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Correlation between XRCC1 Arg399Gln genetic polymorphisms and susceptibility to bladder cancer: a meta-analysis

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Abstract: The relationship between *XRCC1* polymorphisms and bladder cancer has been widely studied. Here, our meta-analysis was conducted to evaluate the correlations between common genetic polymorphisms in XRCC1 and susceptibility to bladder cancer. In order to derive a more precise estimation of the association, 27 clinical case-control studies (which met all the inclusion criteria) were included in this meta-analysis. A total of 8,539 cancer cases and 10,750 controls were involved in this meta-analysis. Overall, no significant association was detected in allelic model (A allele vs T allele odds ratio [OR] =0.87, 95% confidence interval [CI], 0.71–1.06), homozygote comparison (AA vs GG OR =1.12, 95% CI, 0.68–1.85), heterozygote comparison (AT vs TT OR =1.01, 95% CI, 0.81–1.26), dominant model (AA + AG vs GG OR =0.93, 95% CI, 0.85–1.02), and recessive model (AA vs AG + GG OR =1.01, 95% CI, 0.88–1.15), but a moderately significant association was found for AG vs GG (OR =0.241, 95% CI =0.17–0.35). Subgroup analysis based on ethnicity. Ethnicity analysis suggested that genetic polymorphisms in XRCC1 were not correlated with increased bladder cancer risk among Asians (all $P>0.05$). Therefore, we concluded that XRCC1 genetic polymorphism may not contribute to bladder cancer susceptibility in the present meta-analysis, and further well-designed studies with a large sample size are warranted to validate our conclusion.

Keywords: XRCC1, genetic polymorphism, susceptibility, bladder cancer, meta-analysis

Introduction

Bladder cancer is one of the most common health problems worldwide, the seventh most common malignancy in men, and 17th most common in women.[1] It is well-known that the most common risk factors for bladder cancer include tobacco smoking,[2] occupational exposure to chemicals,[3] and schistosomiasis.[1] Whereas, epidemiological studies have shown that genetic variants at one or more loci result in reduced DNA repair capacity and an increased cancer risk.[4–6] In addition, a large number of single nucleotide polymorphisms in common DNA repair genes have also been identified[7] and confirmed to be associated with several sporadic cancers.[8,9]

XRCC1 is located on chromosome 19q13.2–13.3[10,11] with a length of 33 kb, and plays an essential role in DNA repair genes involved in base excision repair[12] and single-strand breaks.[13] To date, XRCC1 is the first cloned human gene associated with single-strand break repair[14] and also related to sister-chromatid exchange.[15] As previously described, there are three single nucleotide polymorphisms leads to amino acid substitutions in Arg194Trp in exon 6 (rs1799782), Arg280His in exon 9 (rs25489), and Arg399Gln in exon 10 (rs25487).[16,17]

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Although several previous studies have evaluated the associations of XRCC1 polymorphisms with bladder cancer risk, the results are still inconsistent. In the present study, we performed a meta-analysis of all eligible studies to demonstrate the effect of XRCC1 Arg399Gln polymorphism on bladder cancer susceptibility.

Materials and methods

Identification of eligible studies

PubMed, Embase, and Web of Science databases were searched in our meta-analysis. Case-control studies of the XRCC1 Arg399Gln polymorphism and bladder cancer susceptibility published before June 1, 2015 were included by using the keywords: "XRCC1", "X-ray repair cross-complementing group 1", "Arg399Gln", "polymorphism", "bladder cancer", and "urothelial carcinoma". The search was limited to English language papers. All reference lists of reviews and retrieved articles were manually screened for further potential studies.

Inclusion and exclusion criteria

The following criteria were used to determine inclusion eligibility: 1) a study that evaluated the correlation of XRCC1 Arg399Gln polymorphisms with bladder cancer susceptibility; 2) case-control study design; 3) full-text published articles; 4) a study that included sufficient genotype data for extraction. Furthermore, articles that did not meet our inclusion criteria were excluded.

Data extraction

Information was extracted carefully from all eligible publications independently and in duplicate by two authors. The following data were collected from each study: the first author's name, year of publication, country of origin, genotyping method, numbers of cases and controls, and evidence of Hardy-Weinberg equilibrium (HWE). The two authors reached consensus on each item.

Statistical analysis

The strength of association between the XRCC1 Arg399Gln polymorphism and bladder cancer was calculated by individual or pooled odds ratios (ORs) and 95% confidence intervals (CIs) using the STATA statistical software (Version 12.0, StataCorp LP, College Station, TX, USA). We evaluated the following comparisons to the XRCC1 Arg399Gln polymorphism including comparison of the variant allele with the wild-type allele (Gln allele vs Arg allele), the variant homozygote with the wild-type homozygote and the heterozygote (Gln/Gln vs Gln/Arg + Arg/Arg), the wild-type homozygote with the variant homozygote and the heterozygote (Arg/Arg vs Gln/Arg + Gln/Gln), and the variant homozygote with the heterozygote and wild-type homozygote (Gln/Gln vs Arg/Arg; Gln/Gln vs Gln/Arg). The statistical significance of the pooled ORs was assessed with the Z test and a P-value of <0.05 was considered significant. Chi-square-based Q test was conducted to measure the heterogeneity between eligible studies, and the existence of heterogeneity was considered significant if $P<0.10$.[11] When the between-study heterogeneity was absent, a fixed-effect model (the Mantel–Haenszel method) was used to pool the data from different studies.[18] Otherwise, a random-effect model (the DerSimonian and Laird method) was applied.[19] To explore the source of heterogeneity among variables such as ethnicity, and HWE status, both subgroup analyses and logistic met regression analyses were performed.[20] Funnel plots and Egger's linear regression test were applied to investigate publication bias.[21]

Results

Study selection and description

A total of 27 eligible studies including 8,539 cases and 10,750 controls met the inclusion criteria. The HWE test was performed to determine the genotype distribution of the controls in all studies included. All of the studies, except for three,[22–24] were not in HWE, and two studies[25,26] lacked sufficient data for calculating the P-value to determine HWE.

Quantitative data synthesis

The study characteristics are summarized in Table 1. The genotype distribution and risk allele frequency of the included studies are summarized in Table 2. Overall, there was no significant correlation between the XRCC1 Arg399Gln polymorphism and bladder cancer risk for A allele vs G allele (OR =0.87, 95% CI =0.71–1.06, P=0.160 for heterogeneity, Figure 1A), the codominant model AA vs GG (OR =1.01, 95% CI =0.81–1.26, P=0.959 for heterogeneity, Figure 1B), the dominant model AA/AG vs GG (OR =0.93, 95% CI =0.85–1.02, P=0.134 for heterogeneity, Figure 1C), and the recessive model AA vs AG/GG (OR =1.01, 95% CI =0.88–1.15, P=0.934 for heterogeneity, Figure 1D), but a moderately significant association was found for AG vs GG (OR =0.241, 95% CI =0.17–0.35, P=0.000 for heterogeneity, Figure 2). In subgroup analysis by ethnicity, no significant association was found between XRCC1 Arg399Gln polymorphism and bladder cancer risk among Asians ($P>0.05$).

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

Study	Year	Country	Method	Number of subjects	
				Case	Controls
Akhmadishina LZ et al[33]	2014	Russian	PCR-RFLP	289	173
Chien-I Chiang CI et al[34]	2014	People's Republic of China	PCR-RFLP	324	647
Volha P et al[35]	2014	Belarus	PCR-RFLP	332	364
Zhi Y et al[36]	2012	People's Republic of China	PCR-RFLP	302	311
Mittal RD et al[37]	2012	India	ARMS PCR	212	250
Gao W et al[38]	2012	USA	PCR+SSCP	192	313
Wang M et al[39]	2010	People's Republic of China	PCR-RFLP	234	253
Wen H et al[26]	2009	People's Republic of China	TaqMan assay	80	291
Mittal RD et al[40]	2008	India	PCR-RFLP	140	90
Fontana L et al[41]	2008	France	TaqMan assay	51	45
Covolo L et al[42]	2008	Italy	PCR-RFLP	197	211
Arizono K et al[43]	2008	Japan	PCR-RFLP	251	251
Andrew AS et al[23]	2008	USA	PCR-RFLP	990	1,253
Sak SC et al[44]	2007	UK	TaqMan assay	532	560
Huang M et al[25]	2007	USA	TaqMan assay	613	696
Figueroa JD et al[45]	2007	USA	TaqMan assay	1,061	996
Karahalil B et al[46]	2006	Turkey	PCR-RFLP	100	100
Andrew AS et al[47]	2006	USA	PCR-RFLP	306	538
Matullo G et al[31]	2006	Italy	PCR-RFLP	124	1,094
Wu X et al[48]	2006	USA	TaqMan assay	613	596
Matullo G et al[49]	2005	UK	PCR-RFLP	311	312
Broberg K et al[50]	2005	Sweden	Mass assay	61	155
Kelsey KT et al[24]	2004	USA	PCR-RFLP	355	544
Sanyal S et al[51]	2004	Sweden	PCR-RFLP	311	246
Shen M et al[28]	2003	France	PCR-RFLP	201	214
Matullo G et al[52]	2001	Italy	PCR-RFLP	124	37
Stern MC et al[27]	2001	USA	PCR-RFLP	233	210

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; AMRS PCR, amplification refractory mutation system polymerase chain reaction; PCR+SSCP, polymerase chain reaction and single-strand conformation polymorphism.

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

Study (year)	Case			Control			HWE test	
	GG	AG	AA	GG	AG	AA	χ^2	*P*-value
Akhmadishina LZ et al[33]	86	143	60	60	88	25	0.639	0.424
Chien-I Chiang CI et al[34]	179	108	37	350	253	44	0.036	0.850
Volha P et al[35]	141	154	37	151	165	48	0.076	0.782
Zhi Y et al[36]	121	151	30	148	143	20	3.571	0.588
Mittal RD et al[37]	67	106	39	102	109	39	1.186	0.276
Gao W et al[38]	85	107	–	136	177	–	–	–
Wang M et al[39]	113	102	19	105	126	22	3.414	0.065
Wen H et al[26]	46	34	–	153	138	–	–	–
Mittal RD et al[40]	37	76	27	73	81	36	2.459	0.117
Fontana L et al[41]	21	25	5	18	18	9	1.25	0.264
Covolo L et al[42]	92	105	–	91	120	–	–	–
Arizono K et al[43]	139	102	10	140	90	21	1.410	0.235
Andrew AS et al[23]	412	456	122	533	536	184	6.586	0.010
Sak SC et al[44]	218	248	66	226	259	75	0.003	0.953
Huang M et al[25]	266	347	–	367	329	–	–	–
Figueroa JD et al[45]	434	494	133	433	453	110	0.273	0.602
Karahalil B et al[46]	49	38	13	41	42	17	1.181	0.277
Andrew AS et al[47]	118	155	33	225	227	86	4.935	0.026
Matullo G et al[31]	54	53	17	484	482	128	0.229	0.632
Wu X et al[48]	266	277	70	267	256	73	0.913	0.339
Matullo G et al[49]	136	135	40	120	145	47	0.087	0.768
Broberg K et al[50]	26	31	4	80	62	13	0.041	0.840
Kelsey KT et al[24]	132	187	36	228	230	86	4.663	0.031
Sanyal S et al[51]	124	155	32	113	110	23	0.260	0.610
Shen M et al[28]	93	87	21	92	98	24	0.168	0.682
Matullo G et al[52]	53	58	13	12	19	6	0.111	0.739
Stern MC et al[27]	96	116	21	88	96	26	0.000	0.982

Abbreviation: HWE, Hardy-Weinberg equilibrium.

Sensitivity analysis

The analysis of sensitivity was examined by sequential omission of individual studies. The significance of the pooled ORs 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, the random effects model was used for single studies in the subgroup analysis to minimize the impact of bias. Funnel plots demonstrated

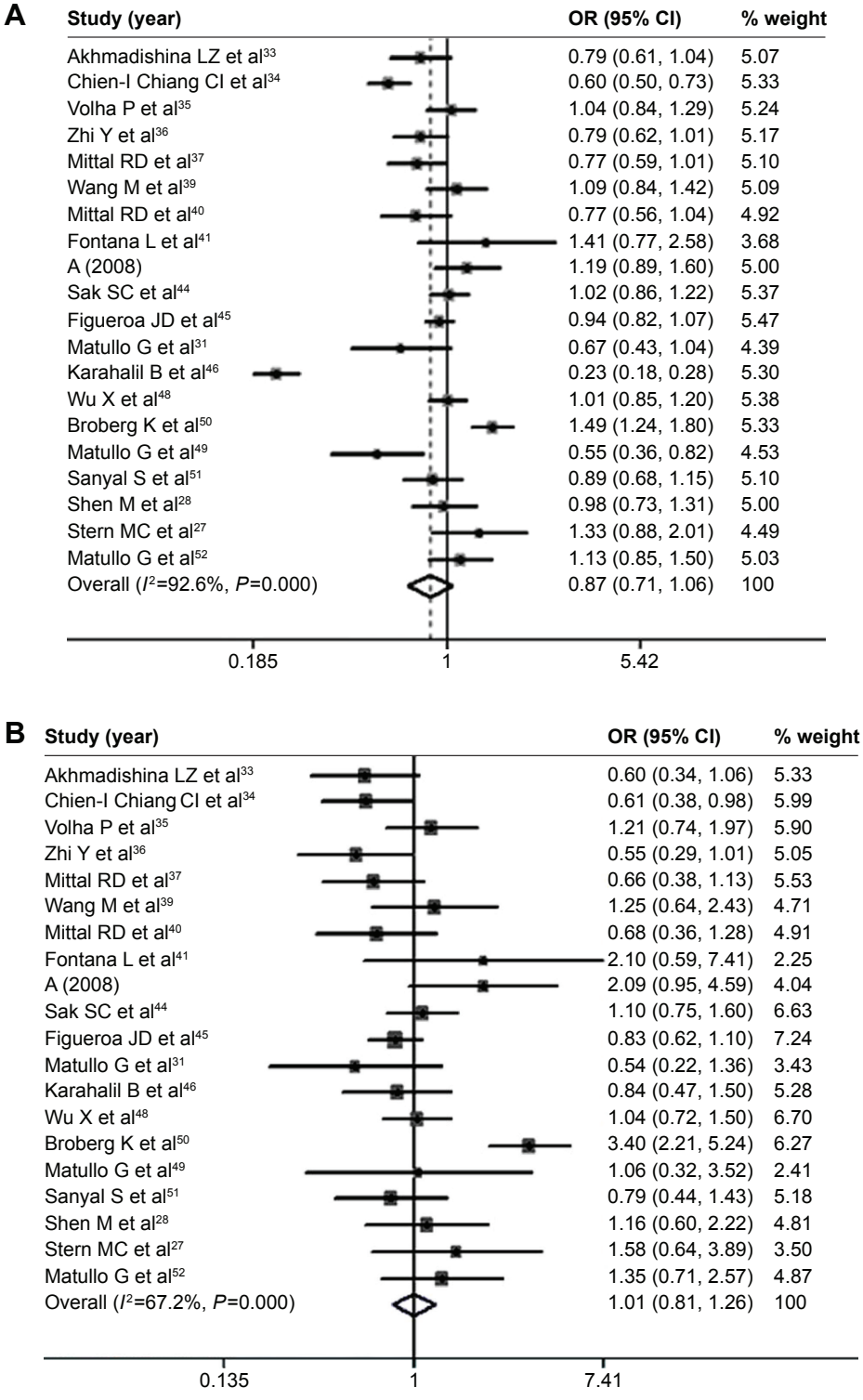

Figure 1 (*Continued*)

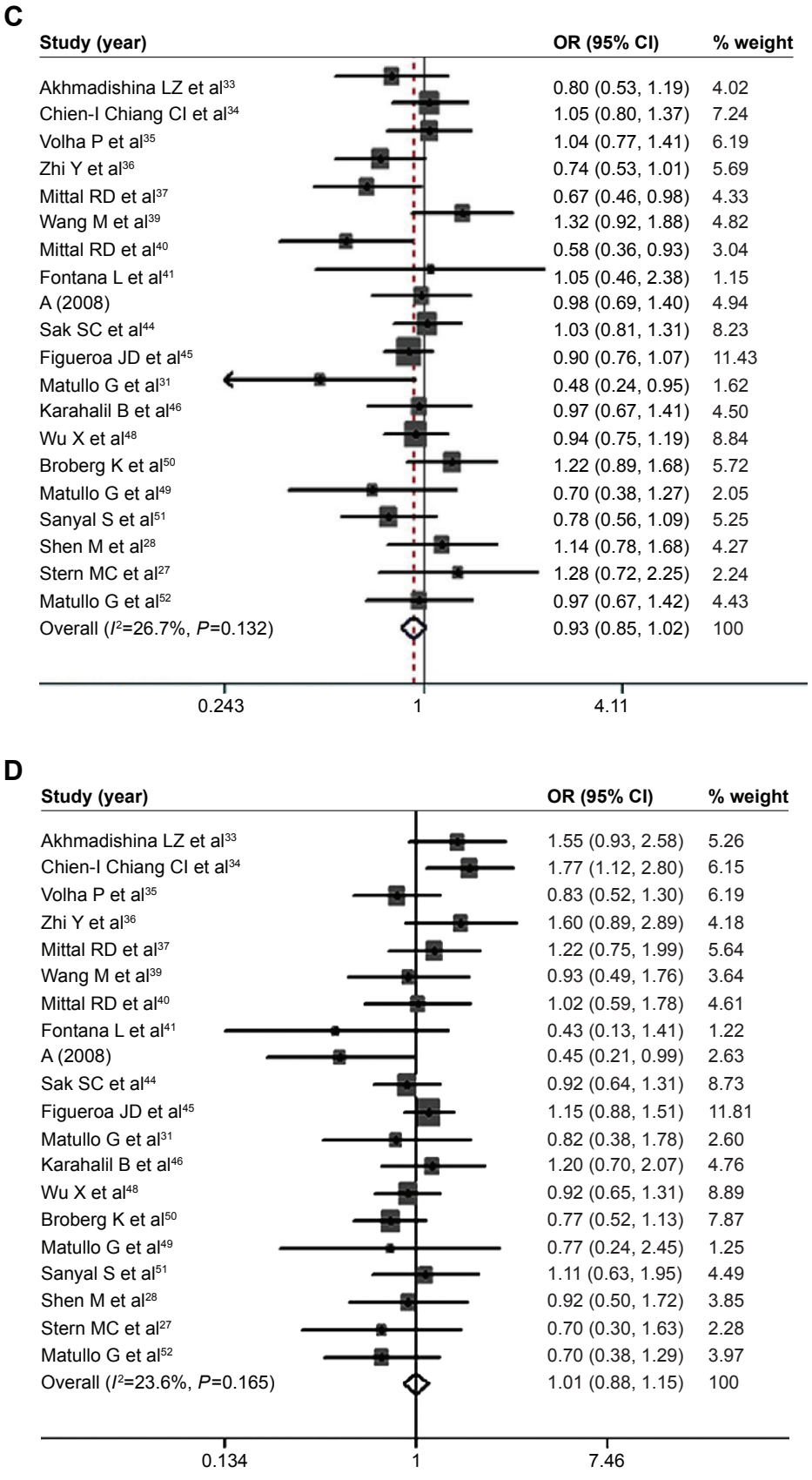

Figure 1 Odds ratios for associations between single nucleotide polymorphism Arg399Gln in XRCC1 and bladder cancer risk.
Notes: (**A**) A allele vs G allele; (**B**) AA vs GG; (**C**) AA + AG vs GG; (**D**) AA vs AG + GG. Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

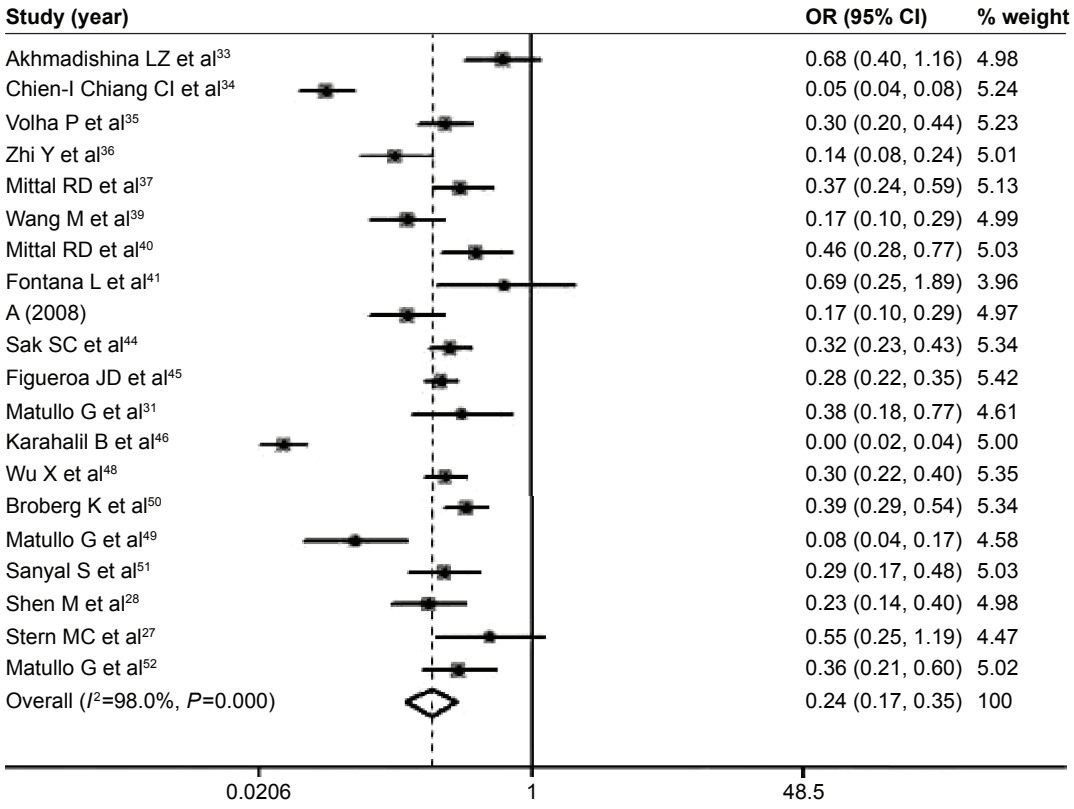

Figure 2 Forest plot of XRCC1 Arg399Gln AG genotypes versus the GG genotype.
Note: Weights are from random effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

evidence of obvious asymmetry (Figure 3). Egger's test displayed strong statistical evidence of publication bias.

Discussion

Few studies have been conducted to investigate the association between the XRCC1 Arg399Gln polymorphism and bladder cancer risk in recent decades. Compared with those who had the Arg/Arg genotype, a slight decrease was found in risk for individuals who carried the Gln/Gln genotype.[27] Subsequently, a case-control investigation was carried out in Northern Italy, and the XRCC1 Arg399Gln polymorphism showed a protective effect on bladder cancer risk among heavy smokers.[28] In comparison with 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, our meta-analysis based on these 27 studies revealed no correlation between the XRCC1 Arg399Gln polymorphism and bladder cancer risk.

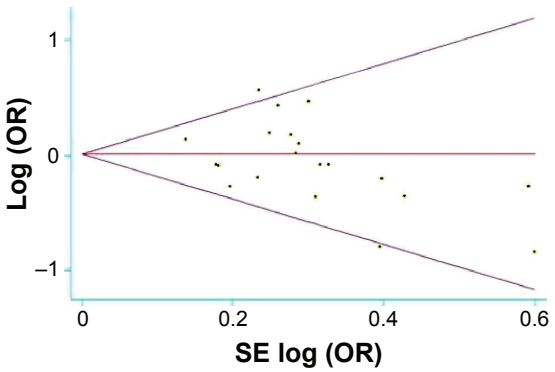

Figure 3 Funnel plot of two single nucleotide polymorphisms Arg399Gln in XRCC1 and bladder cancer risk.
Note: Begg's funnel plot with pseudo 95% confidence limits.
Abbreviations: OR, odds ratio; SE, standard error.

As we know, mutations occurring in the nucleotide bases is the most common type of DNA damage, and they exhibit a high frequency (up to several thousand a day). Consequently, once the XRCC1 protein is lost, it may cause increased cell sensitivity to radiation, oxidative stress, and alkylating agents (eg, camptothecin).[14] To date, more than 300 single nucleotide changes have been identified in the *XRCC1* gene.[29] The Arg399Gln mutation leads to conformational changes in the XRCC1 protein that reduces its affinity for the multicomponent DNA repair protein complex.[29]

Presently, relationships between the XRCC1 Arg399Gln polymorphism and cancer development have been observed in several cancers. As previously reported, the alterations

of XRCC1 are the most widely accepted suggestion to play a role in the pathogenesis of cancers.[30,31] In particular, it has been found that the XRCC1 399Gln/Gln genotype was associated with lung cancer risk, as well as breast cancer risk in African Americans.[32] However, no relationship between the XRCC1 Arg399Gln polymorphism and bladder cancer has been found in recent studies.

Notably, several limitations of our meta-analysis should be mentioned. Firstly, we strictly compiled data according to the rules of HWE, and ruled out three studies that might have caused the overall effects in our meta-analysis. Secondly, our systematic review was based on unadjusted data. Furthermore, the genotype information stratified for the main confounding variables was not available in the original papers.

Taken together, we have shown that there is 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.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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