

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

Nannan Liu¹
Xiawei Fei²
Yi Shen¹
Weifeng Shi¹
Jinhong Ma¹

¹Department of Clinical Laboratory,
The Third Affiliated Hospital of
Suzhou University, Changzhou,
Jiangsu, People's Republic of China;

²Department of Urology Surgery,
Qingpu Branch of Zhongshan Hospital
Affiliated to Fudan University,
Shanghai, People's Republic of China

Abstract: The relationship between *XRCCI* polymorphisms and bladder cancer has been widely studied. Here, our meta-analysis was conducted to evaluate the correlations between common genetic polymorphisms in *XRCCI* 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 *XRCCI* were not correlated with increased bladder cancer risk among Asians (all $P > 0.05$). Therefore, we concluded that *XRCCI* 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: XRCCI, 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 identified⁷ and confirmed to be associated with several sporadic cancers.^{8,9}

XRCCI 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 repair¹² and single-strand breaks.¹³ To date, *XRCCI* is the first cloned human gene associated with single-strand break repair¹⁴ 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}

Correspondence: Jinhong Ma
Department of Clinical Laboratory,
The Third Affiliated Hospital of Suzhou
University, Changzhou 213003, Jiangsu,
People's Republic of China
Tel +86 519 6887 0895
Fax +86 519 8662 1235
Email mjhczyy@126.com

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; ARMS 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

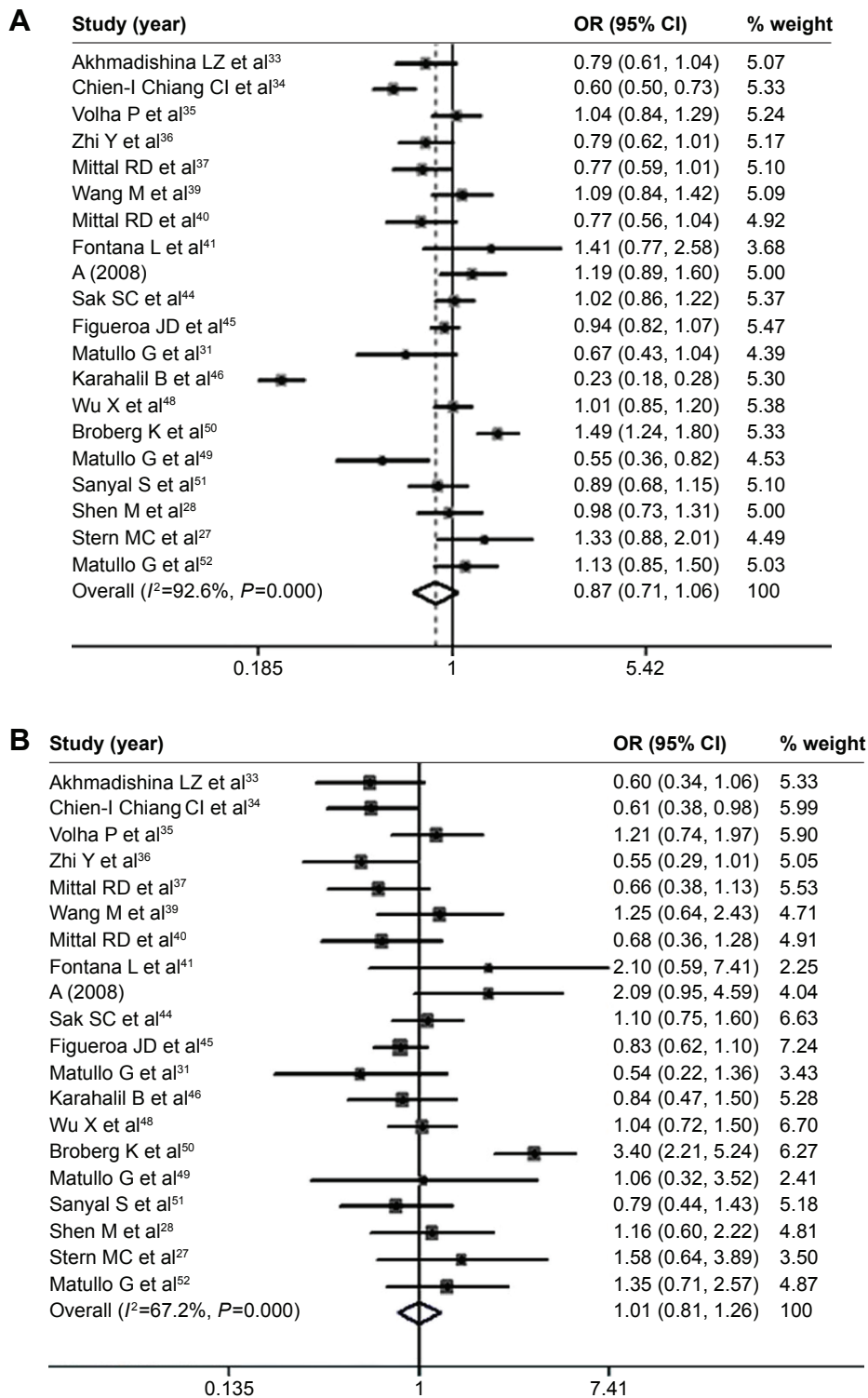


Figure 1 (Continued)

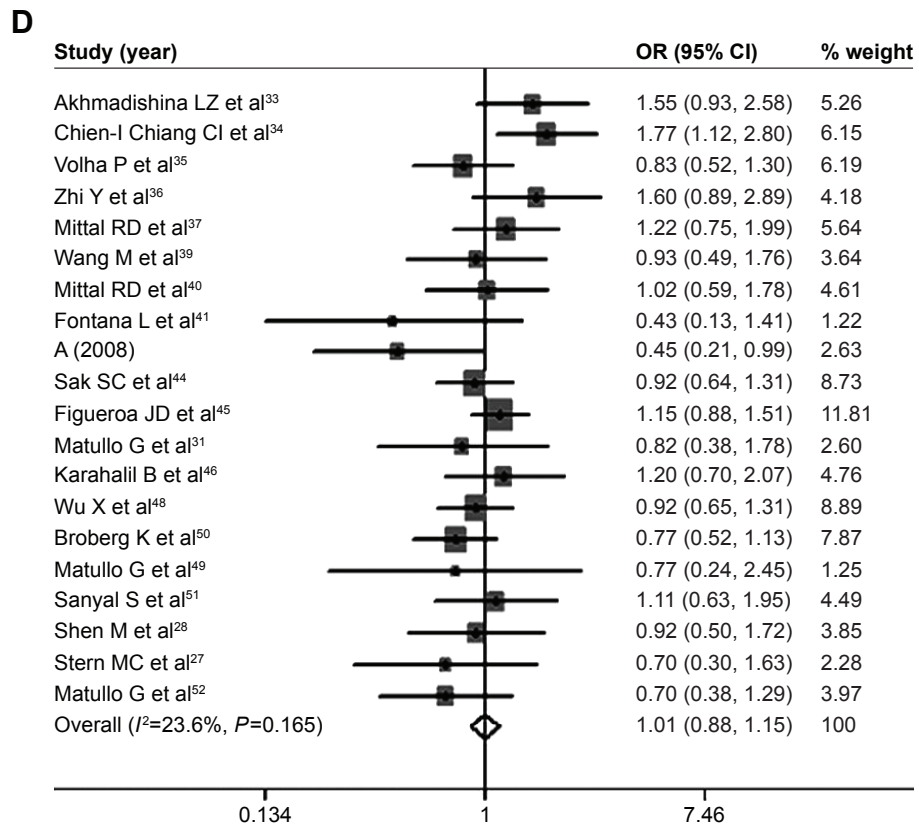
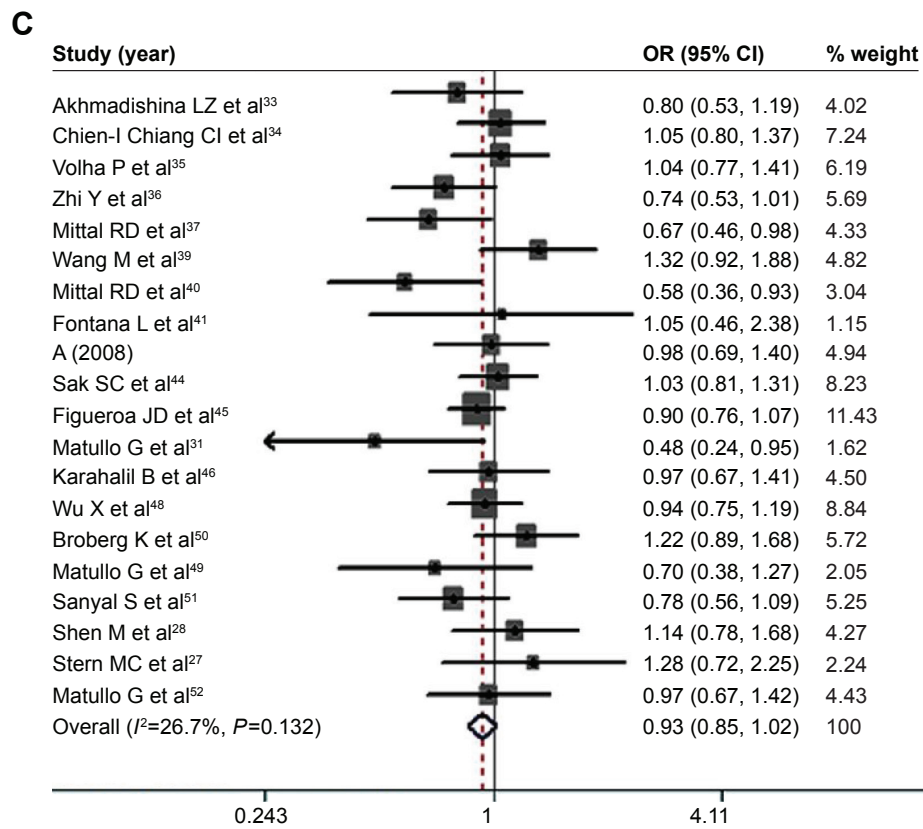


Figure 1 Odds ratios for associations between single nucleotide polymorphism Arg399Gln in XRCC1 and bladder cancer risk. **Notes:** (A) A allele vs G allele; (B) AA vs GG; (C) AA + AG vs GG; (D) AA vs AG + GG. Weights are from random effects analysis. **Abbreviations:** OR, odds ratio; CI, confidence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

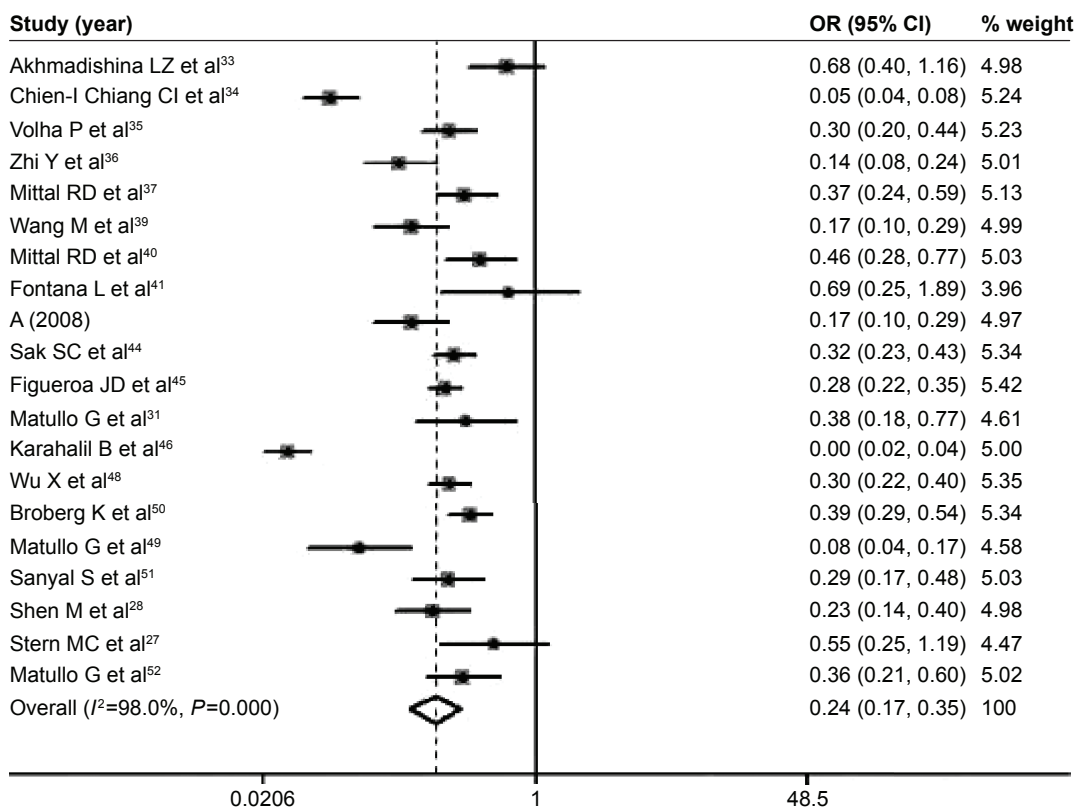


Figure 2 Forest plot of XRCC1 Arg399Gln AG genotypes versus the GG genotype.

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.

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 multi-component 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

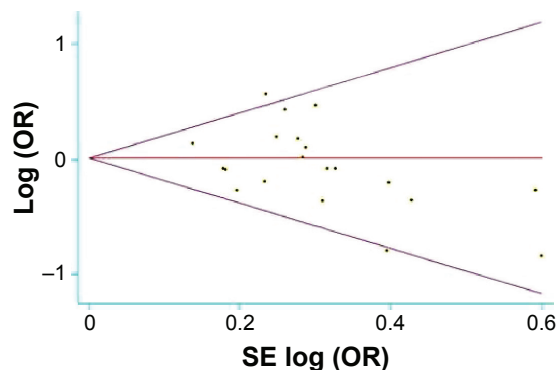


Figure 3 Funnel plot of two single nucleotide polymorphisms Arg399Gln in XRCC1 and bladder cancer risk.

Note: Begg's funnel plot with pseudo 95% confidence limits.

Abbreviations: OR, odds ratio; SE, standard error.

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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