

RESEARCH ARTICLE

XRCC1 Polymorphisms are Associated with Cervical Cancer Risk and Response to Chemotherapy: a Systematic Review and Meta-analysis

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Abstract

Background: Functional single nucleotide polymorphisms of x-ray repair cross-complementing protein 1 (XRCC1) have been suspected to contribute to uterine cervical cancer risk for a long time; however, most previous case-control studies were small sized and biased. Additionally, recent studies suggested that XRCC1 polymorphisms could be a biomarker of response to platinum-based chemotherapy. **Methods:** A comprehensive search was conducted to retrieve eligible studies and odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to measure association strength. **Results:** A total of 13 studies were identified and analyzed. We found that the Arg194Trp polymorphism (Trp vs. Arg, OR=1.342, 95% CI: 1.176) was associated with increased risk of cervical cancer, while no significant association was found with Arg280His (His vs. Arg, OR=1.059, 95% CI: 0.863, 1.299) or Arg399Gln (Gln vs. Arg, OR=1.144, 95% CI: 0.938, 1.394). As for response to platinum-based chemotherapy, the variant XRCC1 399Gln allele (Gln vs. Arg, OR=0.345, 95% CI: 0.163, 0.729) was linked with a poor response; however, the Arg194Trp polymorphism (TrpArg vs. ArgArg, OR=6.421, 95% CI: 1.573, 26.205) predicted a good response. **Conclusion:** The Arg194Trp polymorphism of XRCC1 increases risk of cervical cancer; the variant 399Gln allele predicts poor response to platinum-based chemotherapy, while the Arg194Trp polymorphism indicates a good response.

Keywords: XRCC1 - uterine cervical cancer - SNPs - susceptibility - chemotherapy response

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Introduction

Uterine cervical cancer is one of the worldwide most common malignant cancers and a leading cause of death in women. It has been already demonstrated that there is a strong link between the incidence of cervical cancer and human papillomavirus (HPV) infection (Munoz et al., 2003). Although persistent HPV infection is crucial to the development of cervical cancer, it is not considered to be sufficient (Giuliano et al., 2002). Studies have shown that among women infected with HPV, only a small proportion will develop cervical intraepithelial neoplasia (CIN) or cervical cancer during their life time (Giuliano et al., 2002). It is reasonable to conclude that other factors are also involved in the tumorigenesis of cervical cancer, such as smoking, environmental factors, and genetic factors. X-ray repair cross complementing protein 1 (XRCC1) is one of the most important genes in DNA repair pathways. Studies have demonstrated that functional single nucleotide polymorphisms (SNPs) of XRCC1 are associated with cancer risks, such as lung cancer (Dai et al., 2012), bladder cancer (Narter et al., 2009), gastric cancer (Xue et al., 2011) and other cancers (Przybylowska-Sygut

et al., 2012). There are three most common functional SNPs occurring in the coding sequences of XRCC1 gene (Duell et al., 2000): codon 194 (Arg to Trp), 280 (Arg to His), and 399 (Arg to Gln). Researchers have focused on the relationship between SNPs of XRCC1, especially Arg194Trp and Arg399Gln, and cervical cancer risk (Niwa et al., 2005; Huang et al., 2007); however, these studies are of small sample size and can not provide enough statistic power and easily to be affected by bias.

Recently, neoadjuvant chemotherapy has been adopted to improve the prognosis of patients with cervical cancer (Sardi et al., 1993). Platinum-based chemotherapy regimen was reported with a high response rate (Sardi et al., 1993; Kornovski et al., 2006); however, it is critically important to select appropriate patients since those who have a poor response to chemotherapy usually have a poor response to radiotherapy and a poor prognosis. On the other hand, recent studies suggested that the polymorphisms of XRCC1 may be of a potential role in predicting response to platinum-based chemotherapy (Wu et al., 2012). But the number of studies investigating XRCC1 polymorphisms and chemotherapy responses in cervical cancer is limited. We conducted this meta-analysis and systematic review

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to determine the association of XRCC1 polymorphisms with cervical cancer and investigate the potential role of XRCC1 polymorphisms in predicting response to platinum-based chemotherapy.

Materials and Methods

Searching strategy

Eligible studies were extracted by electronic search of databases. A comprehensive search of major databases was conducted. Databases of PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and SinoMed (CBM) were searched. The following key words and medical subheadings were used: “X-ray repair cross complementing protein 1”, “single nucleotide polymorphism”, and “uterine cervical cancer”. Alternative spellings were also adopted. There was no limitation of languages and the last research was performed on November 19, 2012. References of related studies and reviews were manually searched for additional studies.

Inclusion and exclusion criteria

Eligible studies were selected by two investigators (Shuai and Luo) independently. Studies met following criteria were included: 1) investigating the association between XRCC1 polymorphisms and risk of cervical cancer or response to platinum-based chemotherapy; 2) published full-text articles. Studies with the following criteria were excluded: 1) without detailed genotype data; 2) with no access to full-text articles; 3) abstracts, reviews, and comment. Disagreement between two authors was solved by discussion with another author (Yan).

Data extraction

Data was collected in duplicate by two investigators (Shuai and Li) using a standard data collection form. The following data was collected: first author, year of publication, the country where the study conducted, ethnicity, genotype methods, number of cases and controls, and detailed genotype frequency. Ethnicity was simply classified as Asian, Caucasian and Latin American. Hardy-Winberg equilibrium (HWE) in the controls of each study was tested by chi-square test for goodness of fit and a P value less than 0.05 indicated the disequilibrium of HWE. In the study reported by Huang et al. (2007) and Zhang et al. (2012), the data of patients with CIN was excluded. As for studies investigating XRCC1 polymorphisms and chemotherapy response, chemotherapy regimens and evaluation criteria were also collected.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to identify the association strength of XRCC1 polymorphisms with cervical cancer risk and response to platinum-based chemotherapy. A 95% CI was used for test of statistical significance and a 95% CI without 1 for OR suggesting a significant increased or reduced cancer risk. A number of 5 comparisons were performed for each polymorphism, namely the allele comparison (variant allele vs. wild allele), homozygote comparison (variant homozygote vs. wild homozygote),

heterozygote comparison (variant heterozygote vs. wild homozygote), dominant model, and recessive model, assuming dominant and recessive effects of the variant allele, respectively. Subgroup analyses were carried out to investigate the influences of ethnicities only when investigating XRCC1 polymorphisms and cervical cancer risk. Sensitivity analyses were performed to identify the effect of individual study on the pooled results.

The statistical heterogeneity between studies was tested by chi-square based Q test, and a $p < 0.10$ suggested the existence of significant heterogeneity. The Mantel-Haenszel fixed-effects model and DerSimonian-Laird random-effects model were used to pool the data from different studies. The fixed-effects model was used when there was no significant heterogeneity; on the other hand, the random-effects model was used. Publication bias was detected by Begg's and Egger's test, and a p value less than 0.05 indicated the existence of bias. All statistical analyses were calculated with STATA software (version 10.0; Stata Corp, College Station, Texas USA). And all P values are two-side.

Results

Characteristics of eligible studies

A number of 13 studies (Niwa et al., 2005; Chung et al., 2006; Huang et al., 2007; Kim et al., 2008; Wen; et al., 2008; Cheng et al., 2009; Hong-yu; et al., 2010; Xiao-qin; et al., 2010; Barbisan et al., 2011; Roszak et al., 2011; Settheetham-Ishida et al., 2011; Wen-peng; et al., 2011; Zhang et al., 2012) were identified through searching of databases and manual search, and the detail process of searching and screening is shown in Figure 1. And three full-text articles were excluded for the reasons of only with patients of CIN (Wu et al., 2004), not about XRCC1 polymorphisms (Wang et al., 2009), and small sample size (Farkasova et al., 2008). XRCC1 polymorphisms and cervical cancer risk was reported in 10 studies and the other 3 studies (Chung et al., 2006; Kim et al., 2008; Cheng et al., 2009) investigated XRCC1 polymorphisms and response to chemotherapy. The characteristics of eligible studies were shown in Table 1. The disequilibrium of HWE was detected for Arg280His polymorphism in 1 study (Xiao-qin; et al., 2010) and Arg194Trp polymorphism in 2 studies (Barbisan et al., 2011; Settheetham-Ishida et al., 2011), and the 2 studies were not excluded because no disequilibrium was found in the Arg399Gln polymorphism.

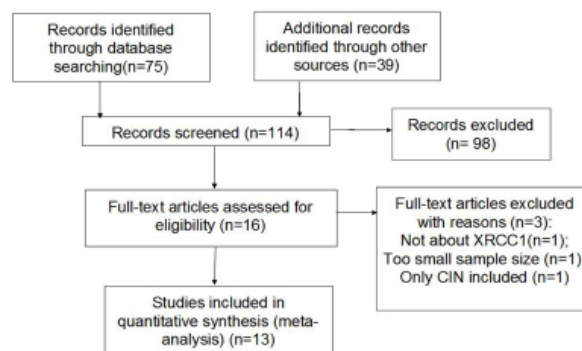


Figure 1. Flow Chart. CIN: cervical intraepithelial neoplasia

Table 1. Characteristics of Eligible Studies for Cervical Cancer Risk

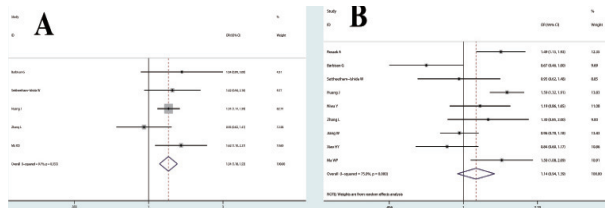
Author	Year	Country	Ethnicity	Polymorphisms	Source of control	Genotyping method	No. of case	No. of control	HWE in control
Roszak A	2011	Poland	Caucasian	Arg399Gln	Population	PCR-RFLP	189	308	0.37
Barbisan G	2011	Argentina	Latin America	Arg194Trp/ Arg399Gln	Hospital	PCR-RFLP	103	114	0.49 for P399; 0.0003 for P194*
Settheetham-Ishida W	2011	Thailand	Asian	Arg194Trp/ Arg399Gln	Hospital	PCR-RFLP	111	118	0.54 for P399; 0.02 for P194*
Huang J	2007	China	Asian	Arg194Trp/	Hospital	MA-PCR	539	473	0.10 for P399; 0.73 for P194; 0.46 for P280
Niwa Y	2005	Japan	Asian	Arg399Gln	Hospital	PCR-RFLP	131	320	0.09 for P399
Zhang L	2012	China	Asian	Arg194Trp/ Arg280His/Arg399Gln	Hospital	MA-PCR	80	177	0.54 for P399; 0.73 for P194; 0.49 for P280
Jiang W	2008	China	Asian	Arg399Gln	Hospital	PCR-RFLP	436	503	0.48 for P399
Xiao HY	2010	China	Asian	Arg399Gln	Hospital	PCR-RFLP	162	183	0.12 for P399
Ma XQ	2010	China	Asian	Arg194Trp/ Arg280His	Hospital	PCR-RFLP	123	175	0.85 for P194; 0.04 for P280*
Ma WP	2011	China	Asian	Arg399Gln	Hospital	PCR-RFLP	200	200	0.06 for P399

HWE, Hardy-Winberg equilibrium; P399, Arg399Gln polymorphism; P194, Arg194Trp polymorphism; P280, Arg280His polymorphism; *disequilibrium of HWE

Table 2. Characteristics of Eligible Studies of XRCC1 Polymorphism and Response

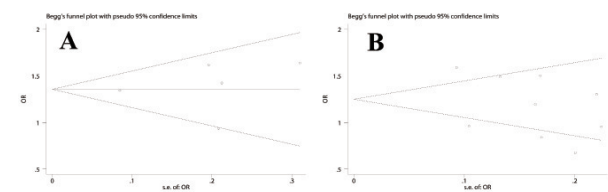
Author	Year	Country	Ethnicity	Polymorphism	Chemotherapy	genotyping method	Evaluation criteria
Cheng XD	2009	China	Asian	Arg194Trp/ Arg399Gln	blemycin+vindesine+cisplatin/blemcin +ifosfamide+cisplatin/taxol+cisplatin	MA-PCR	WHO criteria
Kim K	2008	Korea	Asian	Arg194Trp	5-FU+cisplatin/Paclitaxel+carboplatin/ + cisplatin/5-FU + carboplatin + interferon- γ /Epirubicin + cisplatin	UFT PCR-RFLP	RECIST criteria
Chung HH	2006	Korea	Asian	Arg399Gln	5-FU+cisplatin/5-FU+cisplatin+ adriamycin/5-FU + carboplatin/5-FU+carboplatin+adriamycin/etoposide /cisplatin	PCR-RFLP	clinical and colposcopic evaluation

5-FU, 5-fluorouracil; RECIST, Response Evaluation Criteria in Solid Tumors

**Figure 2. Forest Plot of Allele Comparison for XRCC1 Arg194Trp (A) and Arg399Gln (B)**

Meta-analysis Results

Cervical cancer risk: Detailed meta-analysis results were shown in Table 2. Allele comparison of Arg194Trp shown that the variant 194Trp allele was significantly associated with an increased risk of cervical cancer (Trp vs. Arg, OR=1.342, 95% CI: 1.176, 1.530; Figure 2A). The Arg194Trp polymorphism was also showed increased cancer risk in homozygote comparison (ArgArg vs. TrpTrp, OR=1.984, 95% CI: 1.465, 2.687), dominant model (ArgArg/ArgTrp vs. TrpTrp, OR=1.316, 95% CI: 1.111, 1.559), and recessive model (ArgArg vs. TrpTrp/ArgTrp, OR=1.874, 95% CI: 1.400, 2.509). In the subgroup of Asian population, we obtained the same results. As for XRCC1 Arg280His polymorphism, we did not found any statistical association between Arg280His polymorphism and cervical cancer risk in allele comparison (His vs. Arg, OR=1.059, 95% CI: 0.863, 1.299) or any other comparisons. The XRCC1 variant 399Gln did not increase cervical cancer risk (Gln vs. Arg, OR=1.144, 95% CI: 0.938, 1.394; Figure 2B), and no significant association of Arg399Gln polymorphism was found in homozygote comparison (GlnGln vs. ArgArg, OR=1.247, 95% CI: 0.847, 1.837), heterozygote comparison (GlnArg vs. ArgArg, OR=1.144, 95% CI:

**Figure 3. Funnel Plots. A:** funnel plot of allele comparison for XRCC1 Arg194Trp polymorphism; **B:** forest plot for allele comparison for XRCC1 Arg399Gln polymorphism

0.890, 1.470), dominant model (GlnGln/GlnArg vs. ArgArg, OR=1.164, 95% CI: 0.901, 1.503), or recessive model (GlnGln vs. ArgArg/GlnArg, OR=1.213, 95% CI: 0.904, 1.629). In the subgroup analysis of Asian, we did not found any statistical association of Arg399Gln polymorphism with cervical cancer.

Response to Platinum-Based Chemotherapy: In the analysis of XRCC1 Arg399Gln polymorphism, we found that the variant 399Gln allele (Gln vs. Arg, OR=0.345, 95% CI: 0.163, 0.729) was associated with poor response to chemotherapy and this association was also found in heterozygote comparison (GlnArg vs. ArgArg, OR=0.072, 95% CI: 0.011, 0.477) and dominant model (GlnGln/GlnArg vs. ArgArg, OR=0.215, 95% CI: 0.069, 0.669). When came to Arg194Trp polymorphism, we found that the Arg194Trp polymorphism indicated a good response in heterozygote comparison (TrpArg vs. ArgArg, OR=6.421, 95% CI: 1.573, 26.205) and dominant model (TrpTrp/TrpArg vs. ArgArg, OR=2.864, 95% CI: 1.104, 7.427).

Sensitivity Analysis and Publication Bias: Sensitivity analyses and tests of publication bias were carried out in the analyses of XRCC1 polymorphisms and cancer risk, because the number of studies included for analyses of

response were small. Sensitivity analyses showed that the pooled results were stable and not affected by individual study significantly (data not shown). Funnel plots (Figure 3) showed no evidence of publication bias existed. Begg's test and Egger's test ($P_{Begg}=0.806$ and $P_{Egger}=0.802$ for allele comparison of Arg194Trp; $P_{Begg}=1.000$ and $P_{Egger}=0.836$ for allele comparison of Arg280His; $P_{Begg}=0.348$ and $P_{Egger}=0.259$ for all comparison of Arg399Gln) also did not find evidence of publication bias.

Discussion

DNA alterations can be caused by various environmental and endogenous carcinogens and cumulative DNA damages will lead to activation of oncogenes and carcinogenesis. In addition, it has been documented that HPV infection can result in instability of chromosome and accumulation of DNA damage in the development of cervical cancer (Duensing et al., 2002). XRCC1 belongs to the DNA base excision repair (BER) pathway and repairs single-strand breaks and XRCC1 is crucial to the integrity of chromosome. The XRCC1 protein acts as a scaffold for other DNA repair proteins, like polynucleotide kinase, human AP endonuclease (APE1), DNA polymerase β , DNA ligase III, and poly(ADP-ribose) polymerases (PARP) (Whitehouse et al., 2001). The three SNPs (Arg194Trp, Arg280His, and Arg399Gln) cause amino acid substitutions. Arg194Trp and Arg280His polymorphisms locate at the linker region connecting the domains that interact with PARP and DNA polymerase β , while Arg399Gln resides in PARP-binding domain (Taylor et al., 2002). Additionally, proteins' structure and function can be altered by functional SNPs, which may lead to the susceptibility of individuals to cancers (Tudek, 2007). Thus, it is reasonable to conclude that the functional SNPs of XRCC1 are associated with cervical cancer risks. Similarly, platinum compound will also cause adducts and breaks on the DNA double helix and individual's DNA repair capacity may be related with the efficacy of platinum (Cheng et al., 2009). This interprets molecular mechanism that the functional SNPs of XRCC1 could be potential biomarkers of response to platinum-based chemotherapy.

In the present meta-analysis, we demonstrated that the XRCC1 Arg194Trp polymorphism (Trp vs. Arg, OR=1.342, 95% CI: 1.176) is associated with an increased risk of cervical cancer, while there is no significant association between Arg280His (His vs. Arg, OR=1.059, 95% CI: 0.863, 1.299) and Arg399Gln (Gln vs. Arg, OR=1.144, 95% CI: 0.938, 1.394) polymorphisms and cervical cancer; the variant 399Gln allele (Gln vs. Arg, OR=0.345, 95% CI: 0.163, 0.729) indicated poor response to platinum-based chemotherapy, but the Arg194Trp polymorphism (TrpArg vs. ArgArg, OR=6.421, 95% CI: 1.573, 26.205) was associated with good response in patients with cervical cancer. To our knowledge, this is the first systematic review that validates the relationship between XRCC1 polymorphisms and cervical cancer risk and exploring the potential value of XRCC1 in predicting response to platinum-based chemotherapy.

XRCC Arg194Trp and Arg399Gln polymorphisms

and cervical cancer risk have been mostly studied, and both Arg194Trp and Arg399Gln polymorphisms are suspected with increased risk. Different from previous studies (Huang et al., 2007; Roszak et al., 2011; Wen-peng; et al., 2011), by pooling all available data from included studies, we found that only Arg194Trp polymorphism was associated with increased risk of cervical cancer. Previous case-control studies were of small sample size and the results were biased and unreliable in that studies of small size usually report larger effects (Sterne et al., 2001). With 9 studies and 4347 participants, our meta-analysis could provide enough statistical power to detect modest difference. Sensitivity analyses showed that individual study did not affect the significance of meta-analysis results. In addition, no evidence of publication bias was detected by Begg's test or Egger's test in any of the comparison. Thus, our results about the relationship between XRCC1 polymorphisms and cervical cancer risk are robust and unbiased.

Neoadjuvant chemotherapy has been adopted to improve prognosis of cervical cancer in recent years and only 3 studies (Chung et al., 2006; Kim et al., 2008; Cheng et al., 2009) about XRCC1 polymorphisms and response to platinum-based chemotherapy were identified. Our meta-analysis showed an interesting result: although the variant 399Gln allele was not associated with cervical cancer risk, 399Gln indicated poor response to platinum-based chemotherapy; Arg194Trp polymorphism was associated with an increased risk of cervical cancer; however, Arg194Trp polymorphism predicted a good response. Though, the number of studies in this meta-analysis about the SNPs of XRCC1 and response to chemotherapy is limited, these results highlight the potential role of XRCC1 in translation medicine. And further studies of large sample size are warranted to validate the predictive value of XRCC1 polymorphisms.

Limitation of this meta-analysis should be noted. First, in the analysis of Arg399Gln polymorphism and cancer risk, heterogeneity existed. According to Li and colleagues (Li et al., 2012), sample size may be the source of heterogeneity; however this heterogeneity could not be solved since the number of large-sized studies are limited. Second, only 3 studies were included in the analysis of response to chemotherapy. On the other hand, we believed that all available studies were included in that tried to collect all related studies by manual search the references of relative articles and search of databases without any limitation.

Results of this meta-analysis suggest that Arg194Trp polymorphism of XRCC1 is associated with an increased risk of cervical cancer but not Arg280His or Arg399Gln polymorphisms; the variant 399Gln allele predicts a poor response to platinum-based chemotherapy, while the Arg194Trp polymorphism may be indicative of a good response.

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