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Lack of an association between the XRCC1 Arg399Gln polymorphism and gastric cancer based on a meta-analysis

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ABSTRACT. Association between the XRCC1 Arg399Gln polymorphism and susceptibility to gastric cancer has been investigated; overall, the results have been inconclusive. We made a meta-analysis of 13 case-control studies, including 3278 cases and 6243 controls. Crude odds ratios (OR) with 95% confidence intervals (95%CI) were used to assess this possible association. We found no evidence of a significant association between the XRCC1 Arg399Gln polymorphism and gastric cancer risk (in the additive inheritance model, OR = 0.986, 95%CI = 0.831-1.156, in the dominant inheritance model, OR = 1.044, 95%CI = 0.890-1.224 and in the recessive inheritance model, OR = 0.975, 95%CI = 0.894-1.063). We conclude that the XRCC1 Arg399Gln polymorphism is not a risk factor for developing gastric cancer.

Key words: XRCC1; Polymorphism; Gastric cancer; Susceptibility; Meta-analysis

INTRODUCTION

Gastric cancer remains the second leading cause of cancer-related death and the fourth most common epithelial neoplasia worldwide (Bray et al., 2002; Parkin et al., 2005). Several environmental factors interact causing a cumulative effect in the early steps of gastric carcinogenesis, such as tobacco use (Lee and Hamling, 2009), dietary habit (Gonzalez and Lopez-Carrillo, 2010), and *Helicobacter pylori* infection (Malfertheiner et al., 2010). However, not all of those who are exposed to the risk factors will develop gastric cancer, suggesting inter-individual differences in susceptibility.

DNA repair pathways are responsible for maintaining the integrity of the genome in the face of environmental insults and general DNA replication errors, playing a protective role against mutations that lead to cancer (Lindahl, 2000). Among DNA repair systems, the base excision repair (BER) pathway is responsible for the repair of oxidative DNA damage and single-strand breaks. The X-ray repair cross-complementation group 1 (XRCC1) protein plays an important role in BER (Hung et al., 2005; Li et al., 2009). The XRCC1 protein acts as a scaffolding protein for BER and single-strand break repair. The common polymorphism within the XRCC1 is Arg399Gln (rs25487), which is a G to A substitution at codon 399 in exon 10 of the gene, leading to the amino acid alteration arginine (Arg) to glutamine (Gln). The Arg399Gln polymorphism occurs at a conserved residue in the poly(ADP-ribose) polymerase binding domain of XRCC1. The 399Gln allele has been significantly associated with a higher level of DNA adducts, RBC glycophorin A mutations, micronuclei, sister chromatid exchanges, chromosomal damage, and prolonged cell cycle delay (Lei et al., 2002; Wang et al., 2003; Qu et al., 2005).

Shen et al. (2000) first reported an association between XRCC1 codon 399 polymorphisms and gastric cancer. Since then, several studies have reported the role of the XRCC1 Arg399Gln polymorphism in gastric cancer risk, but the results are inconclusive, partially because of the possibly pigmy effect of the polymorphism on gastric cancer risk and the relatively small sample size in each of the published studies. Recently, Chen et al. (2012) carried out a meta-analysis to test the association of the XRCC1 polymorphism with the risk of gastric cancer, but they did not exclude the studies which departure from Hardy-Weinberg equilibrium (HWE). Therefore, we repeated this meta-analysis to derive a more precise estimation of these associations.

MATERIAL AND METHODS

Identification of studies

To identify all studies that examined the association of XRCC1 Arg399Gln polymorphisms with gastric cancer, we performed a literature search in the Medline, EMBASE, OVID, ScienceDirect, and Chinese National Knowledge Infrastructure (CNKI) databases, without a language limitation, covering all papers published up to June 2011, using the following key words and subject terms: XRCC1, polymorphism, stomach neoplasms, and gastric cancer. We evaluated potentially relevant publications by checking their titles and abstracts and then obtained the most relevant publications for a detailed examination. Moreover, the reference lists of the selected papers were also screened for other potential articles that may have been

missed in the initial search. Only published studies with full-text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

Selection criteria

The following criteria were used for selection of reports for the meta-analysis: a) evaluation of the XRCC1 Arg399Gln polymorphism and gastric cancer risk, b) case-control studies, c) sufficient data to estimate an odds ratio (OR) and 95% confidence interval (95%CI), and d) genotype distribution of control population needed to be in HWE. After searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data extraction

Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was reached based on the majority of the votes. The following data were collected from each study: first author's name, publication date, ethnicity, genotyping methods, genotype frequency, and the design of experiment for obtaining genotyping information on the XRCC1 Arg399Gln polymorphism. Different ethnicities were categorized as Caucasian, Asian and Latin American based on the place of recruitment of the subjects. We did not define any minimum number of patients to include in our meta-analysis.

Statistical analysis

Crude ORs with 95%CIs were used to assess the strength of association between the XRCC1 Arg399Gln polymorphism and gastric cancer risk. The pooled ORs were performed for an additive model (Arg/Arg versus Gln/Gln), a dominant model (Arg/Arg + Arg/Gln versus Gln/Gln) and a recessive model (Arg/Arg versus Arg/Gln + Gln/Gln). The chi-square-based Q-statistical test was performed to assess heterogeneity among studies (Lau et al., 1997). $P > 0.05$ for the Q-test indicated a lack of heterogeneity among studies, so the pooled OR estimate of each study was calculated by the fixed-effects model [Mantel-Haenszel (1959) method]. Otherwise, the random-effects model [DerSimonian and Laird (1986) method] was used. Subgroup analyses were performed by ethnicity and study design. Sensitivity analysis was performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs. An estimate of potential publication bias was assessed by visual inspection of funnel plots (Munafo et al., 2004), in which the standard error of log(OR) of each study was plotted against its log(OR). An asymmetric plot indicated a possible publication bias. The symmetry of the funnel plot was further evaluated by the Egger linear regression test ($P < 0.05$ was considered to be indicative of significant publication bias) (Egger et al., 1997). Statistical analysis was performed using STATA version 10.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

Through literature search and selection based on the inclusion criteria, 13 studies met our inclusion criteria (Shen et al., 2000; Lee et al., 2002; Ratnasinghe et al., 2004; Duarte et al., 2005; Huang et al., 2005; Miao et al., 2006; Song et al., 2006; Zhang et al., 2006; Ruzzo et al., 2007; Capella et al., 2008; Li et al., 2009; Yan et al., 2009; Palli et al., 2010) (Figure 1 and Table 1). The data for this analysis included 3278 cases and 6243 controls. Table 1 lists the identified studies and their main characteristics. There were 4 studies of Caucasians, 8 studies of Asians and one study of Latin Americans. Almost all of the cases were pathologically confirmed. Controls were mainly healthy populations and matched for age. Among these studies, 9 were population-based and two were hospital-based case control studies.

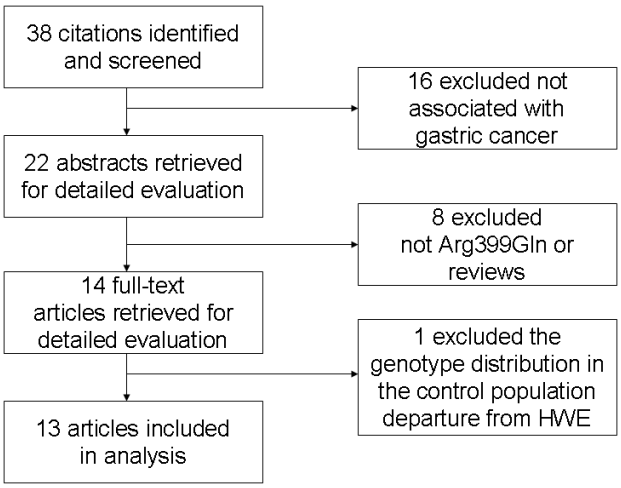

Figure 1. Flow diagram of included/excluded studies. HWE = Hardy-Weinberg equilibrium.

Table 1. Main characteristics of all studies included in the meta-analysis.

Author	Year	Ethnicity	Design	Method	Case	Control	Case			Control			HWE (P)
							GG	GA	AA	GG	GA	AA	
Capella´	2008	Caucasian	Nested	DHPLC	245	1173	100	114	31	473	545	155	0.919
Duarte	2005	Latin American	PB	PCR-RFLP	160	150	73	67	20	70	57	23	0.054
Huang	2005	Caucasian	PB	MALDI-TOF MS	281	390	124	121	36	166	179	45	0.756
Lee	2002	Asian	HB	PCR-RFLP	190	172	110	71	9	94	69	9	0.419
Miao	2006	Asian	PB	PCR-RFLP	500	1000	221	234	45	532	402	66	0.392
Ratnasinghe	2004	Asian	Cohort	Taqman	86	418	49	34	3	192	193	33	0.103
Shen	2000	Asian	PB	PCR-RFLP	188	166	92	83	13	94	59	13	0.387
Song	2006	Asian	PB	DHPLC	102	101	46	48	8	54	44	3	0.088
Yan	2009	Asian	PB	PCR-RFLP	455	650	241	191	23	345	270	35	0.054
Zhang	2006	Asian	PB	PCR-RFLP	236	708	136	82	18	369	275	64	0.219
Ruzzo	2007	Caucasian	PB	PCR-RFLP	91	119	36	45	10	50	59	10	0.198
Li	2009	Asian	HB	PCR-RFLP	455	650	241	191	23	345	270	35	0.055
Palli	2010	Caucasian	PB	Taqman	289	546	123	137	29	250	233	63	0.439

HB = hospital-based study; PB = population-based study; HWE = Hardy-Weinberg equilibrium.

Meta-analysis results

Table 2 lists the main results of the meta-analysis. The overall data showed that the individuals who carried the Arg/Arg genotype did not significantly increase gastric cancer risk compared to those carrying the Gln/Gln genotype (additive model, OR = 0.986, 95%CI = 0.831-1.156) (Figure 2), and no significant association was found in the dominant model (OR = 1.044, 95%CI = 0.890-1.224) or recessive model (OR = 0.975, 95%CI = 0.894-1.063). Thus, the 13 studies were analyzed by stratification based on ethnicity and study design. In the subgroup analysis of ethnicity, there was no significant association between the polymorphism and gastric cancer in Caucasians and Asians. When stratified by study design, there was no significant association between the polymorphism and gastric cancer risk; the details are listed in Table 2.

Table 2. Summary of odds ratio (OR) for the XRCC1 Arg399Gln polymorphism and gastric cancer risk.

Subgroup	Number of comparisons	GG *vs* AA		(GG+GA) *vs* AA		GG *vs* (GA+AA)	
		OR (95%CI)	I-squared (%)	OR (95%CI)	I-squared (%)	OR (95%CI)	I-squared (%)
Ethnicity							
Caucasian	4	0.99 (0.77-1.30)	0.0	1.01 (0.79-1.29)	0.0	0.98 (0.83-1.14)	0.0
Asian	8	0.95 (0.76-1.18)	40.0	1.05 (0.84-1.31)	35.2	0.98 (0.88-1.08)	68.2
Design							
PB	9	0.93 (0.77-1.12)	4.2	1.02 (0.85-1.21)	13.8	0.94 (0.86-1.04)	50.2
Total	13	0.98 (0.83-1.16)	6.6	1.04 (0.89-1.22)	2.9	0.98 (0.89-1.06)	47.9

PB = population-based study; I-squared = the variation in OR attributable to heterogeneity. 95%CI = 95% confidence interval.

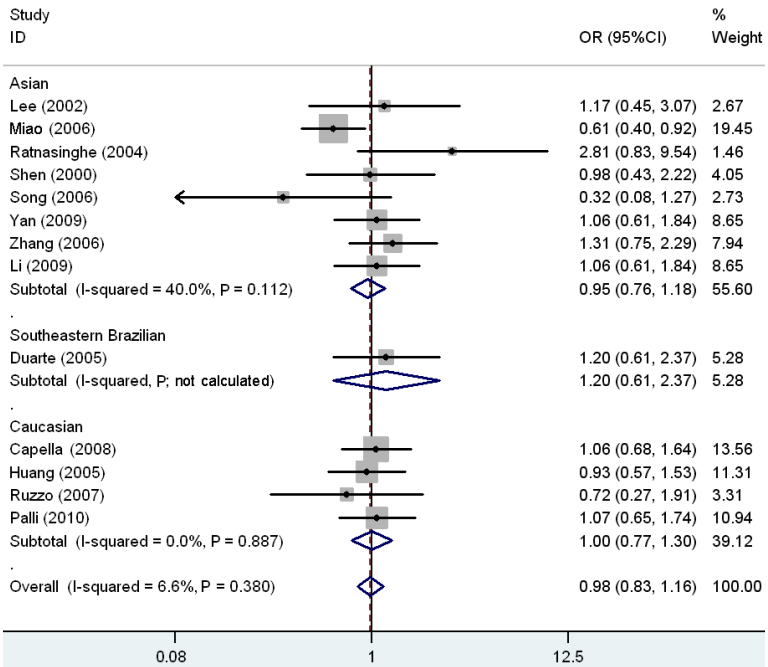

Figure 2. Forest plot of gastric cancer risk associated with the GG genotype compared to the AA genotype. OR = odds ratio; 95%CI = 95% confidence interval.

Sensitivity analysis

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Begg's funnel plots and the Egger test were used to assess publication bias. The shapes of the funnel plots revealed no obvious asymmetry (Figure 3). The Egger test was then used to statistically assess funnel plot symmetry. The results suggested no evidence of publication bias (P = 0.849 for additive model, P = 0.955 for dominant model and P = 0.811 for recessive model). These findings indicated that the results of these meta-analyses were relatively stable and that publication bias unlikely affected the results of the meta-analyses.

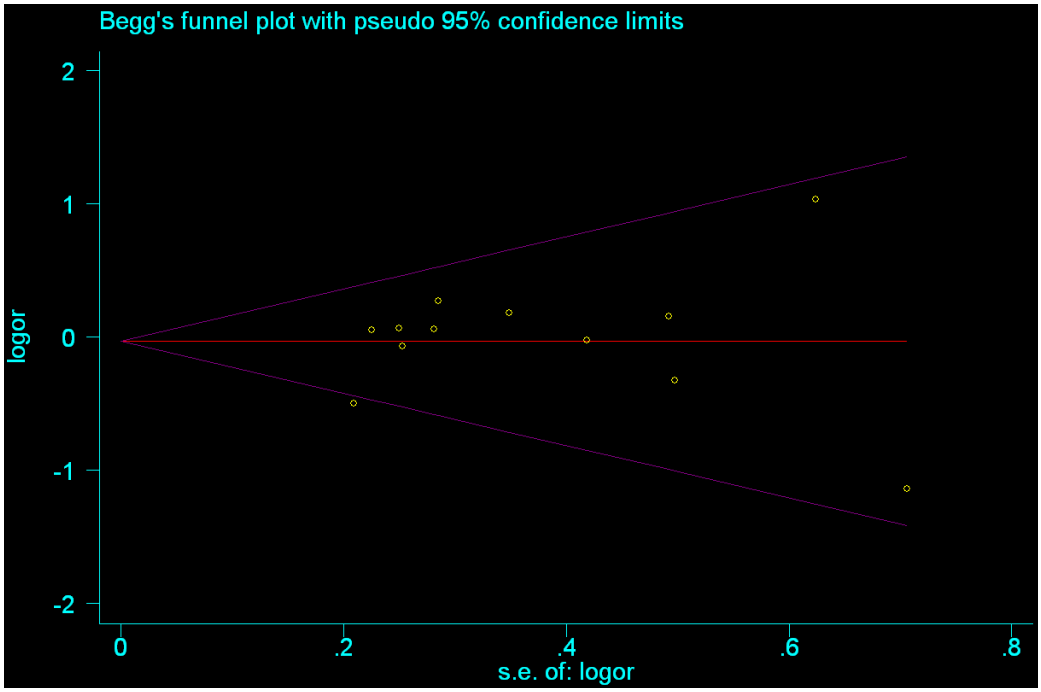

Figure 3. Begg's funnel plot of XRCC1 Arg399Gln and gastric cancer risk (GG *vs* AA).

DISCUSSION

The XRCC1 protein is an important component of the BER pathway, which fixes base damage and DNA single-strand breaks caused by ionizing radiation and alkylating agents (Marintchev

et al., 1999). The Arg399Gln polymorphism is located in the region of the BRCT-I interaction domain of XRCC1 with ADP-ribose polymerase. The presence of the variant 399Gln allele has been shown to be associated with measurably reduced DNA repair capacity as assessed by the persistence of DNA adducts, tumor-suppressor gene P53 mutations, increased red blood cell glycophorin A, elevated levels of sister chromatid exchanges, and prolonged cell-cycle delay (Lunn et al., 1999).

For the relatively small sample size in each of the published studies, it is important to accumulate data from different studies to provide evidence for the association of XRCC1 Arg399Gln with gastric cancer risk. There are some meta-analyses that have tested the associations between XRCC1 Arg399Gln and gastric cancer risk, but they had some limitations. Either the inclusion studies were small (Geng et al., 2008) or the analysis included studies with departure from HWE (Chen et al., 2012). Therefore, we repeated the analysis, and in this meta-analysis, we included a total of 3278 cases and 6243 controls from 13 studies to investigate the associations of the XRCC1 Arg399Gln polymorphism with gastric cancer risk. We found that there were no significant associations between the XRCC1 Arg399Gln polymorphism and gastric cancer risk. In the subgroup analysis of ethnicity and study design, there was also no association.

The association between the XRCC1 Arg399Gln polymorphism and the risk of different kinds of cancers has been extensively studied. Previous meta-analyses indicated that the XRCC1 Arg399Gln polymorphism is not significantly associated with colorectal cancer risk (Wang et al., 2010) or bladder cancer (Wang et al., 2008). However, this polymorphism is associated with the risk of lung cancer (Kiyohara et al., 2006), breast cancer (Saadat and Ansari-Lari, 2009) and prostate cancer (Geng et al., 2009). Thus, the role of this polymorphism in the risk of cancers varies. In the present study, we found that the XRCC1 Arg399Gln polymorphism is not a risk factor for gastric cancer. The effects of this polymorphism on susceptibility to cancer may differ according to cancer type. It may not be uncommon for the same polymorphism to play different roles in cancer susceptibility across different tumor locations, because cancer is an extremely complex disease and because genetic heterogeneity exists in different cancer types (Hirschhorn et al., 2002). Different kinds of cancer should have a different genetic susceptibility.

There are some limitations to this meta-analysis. First, only published studies were included in the meta-analysis. It is possible that some related unpublished studies that might have met the inclusion criteria were missed; therefore, publication bias may have been present, even though statistical analysis indicated this not to be the case. Second, our results were based on unadjusted estimates, and a more precise analysis could have been conducted if individual data were available; this would allow adjustment by other covariates such as age, ethnicity, environmental factors, and lifestyle. Third, in the subgroup analyses, the number of Caucasians was relatively small, not having enough statistical power to explore the association of the polymorphism with gastric cancer susceptibility. However, our meta-analysis also had some advantages. First, substantial numbers of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias was detected, indicating that the pooled result should be reliable.

In summary, our meta-analysis indicates that genetic variations of the XRCC1 Arg399Gln do not have an association with gastric cancer risk.

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