Meta-analysis demonstrates no association between XRCC1 Arg399Gln polymorphism and bladder cancer risk

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ABSTRACT. We examined whether the X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism is a risk factor for bladder cancer by conducting a meta-analysis. We searched the Pubmed and Embase databases for study retrieval. This meta-analysis examined 16 case-control studies, including 892 prostate cancer cases and 1020 healthy controls. Meta-analysis results based on these studies showed no significant association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in comparisons of the glutamine (Gln) allele *vs* arginine (Arg) allele, Arg/Arg *vs* (Gln/Gln + Gln/Arg), Gln/Gln *vs* (Gln/Arg + Arg/Arg), Gln/Gln *vs* Arg/Arg, and Gln/Arg *vs* Arg/Arg [odds ratio (OR) = 0.96, 95% confidence interval (CI) = 0.80-1.16, P = 0.70; OR = 1.13, 95%CI = 0.70-1.82, P = 0.62; OR = 0.92, 95%CI = 0.79-1.07, P = 0.29; OR = 0.90, 95%CI = 0.69-1.16, P = 0.42; OR = 0.89, 95%CI = 0.75-1.05, P = 0.17, respectively]. In subgroup

analysis by ethnicity, no association was observed between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in Caucasian, Mongoloid, or black populations. We identified no association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk.

Key words: Bladder cancer; XRCC1 Arg399Gln; Gene polymorphism; Meta-analysis

INTRODUCTION

Bladder cancer is one of the most common tumors and is the eighth leading cause of cancer death among people in the USA (Siegel et al., 2012). In 2012, bladder cancer accounted for 4.49% (73,510) of all newly diagnosed cancers and 2.58% (14,880) of all deaths in the United States. Although numerous studies have been conducted to understand bladder cancer, the detailed etiology remains largely unknown. Bladder carcinogenesis is a complex, multistep, and multifactor process, in which many factors are implicated. Smoking, exposure to industrially related aromatic amines, and uptake of drugs such as phenacetine, chlorna-phrazine, and cyclophosphamide are the only established risk factors (Steineck et al., 1995; Cohen et al., 2000). Many studies have suggested that genetic factors play an important role in the etiology of bladder cancer (Mattulo et al., 2005; Andrew et al., 2006). DNA damage by carcinogens and failure to accurately repair DNA following mutations are related to carcinogenesis (Sak et al., 2007).

The human X-ray repair cross-complementing group 1 (XRCC1) gene is located on chromosome 19q13.2-13.3 and is 33 kb in length. As a scaffold protein closely associated with the base excision repair (BER) pathway, the predominant DNA damage repair pathway for processing small base lesions derived from oxidation and alkylation damage, XRCC1 interacts with most components of the BER short-patch pathway (Vidal et al., 2001; Campalans et al., 2005; Das et al., 2006). Arg399Gln (exon 10, rs25487 in dbSNP, G/A, arginine to glutamine) is a common polymorphism of XRCC1. The XRCC1 Arg399Gln variant is related to DNA repair based on its location in the COOH-terminal side of the poly (ADP ribose) polymerase-interacting domain within a relatively non-conserved region between conserved residues of the breast cancer 1 C-terminal domain; this indicates that the protein-protein interaction module in many proteins is involved in DNA repair (Masson et al., 1998). In addition, higher levels of sister chromatid exchange (Abdel-Rahman and El-Zein, 2000), aflatoxin B1-DNA adducts, glycophorin A mutations (Lunn et al., 1999), and polyphenol DNA adducts (Duell et al., 2000) may be related to the variant.

Several studies have been performed to elucidate the effect of the XRCC1 Arg399Gln polymorphism on bladder cancer susceptibility. However, the results are inconsistent. The aim of this meta-analysis was to investigate the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk by examining all eligible case-control studies published to date.

MATERIAL AND METHODS

Literature search strategy

Pubmed and Embase database searches were performed to retrieve articles regarding

the XRCC1 Arg399Gln polymorphism and bladder cancer risk up to May 2013 without language restrictions and using the following key words: "XRCC1", "X-ray repair cross-complementing group 1", "polymorphism", and "bladder cancer". The search included only research on human subjects. References including major textbooks, review articles, and included articles were also identified through manual searches to find potentially eligible studies.

Inclusion and exclusion criteria

For inclusion in this meta-analysis, the following criteria were established: 1) case-control study addressed bladder cancer cases and controls; 2) study evaluated the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk; and 3) study included sufficient genotype data for extraction. Studies that were excluded included: 1) non-case-control studies evaluating the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk; and 2) studies based on incomplete raw data with no usable data reported.

Data extraction

Using a standardized form, 2 reviewers independently extracted data from published studies. The following information was extracted from included articles: first author, year of publication, country, ethnicity, study design, source of controls, number of cases and controls, detection methods, allele and genotypes frequency of the polymorphism, and evidence of Hardy-Weinberg equilibrium in controls. Agreement was reached after discussion among the authors to resolve conflicting evaluations.

Statistical analysis

The overall association between the XRCC1 Arg399Gln polymorphism and bladder cancer was calculated by individual or pooled odds ratios (ORs) and 95% confidence intervals (CIs) using Review Manager Version 5.0.25 (provided by The Cochrane Collaboration, available at: http://www.cc-ims.net/revman) and STATA package version 12.0 (Stata Corporation; College Station, TX, USA). We evaluated the following contrasts for the XRCC1 Arg399Gln polymorphism: comparison of the variant allele with the wild-type allele (Gln allele *vs* Arg allele); comparison of the variant homozygote with the wild-type homozygote and the heterozygote (Gln/Gln *vs* Gln/Arg + Arg/Arg); comparison of the wild-type homozygote with the variant homozygote and the heterozygote (Arg/Arg *vs* Gln/Arg + Gln/Gln); and comparison of the variant homozygote with the heterozygote and wild-type homozygote (Gln/Gln *vs* Arg/Arg; Gln/Gln *vs* Gln/Arg). Cochran's Q statistic was used to estimate variations and heterogeneities between studies (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005). When a significant Q-statistic ($P < 0.05$) indicated heterogeneity across studies, the random effects model was used for meta-analysis; otherwise, the fixed effects model was used (Viechtbauer, 2007). Hardy-Weinberg equilibrium in genotype frequencies of controls was calculated using the chi-square test. To determine and explain the diversity among the results of different studies, subgroup analysis was performed. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was assessed by Begg's funnel plot, and funnel plot asymmetry was assessed based on Egger's linear regression test (Peters et al., 2006). P values from Egger's test <0.05 are considered to be statistically significant. All

P values were 2-sided. To ensure the reliability and the accuracy of the results, 2 reviewers (L.M.D. and M.S.L.) independently input data into the statistics software programs and both researchers obtained the same results.

RESULTS

Studies included in the meta-analysis

The search strategy retrieved 46 potentially relevant papers. According to the inclusion criteria, 21 studies were included in this meta-analysis. These 21 selected case-control studies (Stern et al., 2001; Shen et al., 2003; Kelsey et al., 2004; Sanyal et al., 2004; Broberg et al., 2005; Andrew et al., 2006; Karahalil et al., 2006; Matullo et al., 2001, 2005, 2006; Figueroa et al., 2007; Huang et al., 2007; Sak et al., 2007; Andrew et al., 2008; Arizono et al., 2008; Fontana et al., 2008; Wen et al., 2009; Gao et al., 2010; Wang et al., 2010; Mittal et al., 2012; Zhi et al., 2012) included 5759 bladder cancer cases and 6521 controls. All studies were case-control studies that evaluated the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk. All articles were written in English. The Hardy-Weinberg equilibrium test was performed to determine the genotype distribution of the controls in all studies included. All of the studies except for 5 conformed to Hardy-Weinberg equilibrium; 3 studies (Kelsey et al., 2004; Andrew et al., 2006, 2008) were not in Hardy-Weinberg equilibrium, and 2 studies (Huang et al., 2007; Wen et al., 2009) lacked sufficient data for calculating the P value to determine Hardy-Weinberg equilibrium.

The study characteristics are summarized in Table 1. The genotype distribution and risk allele frequency of the studies included are summarized in Table 2. A summary of the meta-analysis findings of the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk is shown in Table 3.

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

First author	Country	Ethnicity	Source of controls	No. of subjects		Method
				Cases	Controls	
Matullo et al. (2001)	Italy	Caucasian	Hospital-based	124	84	PCR-RFLP
Stern et al. (2001)	USA	Caucasian and black	Hospital-based	233 (215/19)*	210 (198/13)	PCR-RFLP
Shen et al. (2003)	Italy	Caucasian	Hospital-based	201	214	PCR-RFLP
Kelsey et al. (2004)	USA	Mixed	Population- based	355	544	PCR-RFLP
Sanyal et al. (2004)	Germany	Caucasian	Population-based	311	246	PCR-RFLP
Broberg et al. (2005)	Sweden	Caucasian	Population-based	61	155	Sequenom
Matullo et al. (2005)	Italy	Caucasian	Hospital-based	311	312	PCR-RFLP/Taqman
Andrew et al. (2006)	USA	Mixed	Population-based	306	538	PCR-RFLP
Karahalil et al. (2006)	Turkey	Caucasian	Population-based	100	100	PCR-RFLP
Matullo et al. (2006)	Mixed	Caucasian	Population-based	124	1094	PCR-RFLP/DHPLC/TaqMan
Sak et al. (2007)	UK	Mixed	Population- and Hospital-based	532	560	Taqman
Figueroa et al. (2007)	Spain	Caucasian	Hospital-based	1061	101	Taqman
Fontana et al. (2008)	France	Caucasian	Hospital-based	51	45	Taqman
Arizono et al. (2008)	Japan	Mongoloid	Hospital-based	251	251	PCR-RFLP
Andrew et al. (2008)	USA	Mixed	Population- and Hospital-based	990	1253	PCR-RFLP/Taqman
Wang et al. (2010)	China	Mongoloid	Hospital-based	234	253	PCR-RFLP
Mittal et al. (2012)	India	Mongoloid	Population-based	212	250	PCR-RFLP
Zhi et al. (2012)	China	Mongoloid	Population-based	302	311	PCR-RFLP

*Represents Caucasians and blacks.

Table 2. Genotype distribution and risk allele frequency in all studies included.

First author	Cases			Controls			HWE test	
	Arg/Arg	Gln/Arg	Gln/Gln	Arg/Arg	Gln/Arg	Gln/Gln	χ^2	P
Matullo et al. (2001)	53	58	13	31	41	12	0.07	0.79
Stern et al. (2001)	96 (87/9)*	116 (106/10)	21 (21/0)	88 (79/9)	96 (92/4)	26 (26/0)	0.00	0.98
Shen et al. (2003)	93	87	21	92	98	24	0.08	0.78
Kelsey et al. (2004)	132	187	36	228	230	86	4.66	0.03
Sanyal et al. (2004)	124	155	32	113	110	23	0.26	0.61
Broberg et al. (2005)	26	31	4	80	62	13	0.04	0.84
Matullo et al. (2005)	136	135	40	120	145	47	0.09	0.77
Andrew et al. (2006)	118	155	33	225	227	86	4.93	0.03
Karahalil et al. (2006)	49	38	13	41	42	17	1.18	0.28
Matullo et al. (2006)	54	53	17	484	482	128	0.23	0.63
Sak et al. (2007)	218	248	66	226	259	75	0.00	0.95
Figueroa et al. (2007)	434	494	133	41	47	13	0.01	0.93
Fontana et al. (2008)	21	25	5	18	18	9	1.25	0.26
Arizono et al. (2008)	139	102	10	140	90	21	1.41	0.24
Andrew et al. (2008)	412	456	122	533	536	184	6.59	0.01
Wang et al. (2010)	113	102	19	105	126	22	3.41	0.06
Mittal et al. (2012)	67	106	39	102	109	39	1.19	0.28
Zhi et al. (2012)	121	151	30	148	143	20	3.57	0.06

*Represents Caucasians and blacks separately.

Table 3. Meta-analysis of the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk.

Contrast	Random effects OR (95%CI)	Fixed effects OR (95%CI)	Heterogeneity		P value for Z-test
			P value	I^2	
Gln allele *vs* Arg allele	0.96 (0.80, 1.16)		<0.00001	77%	0.70
Caucasian	0.87 (0.72, 1.07)		0.004	63%	0.19
Mongoloid	1.21 (0.74, 1.99)		<0.00001	90%	0.44
Black	2.50 (0.66, 9.46)				0.18
Mixed	0.92 (0.75, 1.14)				0.46
Arg/Arg *vs* (Gln/Gln + Gln/Arg)	1.13 (0.70, 1.82)		<0.00001	88%	0.62
Caucasian	1.33 (0.82, 2.15)		<0.00001	79%	0.25
Mongoloid	0.75 (0.14, 4.16)		<0.00001	96%	0.74
Mixed	1.09 (0.78, 1.51)				0.63
Gln/Gln *vs* (Gln/Arg + Arg/Arg)		0.92 (0.79, 1.07)	0.32	12%	0.29
Caucasian		0.86 (0.70, 1.06)	0.73	0%	0.16
Mongoloid	1.01 (0.61, 1.69)		0.04	64%	0.96
Mixed	0.90 (0.63, 1.29)				0.57
Gln/Gln *vs* Arg/Arg	0.90 (0.69, 1.16)		0.010	52%	0.42
Caucasian		0.86 (0.70, 1.06)	0.34	11%	0.08
Mongoloid	1.15 (0.54, 2.45)		0.002	80%	0.71
Mixed	0.87 (0.59, 1.30)				0.51
Gln/Arg *vs* Arg/Arg		0.89 (0.75, 1.05)	0.32	12%	0.17
Caucasian		0.88 (0.70, 1.10)	0.71	0%	0.27
Mongoloid	0.93 (0.54, 1.59)		0.05	62%	0.79
Mixed	0.87 (0.59, 1.30)				0.51

OR = odds ratio; 95%CI = 95% confidence interval.

The meta-analysis revealed no association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in the comparisons of the Gln allele *vs* Arg allele, Arg/Arg *vs* (Gln/Gln + Gln/Arg), Gln/Gln *vs* (Gln/Arg + Arg/Arg), Gln/Gln *vs* Arg/Arg, and Gln/Arg *vs* Arg/Arg (OR = 0.96, 95%CI = 0.80-1.16, P = 0.70; OR = 1.13, 95%CI = 0.70-1.82, P = 0.62; OR = 0.92, 95%CI = 0.79-1.07, P = 0.29; OR = 0.90, 95%CI = 0.69-1.16, P = 0.42; OR = 0.89, 95%CI = 0.75-1.05, P = 0.17, respectively) (Figure 1). In the subgroup analysis based on ethnicity, studies were divided into Caucasian, Mongoloid, black, and mixed populations.

No significant association was observed between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in all populations for all comparisons (all P > 0.05).
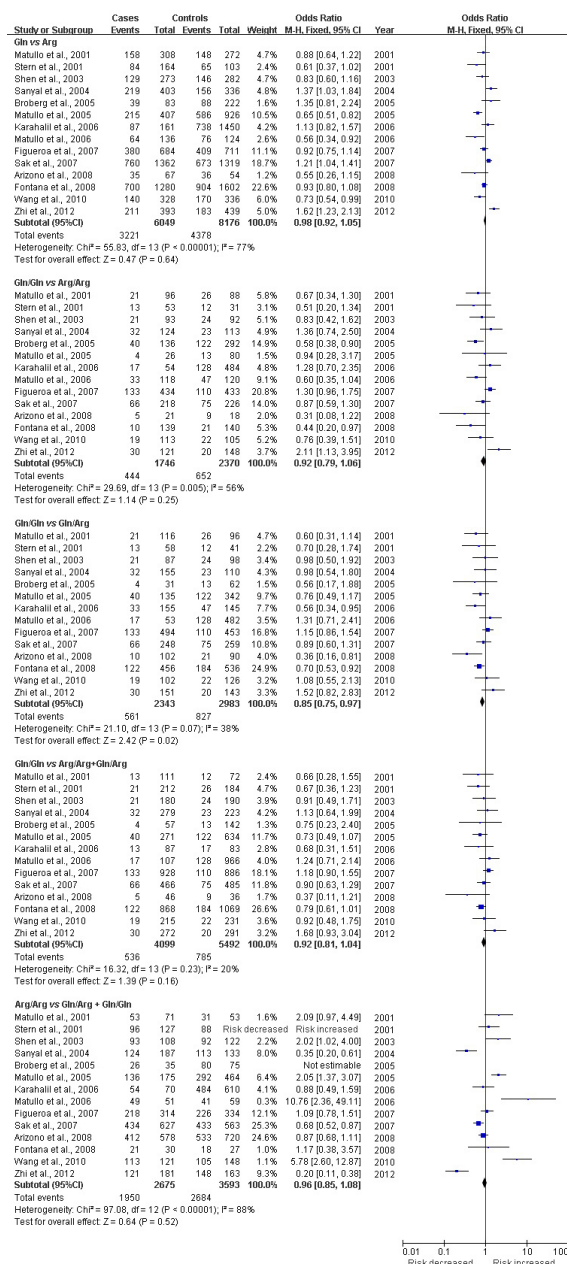

Figure 1. Forest plot of bladder cancer risk associated with the XRCC1 Arg399Gln polymorphism. Squares and horizontal lines correspond to the study-specific odds ratios (ORs) and 95% confidence intervals (CIs). The area of the squares reflects the study-specific weight (inverse of the variance). The diamonds represent the pooled ORs and 95%CI. M.H. = Mantel-Haenszel.

Sensitivity analysis was performed by sequential omission of individual studies. The significance of the pooled OR in all individual and subgroup analyses was not excessively influenced by omitting any single study.

Heterogeneity and publication bias

Heterogeneity among studies was found in all comparisons of the XRCC1 Arg399Gln polymorphism; therefore, random effects model was used for single studies in the subgroup analysis to minimize the impact of bias (Table 3). Publication bias of the meta-analysis of the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk was assessed by Begg's funnel plot (Figure 2) and Egger's linear regression test. The results of all evaluations for publication bias were non-significant. The information related to Egger's publication bias test is shown in Table 4.
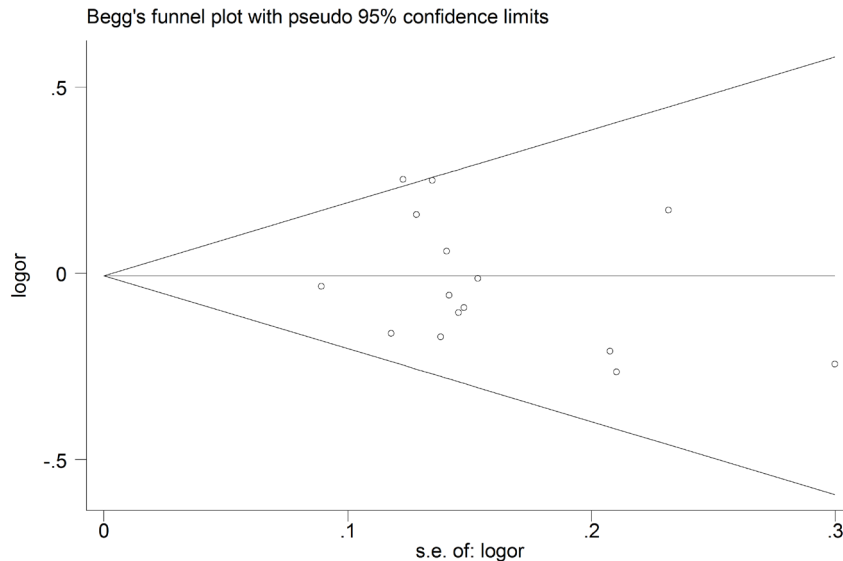

Figure 2. Begg's funnel plot of the Egger test of allele comparison for publication bias (Gln *vs* Arg).

Table 4. Egger's publication bias test for the XRCC1 Arg399Gln polymorphism.

Comparison	Coefficient	Standard error	*t*	P > |*t*|	95%CI
Gln allele *vs* Arg allele	-0.91	1.11	-0.82	0.43	(-3.31-1.49)
Arg/Arg *vs* (Gln/Gln + Gln/Arg)	-1.23	0.96	-1.28	0.22	(-3.31-0.85)
Gln/Gln *vs* (Gln/Arg + Arg/Arg)	-1.39	0.70	-2.00	0.07	(-2.89-0.11)
Gln/Gln *vs* Arg/Arg	-1.36	0.79	-1.73	0.11	(-3.07-0.34)
Gln/Arg *vs* Arg/Arg	0.28	1.14	0.24	0.81	(-2.19-2.74)

DISCUSSION

Few studies have been conducted to investigate the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in recent decades. Stern et al. (2001) found

a slight decrease in risk for individuals who carried the Gln/Gln genotype compared with those who had the Arg/Arg genotype; however, the difference was not statistically significant (age-, gender-, and ethnicity-adjusted OR = 0.7; 95%CI = 0.4-1.4; P = 0.35, for whites and blacks combined). Subsequently, Shen et al. (2003) carried out a case-control investigation in Northern Italy and found that the XRCC1 Arg399Gln polymorphism had a protective influence on bladder cancer among heavy smokers. Arizono et al. (2008) indicated that the Gln/Gln genotype had a protective effect against bladder cancer (adjusted OR = 0.37, 95%CI = 0.14-0.98; P = 0.05) among smokers. However, the overall effects showed no significant difference in different genotypes in bladder cancer. These results were also consistently observed in other studies. The distribution of XRCC1 Arg399Gln genotypes in the 15 studies strictly complied with Hardy-Weinberg equilibrium. Our meta-analysis based on these 15 studies revealed no association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in the comparisons of Gln allele *vs* Arg allele, (Gln/Gln + Gln/Arg) *vs* Arg/Arg, Gln/Gln *vs* (Gln/Arg + Arg/Arg), Gln/Gln *vs* Arg/Arg, and Gln/Arg *vs* Arg/Arg.

Relationships between the XRCC1 Arg399Gln polymorphism and cancer development have been observed for several cancers. Kiyohara et al. (2006) and Mattulo et al. (2006) found that the XRCC1 399Gln/Gln genotype was associated with risk of lung cancer. Duell et al. (2001) identified the same genotype to be associated with breast cancer risk in African Americans. However, no relationships between the XRCC1 Arg399Gln polymorphism and bladder cancer have been found in recent studies.

Relationships between genotypes and pathological grade, clinical stage, or prognosis have been reported. Sanyal et al. (2007) indicated that variant allele carriers of the XRCC1 polymorphism showed a lower risk of recurrence (Stage TaG2; P = 0.05) and death (Stage T2 or greater; P = 0.03) after instillation and radiotherapy compared to non-carriers. Sakano et al. (2006) showed that for patients with bladder cancer after platinum-based chemoradiotherapy, combined genotypes with at least one variant allele in XRCC1 were significantly associated with improved cancer-specific survival compared with the remaining groups. In all included studies, subjects of different nationalities showed different genotype frequencies. However, the different genotypes did not affect the overall results. In the subgroup meta-analysis by ethnicity, no association was observed between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in Caucasian, Mongoloid, and black populations. However, data regarding genotypes in the black population were limited and incomplete. Only Stern et al. (2001) reported detailed data for the genotypes of the black population. Thus, the relationship between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in the black population requires further investigation.

Smoking has been reported to be the most important cause of bladder cancer, and the risk has been shown to be dose-dependent. The relationship between the XRCC1 Arg-399Gln polymorphism and bladder cancer risk differed when smoking status was included in the analysis (Burch et al., 1989; Taylor et al., 1998). Shen et al. (2003) reported that the Arg to Gln substitution may provide protection against bladder cancer in heavily smoking subgroups. Stern et al. (2001) observed that a reduction in bladder cancer risk was associated with decreased smoking, which was slightly more pronounced among Gln/Gln subjects. We attempted to reach a definitive conclusion through subgroup analysis of variant status of smoking. However, division of most studies and varying classification criteria of data did not allow for this analysis.

There were some limitations to our meta-analysis. First, to obtain more reliable results, we strictly compiled data according to the rules of Hardy-Weinberg equilibrium, so that 5 studies were excluded, which may have affected the overall effects of our meta-analysis. Second, we were not able to address sources of heterogeneity existing among studies for each polymorphism. Further subgroup stratifications analysis was not possible because of the limited number of published studies and different classification criteria of the data. In addition, the small sample size was not ideal for detecting small genetic effects. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers; the specific confounding factors adjusted for differed among the studies.

In conclusion, our meta-analysis suggests no association between the XRCC1 Arg-399Gln polymorphism and bladder cancer risk. Additional large-scale studies with adequate methodological quality and controls for possible confounding effects should be conducted.

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