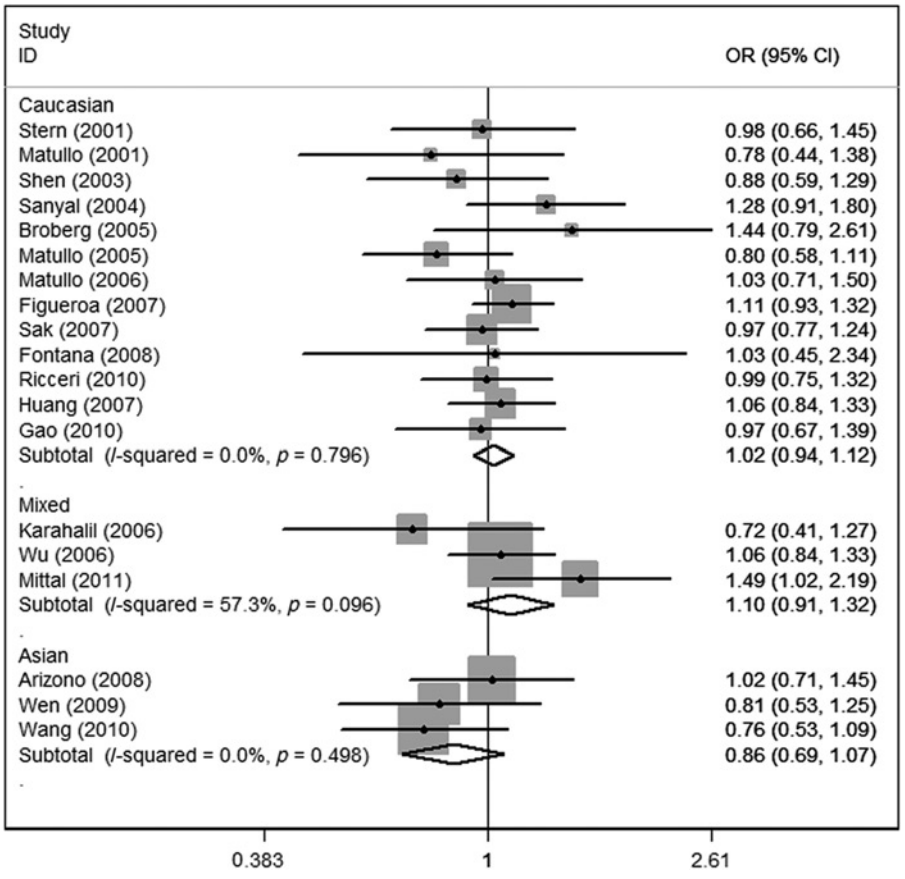

Figure 3 Meta-analysis for the association of bladder cancer risk with XRCC1 Arg399Gln polymorphism (Gln/Gln + Gln/Arg versus Arg/Arg; stratified by ethnicity)

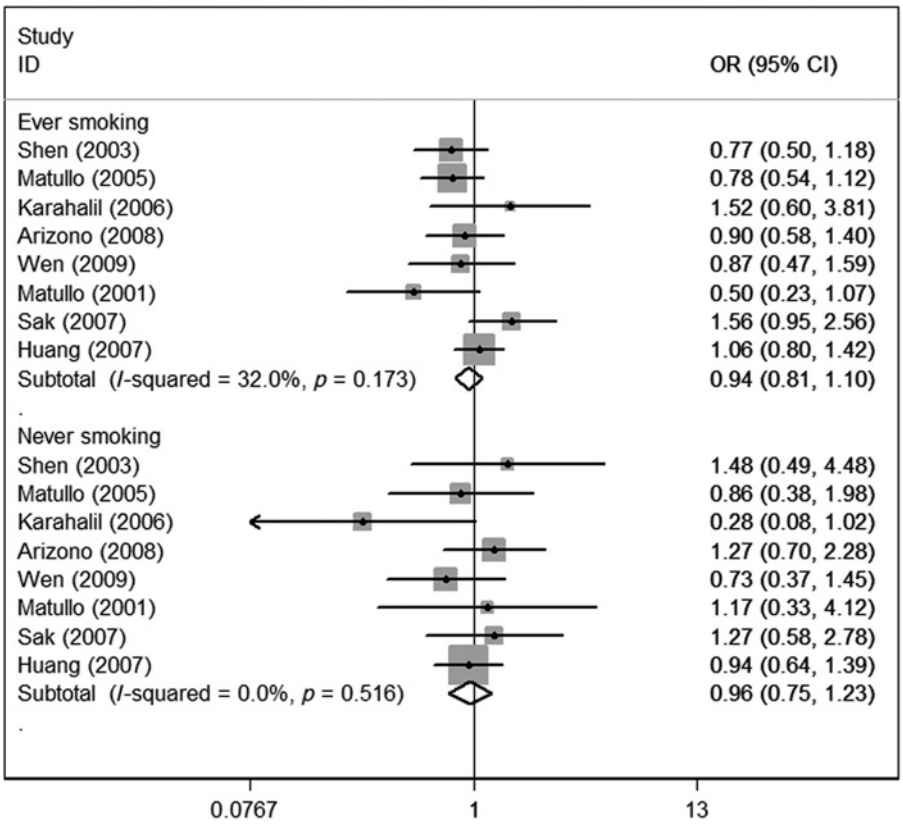

Figure 4 Meta-analysis for the association of bladder cancer risk with XRCC1 Arg399Gln polymorphism (Gln/Gln + Gln/Arg versus Arg/Arg; stratified by smoking status)

plots appeared to be symmetrical for the overall data (Figure 6a). Additionally, results of the Egger's tests also indicate the absence of the publication biases (Figure 6b) (dominant model: $t = -1.09$, $P > 0.05$).

Discussion

For the overall data, the results showed that XRCC1 Arg399Gln genetic polymorphism may not have a marked correlation with bladder cancer risk. Similar results were shown in subgroup analyses according to ethnicity, smoking status and source of controls.

Published meta-analyses regarding the associations of XRCC1 Arg399Gln polymorphism with several other cancer risks have generated conflicting results. XRCC1 Arg399Gln polymorphism has been suggested to increase risks of lung cancer, breast cancer, nasopharyngeal cancer, esophageal cancer and prostate cancer.[51–55] Nevertheless, XRCC1 Arg399Gln polymorphism has been shown to exert little effect on susceptibility to gastric cancer, skin cancer, hepatocellular cancer, colorectal cancer and bladder cancer.[16,56–59] Therefore, XRCC1 Arg399Gln polymorphism might play different roles in the tumorigenesis of different malignancies.

For bladder carcinoma, one previous meta-analysis conducted by Lao *et al.*[15] involving 12 case-control studies suggested that XRCC1 Arg399Gln might decrease bladder cancer risk for the overall data and among ever-smokers, inconsistent with the present meta-analysis. Another meta-analysis conducted by Wang *et al.*[16] only including 10 studies indicated no associations between XRCC1 Arg399Gln polymorphism and bladder cancer risk. However, subgroup analyses had not been considered in this study. Notably, in the meta-analyses by Lao *et al.*[15] and Wang *et al.*,[16] the study[28] whose genetic distributions of the control group exhibited significant deviation from the HWE was not excluded, which might contribute to any bias.[60] Therefore, in the present meta-analysis, we discarded the studies whose controls were not in line with the HWE.[27,28,36] Moreover, the sensitivity analysis confirmed the robustness of the present meta-analysis and hence increased its credibility.

In the subgroup analysis according to ethnicity, no significant associations were found among Asians, Caucasians and mixed ethnicities subgroups, in line with the overall data. Evidence indicates that ethnic polymorphism might lead to disparities in bladder cancer outcomes, possibly due to different health care and socioeconomic classes.[61,62] Nevertheless, the data of the present study suggested that the potential ethnic variation might exert little influence on XRCC1 Arg399Gln polymorphism's association with bladder cancer susceptibility.

Smoking is an important established risk factor for bladder cancer. The data of our meta-analysis showed no association of XRCC1 Arg399Gln variation with bladder cancer among either ever-smokers or never-smokers, inconsistent with the results obtained by Lao *et al.*[15] Evidence

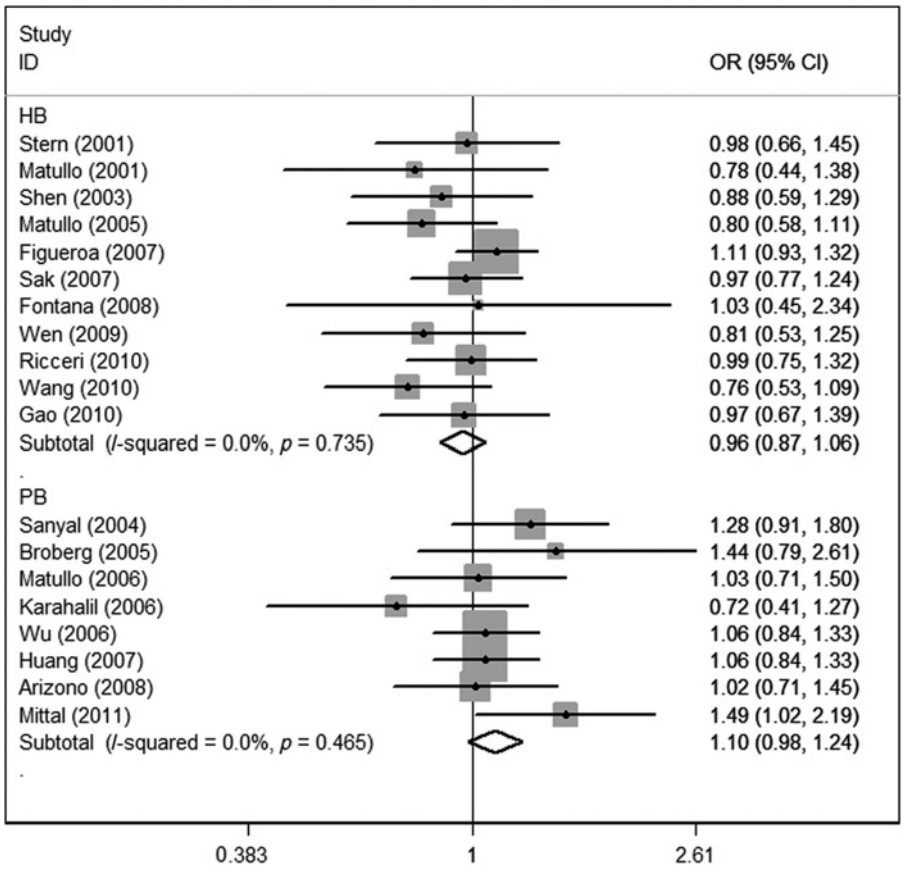

Figure 5 Meta-analysis for the association of bladder cancer risk with XRCC1 Arg399Gln polymorphism (Gln/Gln + Gln/Arg versus Arg/Arg; stratified by source of controls). PB, population-based; HB, hospital-based

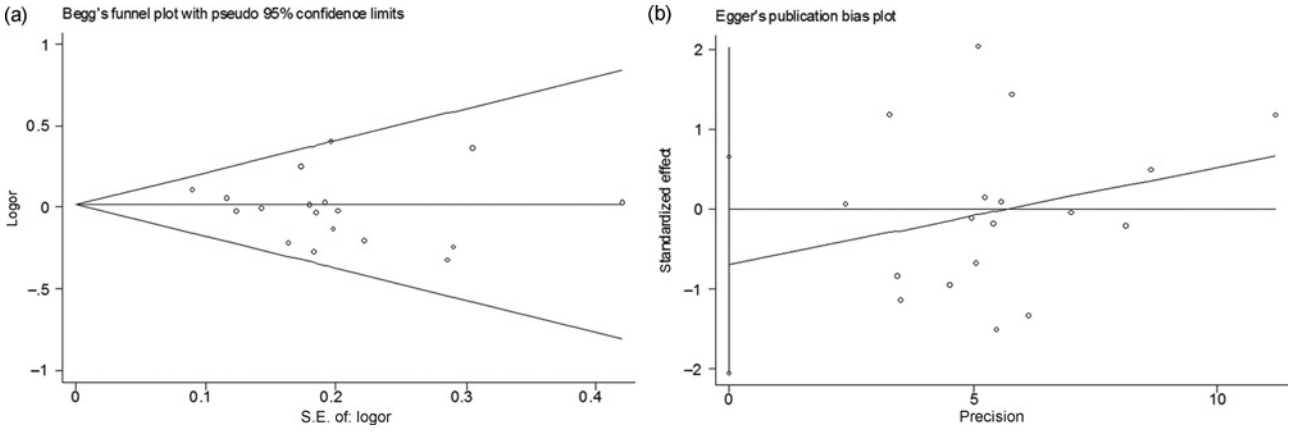

Figure 6 Publication bias test for the overall data (Gln/Gln + Gln/Arg versus Arg/Arg; (a) funnel plot; (b) Egger's linear regression test)

suggests that carcinogen exposure can lead to DNA damage. Since XRCC1 plays a central role in base excision repair pathways, polymorphisms of XRCC1 Arg399Gln could result in diminished capacity to remove DNA adducts and oxidized DNA damage.[13] Unrepaired damage might either lead to two results, cell apoptosis or unregulated cell growth.[63] Therefore, XRCC1 Arg399Gln genetic polymorphism might increase or decrease cancer risk. In meta-analysis by Lao *et al.*,[15] decreased bladder cancer risk was shown for Arg399Gln variation among ever-smokers. However, when we re-conducted the subgroup analysis regarding smoking status, we found that the results in the meta-analysis by Lao *et al.*[15] was unstable, indicated by the sensitivity analysis. The results significantly changed when the included study by Kelsey *et al.*[36] whose controls happened to exhibit marked deviation

from the HWE was excluded. Therefore, we discarded this study[36] from the smoking status database in the present meta-analysis. Interestingly and surprisingly, after the exclusion, the results became insignificant, and the data of these subgroups became stable, which is confirmed by the sensitivity analysis (data not shown).

In the subgroup analysis according to source of controls, significant associations were observed in neither the hospital-based subgroup nor the population-based subgroup. Hospital-based controls might not be truly representative of the general population and thereby may underestimate the bladder cancer risk. Thus, any selection bias might exist. However, the data of the present meta-analysis indicated little influence of the possible selection bias on the results. Notably, use of proper control participants with strict matching criteria is important in future studies for reducing such possible selection bias.

In the present meta-analysis, evident between-study heterogeneities for the overall data were absent in the three genetic comparisons. Thus, the fixed-effect models were utilized. In the subgroup analyses, insignificant heterogeneities were also found in the relevant subgroups, increasing the reliability of the results.

Publication bias is an important problem that should be considered in a meta-analysis. We utilized funnel plots to evaluate the possible publication bias. Then, Egger's linear regression test was used as an approach to evaluating the symmetry of the plot. The results failed to suggest any bias, indicating the robustness and credibility of the results.

Several limitations should be addressed. Firstly, in this meta-analysis, the primary articles only provided data about Caucasians, Asians and mixed ethnicities. Future studies should include data from other ethnicities such as Africans. Secondly, subgroup analyses with respect to age, gender histological types and other factors have not been conducted in the present study due to the lack of relevant data in the primary literature. Thirdly, only studies written in English and several other languages indexed by the common databases were searched. Thus, any selection bias might exist. Additionally, gene–gene and gene–environment interactions should also be considered in the further studies.

Despite the limitations, the results of the present meta-analysis failed to suggest a significant association of XRCC1 Arg399Gln polymorphism with bladder cancer risk. Further investigations with large sample sizes and strict matching criteria in view of confounding factors are needed for clarification of the possible associations.

Author contributions: All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; WZ and LZ conducted the experiments; LC, BZ and ZC analyzed the data; and WZ and ZC wrote the manuscript.

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