Quantitative assessment of the associations between XRCC1 polymorphisms and bladder cancer risk

Yeqing Mao†, Xin Xu†, Yiwei Lin, Hong Chen, Jian Wu, Zhenghui Hu, Yi Zhu, Xianglai Xu and Liping Xie*

Abstract

Background: The XRCC1 polymorphisms have been implicated in bladder cancer risk, but individually published studies show inconsistent results. The aim of our study was to clarify the effects of XRCC1 variants on bladder cancer risk.

Methods: A systematic literature search up to September 13, 2012 was carried out in PubMed, EMBASE and Wanfang databases, and the references of retrieved articles were screened. Crude odds ratios with 95% confidence intervals were used to assess the associations between XRCC1 Arg194Trp and Arg399Gln polymorphisms and bladder cancer risk. Heterogeneity and publication bias were also evaluated.

Results: A total of 14 and 18 studies were eligible for meta-analyses of Arg194Trp and Arg399Gln, respectively. Regrouping was adopted in accordance with the most probable appropriate genetic models. No obvious heterogeneity between studies was found. For overall bladder cancer, the pooled odds ratios for Arg194Trp and Arg399Gln were 1.69 (95% confidence interval: 1.25 to 2.28; \(P = 0.001\)) and 1.10 (95% confidence interval: 1.03 to 1.19; \(P = 0.008\)), respectively. After excluding the studies that were not in Hardy–Weinberg equilibrium, the estimated pooled odds ratio still did not change at all.

Conclusions: The meta-analysis results suggest that XRCC1 Arg194Trp and Arg399Gln polymorphisms may be associated with elevated bladder cancer risk.

Keywords: XRCC1, Polymorphism, Bladder cancer, Meta-analysis

Background

Bladder cancer is an important health problem worldwide. It is the seventh most common malignancy in men and seventeenth in women [1]. An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide [2]. However, the mechanism of bladder cancer is not completely clear and is considered to be a multifactorial process. The most established risk factors for bladder cancer include cigarette smoking, occupational exposure to arylamines and schistosomal infection [1]. These exogenous mutagens or carcinogens produce a wide range of DNA lesions, bulky DNA adducts, and DNA strand breaks. Epidemiologic evidence has shown that genetic variants at one or more loci result in reduced DNA repair capacity and an increased cancer risk [3-5].

DNA carrying essential heritable information must remain stable in order to undertake its key physiologic functions, but it is continually vulnerable to many types of endogenous and/or exogenous damage; thus, genetic alterations could accumulate and tumorigenesis may occur because of the damaged DNA. The DNA repair system plays a pivotal role in maintaining the genome integrity and stability through the reversal of DNA damage. If accumulated genetic alterations occurred in corresponding DNA repair genes, their reversal capacity could be damaged, possibly increasing the risk of cancer in carriers [6]. A large number of SNPs in common DNA repair genes have been identified [7] and confirmed to be associated with several sporadic cancers [8,9].
X-ray repair cross-complementing group 1 (XRCC1), located on chromosome 19q13.2–13.3, with 33 kb in length, is an important component of base excision repair (BER) [10]. BER consists of a series of consecutive steps from the recognition and excision of a damaged base to the ligation of broken points, which are mainly conducted by XRCC1. When damage occurs, XRCC1 recruited by DNA glycosylases, acts as a platform by regulating and coordinating a whole list of BER proteins and single strand break repair (SSBR) machinery [11,12]. Although there are more than 300 validated SNPs in the XRCC1 gene reported in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), two genetic changes including Arg194Trp on exon 6 (rs1799782 in dbSNP, C/T) and Arg399Gln on exon 10 (rs25487 in dbSNP, G/A) are the most extensively studied. Many previous studies have been conducted to evaluate the associations of XRCC1 polymorphisms with bladder cancer risk. However, the results of these studies remain inconsistent and contradictory, partially because a single study may be too underpowered to detect a possible small effect of the polymorphism on bladder cancer, especially when the sample size is relatively small. Thus, to clarify the effect of XRCC1 variants (Arg194Trp and Arg399Gln) on bladder cancer risk, we performed a meta-analysis of all eligible studies.

Methods

Publication search
We carried out a systematic literature search in EMBASE, PubMed and Wanfang databases, covering all the papers published from their inception to September 13, 2012, using the following key words: (XRCC1 or X-ray repair cross-complementation group 1) and (bladder cancer or bladder neoplasm or bladder tumor or urothelial cancer or urinary tract cancer) and (polymorphism or variation or genotype or gene). There was no language restriction. We evaluated potentially relevant papers by checking their titles and abstracts and all the studies matching the eligible criteria were retrieved. Additional studies were identified by a manual search of the references from retrieved articles and reviews.

Inclusion criteria
Studies included in the present meta-analysis had to meet all the following criteria: (a) evaluation of the XRCC1 Arg194Trp and Arg399Gln polymorphisms and the risk of bladder cancer, (b) had a case–control design or nested case–control design, (c) had sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI). If multiple publications from the same population were available, the most recent or largest study was eligible for inclusion in this meta-analysis.

Data extraction
Data were extracted independently by two authors using a predefined data collection form, with disagreements being resolved by consensus. For each study, the following information was collected: first author’s last name, publication year, the country in which the study was carried out, ethnicity, numbers of cases and controls, genotyping methods, genotypes, and allele frequency information.

Quality assessment
The quality of each study was independently appraised by the same two authors using the quality assessment criteria, which were modified on the basis of previously published meta-analysis of molecular association studies [13,14]. The criteria consist of seven parameters of quality: representativeness of the cases, representativeness of the controls, ascertainment of bladder cancers, control selection, genotyping examination, Hardy–Weinberg equilibrium (HWE) and total sample size. (The criteria are described in detail in Additional file 1: Table S1). Scores ranged from 0 (worst) to 15 (best). Studies scoring <9 were classified as low quality, and those ≥9 as high quality. Disagreements were resolved by a joint reevaluation of the original article with a third investigator.

Statistical methods
HWE in cases and controls was examined again in our meta-analysis using the goodness-of-fit test (significant at the 0.05 level). The ORs and their 95% CIs were used to calculate and assess the strength of the association between XRCC1 Arg194Trp and Arg399Gln polymorphism and the risk of bladder cancer. If there was a statistical heterogeneity among studies, the combined ORs and 95% CIs were estimated by the DerSimonian and Laird method [15] in a random-effect model. Otherwise, the ORs were obtained by the Mantel–Haenszel method [16] in a fixed effect model.

ORs 1, 2, and 3 (OR1, OR2, and OR3) were calculated for the genotypes: 1) TT versus CC, 2) CT versus CC, and 3) TT versus CT for Arg194Trp; and 1) AA versus GG, 2) GA versus GG, and 3) AA versus GA for Arg399Gln, respectively. These pairwise differences were used to determine the most appropriate genetic model. If OR1 = OR3 ≠ 1 and OR2 = 1, a recessive model is implied. If OR1 = OR2 ≠ 1 and OR3 = 1, a dominant model is suggested. If OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete overdominant model is indicated. If OR1 > OR2 > 1 and OR1 > OR3 > 1, or if OR1 < OR2 < 1 and OR1 < OR3 < 1, then a codominant model is suggested.

Homogeneity of ORs across studies was tested by a Chi-square-based Q statistic and the I² score. Heterogeneity was considered significant if the P-value was <0.10. The value of I² was used to assess the degree of heterogeneity.
(I² <25% no heterogeneity; I² = 25% to 50% moderate heterogeneity; I² >50% large or extreme heterogeneity).

Sensitivity analysis was performed in which the meta-analysis estimates were computed after omission of every study in turn. Cumulative meta-analyses of associations for each SNP were also conducted through assortment of studies with publication time.

Evaluation of publication bias
Publication bias was assessed using Begg's test (rank correlation method) [17] and Egger's test (linear regression method) [18]. P <0.05 was considered to be representative of a significant statistical publication bias. All of the statistical analyses were performed with STATA 11.0 (StataCorp, College Station, TX), using two-sided P-values.

Results
Characteristics of all included studies
Twenty studies were included in this meta-analysis on the associations of the XRCC1 genetic polymorphisms with the risk of bladder cancer. Of the selected studies, 14 [19-32] were preliminarily appropriate for meta-analysis of the associations with bladder cancer regarding Arg194Trp, and 18 [19-22,24-28,30-38] were relevant to the association with Arg399Gln. Tables 1 and 2 present the basic characteristics of each study included in our meta-analysis and the corresponding genotype distributions among cases and controls. The literature search and study selection procedures are shown in Figure 1.

Quantitative synthesis
For the Arg194Trp SNP, OR1, OR2, and OR3 were 1.835 (95%CI: 1.343 to 2.507), 1.026 (95%CI: 0.920 to 1.146), and 1.581 (95%CI: 1.154 to 2.165), respectively, suggesting a recessive effect of the putative susceptibility allele T. Thus, the original grouping was collapsed, and CC and CT were combined, in accordance with a recessive model, into a C carrier group, the latter of which was compared with the TT genotype group.

For the Arg399Gln SNP, OR1, OR2, and OR3 were 0.958 (95%CI: 0.850 to 1.080), 1.095 (95%CI: 1.014 to 1.183), and 0.884 (95%CI: 0.785 to 0.997), respectively, indicating that a complete overdominant model was applicable, that is, heterozygotes are at higher risk of bladder cancer than either homozygotes (GG or AA).

As shown in Figures 2 and Table 3, the XRCC1 Arg194Trp polymorphism was associated with an increased risk for bladder cancer in all subjects (OR = 1.69, 95% CI = 1.25 to 2.28, P = 0.001). Similarly, the Arg399Gln polymorphism was also found to be significantly associated with increased risk of bladder cancer (OR = 1.10, 95% CI = 1.03 to 1.19, P = 0.008).

Evaluation of heterogeneity
For the Arg399Gln polymorphism, most I² values of heterogeneity were 0% and all P values were more than

Table 1 Main characteristics of the studies included in an analysis of the XRCC1 Arg194Trp polymorphism and bladder cancer risk

| Study          | Ethnicity | Country | Sample size (Frequency of T allele, %) | HWE in control | Quality score | Genotyping method |
|---------------|-----------|---------|----------------------------------------|----------------|--------------|-------------------|
|               |           |         | Case no (Frequency of T allele, %)      |                |              |                   |
|               |           |         | Control no                             |                |              |                   |
| Stern [19]    | Caucasian | US      | 235 (5.63)                             | 213 (8.63)     | Yes          | 8 PCR-RFLP        |
| Wu [20]       | Asian     | China   | 155 (33.87)                            | 155 (27.42)    | Yes          | 9 PCR-RFLP        |
| Matullo [21]  | Caucasian | Mixed   | 131 (6.45)                             | 1,094 (6.63)   | Yes          | 13 Taqman         |
| Wu [22]       | Caucasian | US       | 696 (6.43)                             | 629 (6.42)     | Yes          | 11 Taqman         |
| Zhang [23]    | Asian     | China   | 242 (33.47)                            | 225 (26.22)    | No           | 12 PCR-RFLP       |
| Sak [24]      | Caucasian | UK       | 547 (5.79)                             | 579 (5.96)     | Yes          | 12 Taqman         |
| Figueroa [25] | Caucasian | Spain    | 1,150 (6.11)                           | 1,149 (5.72)   | Yes          | 12 Taqman         |
| Andrew [26]   | Caucasian | US, Italy | 1,029 (6.49)                          | 1,281 (7.15)   | Yes          | 12 Taqman         |
| Hsu [27]      | Asian     | Taiwan  | 221 (34.86)                            | 223 (33.26)    | No           | 7 PCR-RFLP        |
| Fontana [28]  | Caucasian | France   | 51 (3.92)                              | 45 (5.56)      | Yes          | 6 Taqman          |
| Narter [29]   | Caucasian | Turkey   | 83 (21.93)                             | 45 (23.61)     | Yes          | 4 PCR-RFLP        |
| Wang [30]     | Asian     | China    | 234 (31.62)                            | 253 (23.72)    | Yes          | 8 PCR-RFLP        |
| Bianchino [31]| Caucasian | Italy    | 32 (12.50)                             | 242 (7.02)     | Yes          | 5 PCR-RFLP        |
| Mittal [32]   | Asian     | India    | 212 (10.14)                            | 250 (9.00)     | Yes          | 10 PCR-RFLP       |

HWE, Hardy–Weinberg equilibrium.
Table 2 Main characteristics of the studies included in an analysis of the XRCC1 Arg399Gln polymorphism and bladder cancer risk

| Study    | Ethnicity | Country     | Sample size (Frequency of A allele, %) | HWE in control | Quality score | Genotyping method |
|----------|-----------|-------------|----------------------------------------|----------------|---------------|-------------------|
| Stern [19] | Caucasian | US          | 235 (34.58) 213 (36.55)                 | Yes            | 8             | PCR-RFLP          |
| Shen [33]  | Caucasian | Italy       | 201 (32.09) 214 (34.11)                 | Yes            | 9             | PCR-RFLP          |
| Sanyal [34] | Caucasian | Sweden      | 311 (35.21) 246 (31.71)                 | Yes            | 9             | PCR-RFLP          |
| Broberg [35] | Caucasian | Sweden      | 61 (31.97) 155 (28.39)                 | Yes            | 9             | MALDI-TOF         |
| Wu [20]    | Asian     | China       | 155 (27.74) 155 (46.45)                 | Yes            | 8             | PCR-RFLP          |
| Matullo [21]| Caucasian | Mixed       | 131 (35.08) 1,094 (33.73)               | Yes            | 11            | Taqman            |
| Wu [22]    | Caucasian | US          | 696 (34.01) 629 (33.72)                 | Yes            | 10            | Taqman            |
| Karahalil [36] | Caucasian | Turkey     | 100 (32.00) 100 (36.00)                 | Yes            | 7             | Taqman            |
| Sak [24]   | Caucasian | UK          | 547 (35.71) 579 (36.52)                 | Yes            | 11            | Taqman            |
| Figueroa [25] | Caucasian | Spain      | 1,150 (35.82) 1,149 (33.79)            | Yes            | 11            | Taqman            |
| Andrew [26] | Caucasian | US, Italy  | 1,029 (35.35) 1,281 (36.07)            | No             | 10            | Taqman            |
| Hsu [27]   | Asian     | Taiwan      | 221 (25.71) 223 (25.46)                 | Yes            | 8             | PCR-RFLP          |
| Arizono [37] | Asian    | Japan       | 251 (24.30) 251 (26.29)                 | Yes            | 8             | PCR-RFLP          |
| Fontana [28] | Caucasian | France     | 51 (34.31) 45 (40.00)                   | Yes            | 5             | Taqman            |
| Wang [30]  | Asian     | China       | 234 (32.26) 253 (29.45)                 | Yes            | 7             | PCR-RFLP          |
| Bianchino [31] | Caucasian | Italy      | 32 (43.75) 242 (30.99)                 | No             | 4             | PCR-RFLP          |
| Mittal [32] | Asian     | India       | 212 (43.40) 250 (37.40)                 | Yes            | 9             | PCR-RFLP          |
| Zhi [38]   | Asian     | China       | 302 (34.93) 311 (29.42)                 | Yes            | 10            | PCR-RFLP          |

HWE, Hardy–Weinberg equilibrium.
Figure 2 (See legend on next page.)
0.10, indicating no statistically significant heterogeneity between studies (Table 3). Similarly, for the Arg194Trp polymorphism, there was also no obvious heterogeneity between studies.

Sensitivity analysis
In the sensitivity analysis, the influence of each study on the pooled OR was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure proved that our results were reliable and robust. In addition, when excluding the studies that were not in HWE, the estimated pooled OR still did not change at all (data not shown).

Cumulative meta-analysis
Cumulative meta-analyses of the two associations were also conducted via the assortment of studies by publication time. The 95% confidence intervals became increasingly narrower with increasing sample size, indicating that the precision of the estimates was progressively boosted by the continual addition of more cases (data not shown).

Publication bias
There was no evidence of significant publication bias either with the Begg’s test (Figures 3, \( P = 0.640 \) for Arg194Trp; \( P = 0.820 \) for Arg399Gln) or with Egger’s test (\( P = 0.345 \) for Arg194Trp; \( P = 0.248 \) for Arg399Gln).

Discussion
The Arg194Trp and Arg399Gln polymorphisms are the most well characterized XRCC1 polymorphisms, but the reported associations with bladder cancer risk among studies are inconsistent. Our present meta-analysis incorporating 20 case–control studies suggests that the Arg194Trp and Arg399Gln polymorphisms are significantly associated with increased bladder cancer risk.

In this meta-analysis, publication bias was not observed. And there was no obvious heterogeneity between studies. In addition, when repeating the meta-analysis by omitting

---

**Table 3** Meta-analysis of the association between the XRCC1 Arg194Trp and Arg399Gln genetic polymorphisms and the risk of bladder cancer

| Polymorphism | Stratification factor | Sample size | Number of studies | Test of association | Test of heterogeneity |
|--------------|-----------------------|-------------|-------------------|---------------------|-----------------------|
|              |                       | Case | Control | Overall | 4,751 | 6,102 | 14 | 1.69 (1.25-2.28) | 0.001 | 3.39 | F | 35.9 | 0.112 |
| Arg194Trp    | Study in HWE          | 4,301 | 5,659 | 12 | 2.07 (1.36-3.15) | 0.001 | 3.38 | F | 0.0 | 0.575 |
|              | Ethnicity             | Asian | 1,051 | 1,101 | 5 | 1.97 (1.04-3.74) | 0.038 | 2.08 | R | 64.1 | 0.025 |
|              |                       | Caucasian | 3,700 | 5,001 | 9 | 1.44 (0.75-2.74) | 0.270 | 1.10 | F | 0.0 | 0.538 |
|              | Study quality         | High | 3,956 | 5,111 | 8 | 2.08 (1.36-3.18) | 0.001 | 3.36 | F | 0.0 | 0.458 |
|              |                       | Low  | 795 | 991 | 6 | 1.35 (0.88-2.08) | 0.352 | 0.93 | R | 71.6 | 0.030 |
| Arg399Gln    | Overall               | 5,654 | 7,136 | 18 | 1.10 (1.03-1.19) | 0.008 | 2.67 | F | 0.0 | 0.596 |
|              | Study in HWE          | 4,632 | 5,641 | 16 | 1.08 (1.00-1.18) | 0.053 | 1.94 | F | 0.0 | 0.858 |
|              | Ethnicity             | Asian | 1,364 | 1,438 | 6 | 1.14 (0.98-1.33) | 0.082 | 1.74 | F | 0.0 | 0.562 |
|              |                       | Caucasian | 4,290 | 5,698 | 12 | 1.09 (1.01-1.19) | 0.037 | 2.09 | F | 0.0 | 0.460 |
|              | Study quality         | High | 4,407 | 5,675 | 10 | 1.10 (1.01-1.19) | 0.028 | 2.20 | F | 0.0 | 0.819 |
|              |                       | Low  | 1,247 | 1,461 | 8 | 1.13 (0.97-1.33) | 0.122 | 1.55 | R | 28.1 | 0.204 |

CI, confidence interval; F, fixed-effect model; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; R, random-effect model.
each study, one at a time, the estimated pooled OR still did not change at all. In view of these findings, we are convinced that the results of our meta-analysis, in essence, are sound and reliable.

The results of the present study are in contrast with a previous meta-analysis published in 2008 [39], which concluded that there was no association between the XRCC1 polymorphisms and the risk for bladder cancer. However, this study only included ten studies with limited sample size (3,749 cases and 3,947 controls) and, thus, it may lack sufficient statistical power to detect the real association and may have generated a fluctuated risk estimate.

Our findings have some biological plausibility. It is widely accepted that certain genetic variants associated with repair of DNA substantially increase the risk of cancer in carriers because of the alteration of BER functions [40]. BER is the primary DNA damage repair pathway for the repairing of small base lesions resulting from oxidation and alkylation damage [41]. As one of the most important proteins in BER, XRCC1 is closely related to BER pathway coordination by interacting with most members of the BER short-patch pathway. SNP of XRCC1 may increase the risk of some types of cancer by damaging the interaction of XRCC1 with other enzymatic proteins and, consequently, altering DNA repair activity [42]; this may result in carcinogenesis, including a higher incidence of bladder cancer. Similar to the results of our study, XRCC1 polymorphisms are also reported to be associated with some other cancers. The previous three meta-analyses have confirmed that the Arg399Gln polymorphism is associated with risk of childhood acute lymphoblastic leukemia [43], breast cancer [44], and prostate cancer among Asians [45]. Dai et al. reported that the XRCC1 Arg194Trp polymorphism is associated with an increased lung cancer risk [46] and the study conducted by Li et al. suggested that the Arg194Trp polymorphism may be associated with cervical cancer risk [47]. By contrast, in our study, the Arg194Trp polymorphism was associated with disease risk only in Asians, but not in Caucasians. This is mainly because the number of Caucasians is four-fold higher than that of Asians and, therefore, the power to detect association is higher.

Several limitations of this meta-analysis should be mentioned. First, the eligibility criteria for the inclusion of subjects and sources of controls were different from each other. No guarantee could be made among all those eligible studies that there were no potential bladder cancer cases in the controls. Second, because of the lack of the individual original data, our results were just based on unadjusted estimates, and gene–gene and gene–environmental interactions were not addressed in this meta-analysis. Third, although the Begg’s test and Egger’s test did not reveal any evidence of obvious publication bias, some inevitable publication bias may exist, because only studies published in English and Chinese were included in our meta-analysis. Finally, as shown in Table 3, a borderline conclusion (OR: 1.08 (1.00 to 1.18)) of the Arg399Gln section was drawn when two studies without HWE were excluded. This conclusion actually owed much to one study [26] with a relatively large population weight, which implies the need for more well-designed studies in future.

Conclusions

In conclusion, despite some limitations, the results of our meta-analysis suggest that two polymorphisms in XRCC1 (Arg194Trp and Arg399Gln) may contribute to bladder cancer development. Whether it could be applied to genotyping for clinical assessment requires large-scale population studies among different ethnicities and regions.
Additional file

**Additional file 1: Table S1.** Score of quality assessment.

**Abbreviations**
BER: base excision repair; CI: confidence interval; HWE: Hardy–Weinberg equilibrium; OR: odds ratio; SNP: single nucleotide polymorphism; XRCC1: X-ray repair cross-complementing group 1.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**
LPX, YQM and XX developed the study concept and participated in its design, data extraction, statistical analysis, manuscript drafting and editing. YWL and HC participated in the literature research, manuscript drafting and editing. JW and ZHH participated in design and data extraction. XLX and YZ reviewed and approved the final manuscript.

**Acknowledgements**
This study was supported by grants from the National Key Clinical Specialty Construction Project of China, Key medical disciplines of Zhejiang province, Combination of traditional Chinese and Western medicine key disciplines of Zhejiang Province (2012-ZX-A23), Health sector scientific research special project (201002010), National Natural Science Foundation of China (Grant No. 30900552) and Zhejiang Provincial Natural Science Foundation of China (Z2090356).

**Received:** 6 November 2012 Accepted: 13 January 2013

**References**
1. Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, Steineck G, Kogevinas M, Rojas CV, Schüz J, van den Brandt PA: Polymorphisms of DNA repair genes and cancer risk in non-smokers in a cohort study. *Carcinogenesis* 2010, 31:1251–1255.
2. Kaur I, Li X, Atija A: Systematic review and meta-analysis of the association between complement component 3 and age-related macular degeneration: a HuGe review and meta-analysis. *Am J Epidemiol* 2011, 173(3):1365–1379.
3. Yu H, Liu H, Wang LE, Wei Q: A functional NQO1 609C>T polymorphism and risk of gastrointestinal cancers: a meta-analysis. *PLOS One* 2012, 7(3):e30566.
4. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986, 7:177–188.
5. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959, 22:719–748.
6. Beggs CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994, 50:1088–1101.
7. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997, 315:629–634.
8. Sterne MC, Umbach DM, van Gils CH, Lunn RM, Taylor JA: DNA repair gene XRCC1 polymorphisms, smoking, and bladder cancer risk. *Cancer Epidemiol Biomarkers Prev* 2001, 10:125–131.
9. Wu W: Study on the Relationship between polymorphisms of NQ10 and XRCC1 Genes and the Susceptibility to Bladder Cancer (D). Lanzhou: Lanzhou University; 2005 (Chinese).
10. Matullo G, Dunning AM, Guarrera S, Baynes C, Pollodoro S, Garte S, Atrup H, Malaveille C, Peluso M, Airoldi L, Veglia F, Gormally E, Hoek G, Kryzanowski M, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Lissens J, Boeving H, Trichopoulou A, Palli D, Krogh V, Tornion R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Lund E, Pera G, Martinez C, Dorrondo-M et al: DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. *Carcinogenesis* 2006, 27:997–1007.
11. Wu X, Gu J, Grossman HB, Amos CI, Etzel C, Huang M, Zhang Q, Millikan RE, Lerner S, Dinney CP, Spitz MR: Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. *Am J Hum Genet* 2006, 78:464–479.
12. Zhang W, Wang YB, Cheng JR, Shao CX, Fang RR, Yuan JM, Gao YT: A case–control study of polymorphism of XRCC1 gene and the risk of bladder cancer. *China Cancer* 2006, 15:667–672. [In Chinese].
13. Sak SC, Barrett JH, Paul AB, Bishop DT, Kiltie AE: DNA repair gene XRCC1 polymorphisms and bladder cancer risk. *BMJ* 2007, 8:13.
14. Figueroa JD, Malats N, Real FX, Paul AB, Bishop DT, Kiltie AE, Malats N, Sacerdote C, Moore JH, Kelsey KT, Demidenko E, Vinue P, Matullo G: DNA repair polymorphisms modify bladder cancer risk: a multi-factor analytic strategy. *Hum Reprod* 2008, 65:105–118.
15. Hsu LI, Chiu AW, Huan SK, Chen CL, Wang YH, Hsieh FL, Chou WL, Wang LH, Chen CJ: SNPs of GSTM1, T1, P1, epoxide hydrolase and DNA repair enzyme XRCC1 gene and risk of urinary transitional cell carcinoma in southwestern Taiwan. *Toxicol Appl Pharmacol* 2006, 228:144–155.
16. Zaniani L, Bosveld R, Delord L, Guy L, Chalabi N, Kwiatkowski F, Sathi S, Rabau N, Boiteux JP, Chamoux A, Bigion YJ, Bernard-Gallon DJ: DNA repair gene ERCC2, XPC, XRCC1, XRCC3 polymorphisms and associations with cancer risk. *Cancer Epidemiol Biomarkers Prev* 2002, 11:1513–1520.
17. Miller MC, 3rd, Mahenweiser HW, Bell DA: Genetic variability in susceptibility and response to toxins. *Toxicol Lett* 2001, 120:269–280.
18. Alberg AJ, Jorgensen TJ, Ruczinski I, Wheless L, Shaput YJ, Berthier-Schaad Y, Kesing B, Hrumoff B, Jeuland KR, Kao WH, Francis L, Alani RM, Smith MW, Stickland PT: DNA repair gene variants in relation to overall cancer risk: a population-based study. *Carcinogenesis* 2013, 34:86–92.
19. Kury S, Buecher B, Roubi-du-Pont S, Scoul C, Colman H, Le Neel T, Le Houerou C, Farrou C, Ollivry J, Lafraise B, Chupin LD, Sébille V, Bézieau S: Loss of penetrance alleles predisposing to sporadic colorectal cancers: a French case-controlled genetic association study. *BMC Cancer* 2008, 8:232.
20. Chou WC, Wang HC, Wong FH, Ding SL, Wu PE, Shieh SY, Shen CY: Chk2-dependent phosphorylation of XRCC1 in the DNA damage response promotes base excision repair. *EMBO J* 2008, 27:3140–3150.
21. Campalans A, Marins S, Nakajimna Y, O’Connor TR, Boiteux S, Radicella JP: XRCC1 interactions with multiple DNA glycosylases: a model for its recruitment to base excision repair. *DNA Repair* (Amst) 2005, 4:826–835.
22. Marins S, Vidal AE, Sossou M, Menissier-de Murcia J, The Page F, Boiteux S, de Murcia G, Radicella JP: Role of XRCC1 in the coordination and stimulation of oxidative DNA repair damage initiated by the DNA glycosylase hOGG1. *J Biol Chem* 2003, 278:44066–44074.
and bladder cancer risk in a case–control study in northern Italy. Cancer Epidemiol Biomarkers Prev 2003, 12:1234–1240.

34. Sanyal S, Festa F, Sakano S, Zhang Z, Steineck G, Norming U, Wijkstra H, Larsson P, Kumar R, Henningsk K: Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis 2004, 25:729–734.

35. Broberg K, Bjork J, Paulsson K, Hoglund M, Albin M: Constitutional short telomeres are strong genetic susceptibility markers for bladder cancer. Carcinogenesis 2005, 26:1263–1271.

36. Karahalil B, Kocabas NA, Ozcelik T: DNA repair gene polymorphisms and bladder cancer susceptibility in a Turkish population. Anticancer Res 2006, 26:4955–4958.

37. Arizono K, Osada Y, Kuroda Y: DNA repair gene hOGG1 Codon 326 and XRCC1 Codon 399 polymorphisms and bladder cancer risk in a Japanese population. Jpn J Clin Oncol 2008, 38:186–191.

38. Zhi Y, Yu J, Liu Y, Wei Q, Yuan F, Zhou X, Song B, Chen Z, Yang J: Interaction between polymorphisms of DNA repair genes significantly modulated bladder cancer risk. Int J Med Sci 2012, 9:496–505.

39. Wang C, Sun Y, Han R: XRCC1 genetic polymorphisms and bladder cancer susceptibility: a meta-analysis. Urolology 2008, 72:869–872.

40. Monaco R, Rosal R, Dolan MA, Pincus MR, Brandl-Rauf PW: Conformational effects of a common codon 399 polymorphism on the BRCT1 domain of the XRCC1 protein. Protein J 2007, 26:541–546.

41. Maynard S, Schumman SH, Harboe C, de Souza-Pinto NC, Bohr VA: Base excision repair of oxidative DNA damage and association with cancer and aging. Carcinogenesis 2009, 30:2–10.

42. Tudek B: Base excision repair modulation as a risk factor for human cancers. Mol Aspects Med 2007, 28:258–275.

43. Wu K, Su D, Lin K, Luo J, Au WW: XRCC1 Arg399Gln gene polymorphism and lung cancer susceptibility: a meta-analysis of 44 case–control studies. Mol Biol Rep 2012, 39:9535–9547.

44. Li Y, Liu F, Tan SQ, Wang Y, Li SW: X-ray repair cross-complementing group 1 (XRCC1) genetic polymorphisms and cervical cancer risk: a HuGE systematic review and meta-analysis. PLoS One 2012, 7:e44441.

doI:10.1186/1477-7819-11-58

Cite this article as: Mao et al.: Quantitative assessment of the associations between XRCC1 polymorphisms and bladder cancer risk. World Journal of Surgical Oncology 2013 11:58.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at www.biomedcentral.com/submit