RESEARCH ARTICLE

Gene Polymorphism of XRCC1 Arg399Gln and Cervical Carcinoma Susceptibility in Asians: A Meta-analysis Based on 1,759 Cases and 2,497 Controls

Yi-Ting Liu, Jing-Pu Shi*, Ling-Yu Fu, Bo Zhou, Hai-Long Wang, Xiao-Mei Wu

Abstract

Many epidemiological studies in Asian populations have investigated associations between the Arg399Gln gene polymorphism of X-ray repair cross complementing gene 1 (XRCC1) and risk of cervical carcinoma, but no conclusions have been available because of controversial results. Therefore a meta-analysis was conducted for clarification. Relevant studies were identified by searching the Pubmed, Embase, the Web of Science, Cochrane Collaboration's database, Chinese National Knowledge Infrastructure (CNKI), Wanfang database and China Biological Medicinse (CBM) until September, 2012. A total of eight studies were included in the present meta-analysis, which described 1,759 cervical carcinoma cases and 2,497 controls. Odds ratios (ORs) and corresponding 95% confidence intervals (95%CIs) as effect size were calculated by fixed-effect or random-effect models. The overall results indicated that the XRCC1-399G/A polymorphism was marginally associated with cervical carcinoma in Asians: OR (95%CI): 1.16 (1.07, 1.26) in the G/A vs G/G inheritance model, 1.24 (0.87, 1.76)in A/A vs G/G inheritance model, 1.13 (1.01, 1.27) in the dominant inheritance model and 1.18 (0.94, 1.47) in the recessive inheritance model. Subgroup analyses on sample size showed no significant correlation in the small-sample size group but the large-sample size group was consistent with the outcomes of overall meta-analysis. In the subgroup analysis by regions, we only found significant association under the G/A vs G/G inheritance model in the Chinese population. For the non-Chinese populations, no correlation was detected in any genetic inheritance model. In the Asian populations, XRCC1-399G/A gene polymorphism was implied to be associated with cervical carcinoma.

Keywords: XRCC1- cervical carcinoma - 399G/A gene polymorphism - meta-analysis - Asians

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Introduction

Cervical cancer is the second most common female -related cancer worldwide, following with breast cancer. In Asian countries, where widespread screening is still unavailable, cervical cancer accounts for 15% of female cancers. Recognizing its etiology can provide the basis for preventing and treatment of the disease. A strong link between the incidence of cervical carcinoma and oncogenic subtypes of the human papillomavirus has been demonstrated (Coppleson et al., 1986). Persistent HPV infection is the main contributor to the development of cervical carcinoma and its progenitor lesion, cervical intraepithelial neoplasia (Walboomers et al., 1999; Giuliano et al., 2002). HPV infection is vital to the development of cervical carcinoma , it is not considered a sufficient isolated element to cause this malignancy. In a group of HPV-infected women, only a few can develop cervical carcinoma (Giuliano et al., 2002). This implied that factors other than HPV infection, including genetic factors, environmental factors, contraceptive use, and smoking can play a causative role in cervical cancer (Roszak et al., 2011).In humans , exposure to different endogenous and exogenous mutagens and carcinogens can lead to various types of DNA damage. These alterations, if not repaired, can result in genetic instability, mutagenesis and carcinoma (Goode et al., 2002). DNA damage can be corrected by the base excision repair (BER) pathway, which uses X-ray repair cross complementing 1 (XRCC1) as a scaffold protein in the formation of a complex of several enzymes responsible for DNA repair (Tudek et al., 2007). XRCC1 is located on the long arm of human chromosome 19(19q 13.2- 13.3) with 17 exons (Lamerdin et al., 1995). Shen et al sequenced its coding regions in 12 healthy Caucasian people and found 3 genetic variants resulting in amino acid changes respectively at codons 194, 280 and 399 (Shen et al., 1998).

Cancer epidemiologic studies revealed that there was significantly association between XRCC1 codon 399 glutamine(gln) and increased risks of lung cancer and

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breast cancer, but reduced or no risk of bladder cancer , esophageal cancer or skin cancer (Lee et al., 2001; Matullo et al., 2001; Nelson et al., 2002; Duell et al., 2011). But there were conflicting results related to the contribution of XRCC1 Arg399gln (XRCC1-399G/A) gene polymorphism to cervical carcinoma especially in Asian populations . The aim of this study was to further explore the association between XRCC1-399 gene polymorphism and cervical carcinoma risk in Asians by the method of a meta-analysis, which could enhance the statistical power and received a more reliable conclusion compared to a single study.

Materials and Methods

Search strategy

To search for all the studies that examined the association of the XRCC1-399G/A gene polymorphisms with cervical carcinoma in Asians , we conducted a computerized literature search of the Pubmed, Embase, the Web of Science, Cochrane Collaboration's database, Chinese National Knowledge Infrastructure (CNKI), Wanfang database and China Biological Medicine (CBM) (up to September, 2012), using the following keywords and subject terms: 'cervical carcinoma OR cervical cancer OR cervical tumor', 'X-ray repair cross complementing gene 1 OR XRCC1', 'polymorphism OR allele OR genotype'. Meanwhile, the reference lists of eligible studies and relevant review papers were manually retrieved and screened to identify the eligible studies. The search was done with language limitation in English and Chinese. For studies on the same population or with overlapping data, only the most recent one or the one with the largest group of subject was included in this meta-analysis.

Inclusion and exclusion criteria

Studies included in this analysis had to meet the following inclusion criteria: (1) the study must explore the association between XRCC1-399 G/A gene polymorphism and cervical carcinoma; (2) the populations must be Asians, such as Chinese, Thais et al; (3) the study must be a case-control study; (4) outcome of cases had to be defined as diagnosis of cervical carcinoma; (5) the study must provide total number of cases and controls, and also the number of cases and controls for each genotype.

The major reasons for exclusion were: (1) being a review, editorial or comment; (2) duplicated studies; (3) laboratory molecular or animal studies.

Quality assessment criteria

Based on Newcastle-Ottawa (Stang et al., 2010) quality assessment scale, all included case-control studies were assessed independently by two reviewers (Bo. Zhou and Xiaomei.Wu). Disagreement was resolved by consulting the third reviewer (Lingyu. Fu). The assessment scale included the following aspects, the selection method of case and control group, the comparability of two groups and assessment method of contacting exposure. The indicators are represented by stars (*). The more the stars are, the better the quality will be. It would be best of ten stars. Generally, more than five stars of a study is considered to be selected in the meta-analysis.

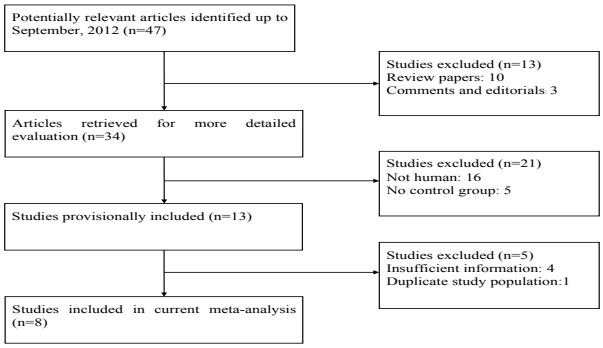

Figure 1. Selection of Included Studies

Eligible study selection

Figure1 showed the study selection process. Eligible studies were identified through four steps, reviewing titles, abstracts, full texts and browsing reference lists of eligible studies and relevant review papers. In total, only eight studies met all criteria (Wu et al., 2004; Niwa et al., 2005; Huang et al., 2007; Jiang et al., 2009; Xiao et al., 2010; Ma et al., 2011; Settheetham et al., 2011; Zhang et al., 2012).

Data extraction

For studies with inadequate information, authors were contacted if possible. The following data were extracted: The first author's name and year of publication, countries of participants, number of stars, goodness-in-fitness of Hardy-Weinberg Equilibrium (HWE) in control group, number of cases and controls, genotypes and their number in case and control groups.

Statistical methods

The strength of the association between cervical carcinoma and the XRCC1-399 polymorphism in Asians was estimated by odds ratio (OR) value and 95% confidence interval (CI), based on the genotype frequencies in cases and controls. The OR values and 95%CI were calculated respectively according to the co-dominant inheritance model (G/A vs G/G; A/A vs G/G), the dominant inheritance (G/A + A/A vs G/G)and recessive inheritance model (A/A vs G/G+G/A). Z-test determined the significance of the pooled OR and $P<0.05$ was considered as statistically significant. Heterogeneity was tested by the I^2 statistic (Higgins et al., 2003). When the test for heterogeneity was less than moderate (I^2 <50%), the fixed effect model was performed, otherwise, a random-effect model was considered. Subgroup analysis was performed by sample size. Asymmetry of the funnel plot was conducted to estimate the potential publication bias (Bannett et al., 2004). In order to complement the funnel plot, Begg's correlation and Egger's regression method were used ($P<0.05$ was considered to be statistically significant) (Begg et al., 1994; Egger et al., 1997). Sensitivity analysis was perfomed for all studies except those with borderline eligibility. Meta-analysis was conducted using STATA 11 for Windows (Stata, College Station, TX, USA).

Table 1. Characteristics of all Studies Included in the Meta-analysis

Author	Year	Country and area	Sample size		GG (genotype)		GA (genotype)		AA (genotype)		HWE	*
			Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls		
Wu et al.	2004	Taiwan	100	196	54	114	38	73	8	9	Yes	8
Niwa et al.	2005	Japan	131	320	69	185	49	109	13	26	Yes	7
Huang et al.	2007	China	539	800	289	528	203	235	47	37	Yes	8
Jiang et al.	2009	China	436	503	228	268	184	194	24	41	Yes	6
Xiao et al.	2010	China	162	183	91	94	56	68	15	21	Yes	8
Ma et al.	2011	China	200	200	108	133	76	55	16	12	Yes	7
Wannapa et al.	2011	Thailand	111	118	66	69	41	44	4	5	Yes	6
Zhang et al.	2012	China	80	177	43	109	31	58	6	10	Yes	8

HWE, Hardy-Weinberg Equilibrium; *number of stars according to Newcastle-Ottawa quality assessment scale

Table 2. Pooled Analyses for the Effects of XRCC1-399G/A Gene Polymorphisms on Cervical Carcinoma Risk

Groups	G/A vs G/G		A/A vs G/G		dominant model		recessive model	
	OR(95%CI)	P_{het}	OR(95%CI)	P_{het}	OR(95%CI)	P_{het}	OR(95%CI)	P_{het}
Small-sample size[a]	1.02(0.87,1.19)	0.629	1.06(0.69,1.61)	0.425	1.02(0.89,1.17)	0.447	1.05(0.69,1.62)	0.54
Large-sample size[a]	1.22(1.11,1.33)	0.109	1.32(0.78,2.25)	0.008	1.20(1.02,1.42)	0.014	1.22(0.95,1.59)	0.019
Chinese[b]	1.19(1.09,1.30)	0.046	1.21(0.73,2.01)	0.005	1.16(0.97,1.37)	0.003	1.15(0.90,1.48)	0.022
Non-Chinese[b]	1.06(0.90,1.26)	0.835	1.32(0.83,2.12)	0.646	1.08(0.93,1.25)	0.765	1.27(0.79,2.06)	0.658
Total	1.16(1.07,1.26)	0.132	1.24(0.87,1.76)	0.029	1.13(1.01,1.27)	0.017	1.18(0.94,1.47)	0.086

P_{het}, P value for heterogeneity; [a]The total number of participants for a large sample-sized study was ≥ 400 and < 400 for a small-sized study; [b]Controls of the Chinese case-control study were selected from China region; Controls of non-Chinese case-control study were selected from other countries and areas

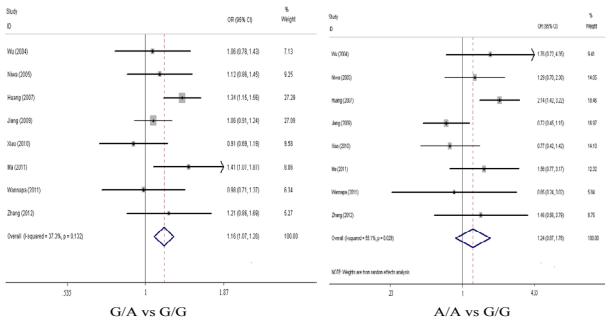

Figure 2. Forest Plot of Association Between XRCC1-399 Gene Polymorphism and Cervical Carcinoma in Co-dominant Inheritance Model

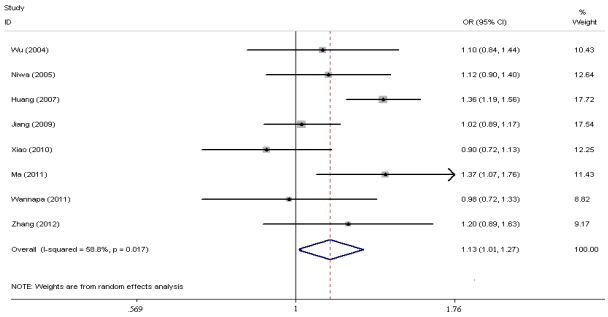

Figure 3. Forest Plot of Association Between XRCC1-399 Gene Polymorphism and Cervical Carcinoma in Dominant Inheritance Model

Results

Studies and data included in the meta-analysis

The characteristics of all included studies were list in Table 1. In total, eight case-control studies were included in this meta-analysis. Sample sizes ranged from 80 to 800, with a total of 1759 cases and 2497 controls. No studies was excluded in the meta-analysis because of high quality, quality assessment showed explicit diagnostic criteria, reasonable gene detection method and clear results.

Analysis of XRCC1-399 genetic polymorphism and cervical carcinoma

Table2 showed the results of combined meta-analysis for XRCC1-399G/A polymorphism. In total, there was a significant association in Asians between the XRCC1-399G/A gene polymorphism and cervical carcinoma under the G/A vs G/G genetic inheritance model (OR: 1.16, 95%CI: 1.07, 1.26) and a dominant genetic model(OR: 1.13, 95%CI: 1.01, 1.27). No significant association between the XRCC1-399G/A gene polymorphism and cervical carcinoma was observed in the A/A vs G/G genetic model (OR: 1.24, 95%CI: 0.87, 1.76) or the recessive genetic model (OR: 1.18, 95%CI: 0.94, 1.47) (Figure 2-4). The results indicated that GG genotype was associated with decreased risk of cervical carcinoma for Asians. Additionally, GA genotype carries might have a higher risk of cervical carcinoma.

Studies with a total size of < 400 were included in subgroup 1 of small-sample size, and the residual studies with a total size of ≥ 400 were included in subgroup 2 of large-sample size. In the subgroup analyses on sample size, no significant correlation was found in the small-sample size group but the large-sample size group was in consistent with the outcomes of overall meta-analysis [OR (95%CI): 1.22 (1.11, 1.33) in G/A vs G/G inheritance model, 1.32 (0.78, 2.25) in A/A vs G/G inheritance model, 1.20 (1.02, 1.42) in the dominant inheritance model and 1.22 (0.95, 1.59) in the recessive inheritance model] (Table2).

In the subgroup analysis by regions, studies were categorized into two groups: China, other countries and areas. In Chinese population, significant association between XRCC1-399G/A gene polymorphism and

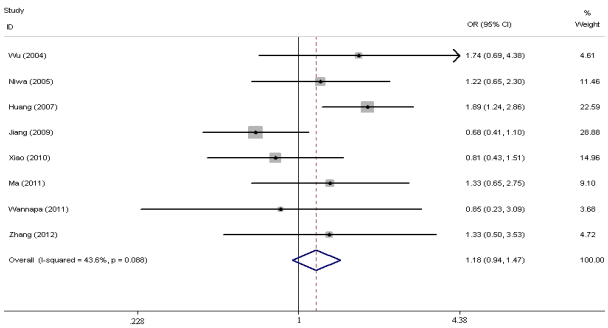

Figure 4. Forest Plot of Association Between XRCC1-399 Gene Polymorphism and Cervical Carcinoma in Recessive Inheritance Model

cervical carcinoma was observed in the G/A vs G/G genetic inheritance model (OR: 1.19, 95%CI: 1.09, 1.30). No significant correlation was found in other genetic inheritance models. For the subgroup of non-Chinese populations, we detected no significant association in any genetic inheritance models (Table2).

Sensitive analyses

A single study involved in the meta-analysis was sequentially removed each time to reflect the influence of the individual data-set to the pooled OR, and the corresponding pooled OR were not materially altered (data not shown), indicating that our results were statistically robust and reliable.

Publication bias

No evidence of significant publication bias was found in this meta-analysis, reflected by P values from Egger's regression asymmetry test and Begg's adjusted rank correction test. There was also no publication bias examining by funnel plot. The results of Egger's regression asymmetry test showed that P=0.483 in the co-dominant inheritance model of G/A vs G/G, P=0.761 in the co-dominant inheritance model of A/A vs G/G, P=0.583 in the dominant inheritance model and P=0.811 in the recessive inheritance model. The results of Begg's adjusted rank correlation test showed that P=0.902 in the co-dominant inheritance model of G/A vs G/G and A/A vs G/G, P=0.711 in the dominant inheritance model and P=0.902 in the recessive inheritance model.

Discussion

It has been well known that DNA repair is a vital mechanism in maintenance of genetic stability and protection against carcinoma initiation. Niwa et al. (Niwa et al., 2005) indicated that the XRCC1-399G/A polymorphism might be important in relation to the risk of cervical cancer. Although a series of relevant studies with respect to XRCC1-399G/A gene polymorphism on the risk of cervical carcinoma had been widely conducted, always no clear consensus results can be reached. This situation made us feel very confused, thus more and more efforts were made to further pursue the possible association. Barbisan et al. (2011) suggested that XRCC1 genotypes and haplotypes contributed in reducing the risk of cervical cancer development in Argentine women. This positive result was partly confirmed by Roszak et al. (2011) who studied on Polish women. However, a more recent research by Xiao et al. (2010) reported Arg399Gln polymorphism had no correlation with pathogenesis of cervical cancer in Chinese people. Abdel Rahman et al. (2000) and Lunn et al. (1999) reported 399Gln allele frequencies of Egyptians, Caucasian, African-Americans and Asians were respectively 14%, 37%, 17% and 26%, indicating that XRCC1 allele frequencies existed racial and geographic specificity. Therefore our analyses limited the study population to Asians. Therefore, our analyses limited the study population to Asians. In recent years, meta-analysis as a practical statistical method has been widely used to gain more reliable evidence. Based on a large number of original studies with the homogeneous design for the same topic, meta-analysis can greatly enlarge the sample size, enhance statistical power and reduce the bias .

In this meta-analysis, we found that the XRCC1-399G/A polymorphism was marginally associated with cervical carcinoma in Asians. There were statistically significant in dominant inheritance model and co-dominant inheritance model of G/A vs G/G. The results indicated that GG genotype was associated with decreased risk of cervical carcinoma for Asians. Additionally, GA genotype carries might have a higher risk of cervical carcinoma. In the subgroup analyses on sample size, no significant correlation was found in the small-sample size group but the large-sample size group was in consistent with the outcomes of overall meta-analysis. This was significant because the large-sample size group weighed more, so it was closer to the overall authenticity. In a certain extent, the sample size could be explained for the heterogeneity. But in the subgroup analyses on regions, we only found significant association under the G/A vs G/G inheritance model in the Chinese population. For the non-Chinese populations, no correlation was detected in any genetic inheritance model.

There were several limitations of this meta-analysis that merit to note. First, the sample size was still relatively small for the stratified analysis. Second, only published studies in English and Chinese were included in the meta-analysis, therefore, publication bias may have occurred, even though the use of a statistical test did not show it. Third, most of the included studies had conducted on Asians and many on Chinese, so that the results must be explained with caution. Further studies concerning populations in other areas are required to diminish the ethnic variation-produced bias. Fourth, there were multiple genetic testing techniques utilized by different studies, which was both a weakness and strength of this analysis. What is more, meta-analysis exists inherent limitations (Kaizar et al., 2005). Despite the limitation, our meta-analysis significantly increased the statistical power based on substantial number of cases and controls from different studies.

In conclusion, this meta-analysis suggested that the XRCC1-399G/A gene polymorphism in Asians was associated with cervical carcinoma based on current published data. The subgroup analyses on sample size showed the large-sample size group was in consistent

with the outcomes of overall meta-analysis. It is of great essentiality to conduct large-sample size studies regarding the relationship between XRCC1 gene polymorphism and cervical carcinoma, which would greatly help summarize the results from published papers.

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