Human Genome Epidemiology (HuGE) Review

X-Ray Repair Cross-Complementing Group 1 (XRCC1) Genetic Polymorphisms and Gastric Cancer Risk: A HuGE Review and Meta-Analysis

HuiPing Xue, Peihua Ni, Bing Lin, Hong Xu, and Gang Huang*

* Correspondence to Prof. Gang Huang, Department of Nuclear Medicine, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, People's Republic of China (e-mail: huang2802@163.com).

Initially submitted February 16, 2010; accepted for publication October 8, 2010.

The authors performed a systematic review and meta-analysis of associations of the x-ray repair cross-complementing 1 gene (XRCC1) single nucleotide polymorphisms (SNPs) Arg194Trp, Arg280His, and Arg399Gln with gastric cancer risk, based on eligible studies retrieved from electronic databases for the period January 2000–December 2009. Ultimately, 12, 6, and 3 studies were found to be eligible for meta-analyses of Arg399Gln, Arg194Trp, and Arg280His, respectively. Regrouping was adopted in accordance with the most probably appropriate genetic models. Potential sources of heterogeneity were sought out. For overall gastric cancer, the pooled odds ratios for Arg399Gln, Arg194Trp, and Arg280His were 1.04 (95% confidence interval (CI): 0.90, 1.20; \( P = 0.572 \)), 0.83 (95% CI: 0.68, 1.01; \( P = 0.059 \)), and 1.18 (95% CI: 0.92, 1.50; \( P = 0.194 \)), respectively. After stratification of the Arg399Gln SNP data by anatomic type (cardia vs. noncardia), the pooled odds ratio was 1.07 (95% CI: 0.84, 1.37; \( P = 0.568 \)). The authors conclude that the 3 SNPs evaluated are not associated with risk of gastric cancer. The Arg399Gln SNP is not associated with the cardia type of gastric cancer. Evidently, the heterogeneity regarding the Arg399Gln SNP across studies is not explained by ethnicity, genotyping technique, sample size, or date of publication.

association; epidemiology; genetics; genome, human; polymorphism, single nucleotide; stomach neoplasms; X-ray repair cross complementing protein 1; XRCC1

Abbreviations: ADPRT, adenosine diphosphate ribosyl transferase; APE, apurinic/apyrimidinic endonuclease; BER, base excision repair; CI, confidence interval; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism; XPD, xeroderma pigmentosum complementary group D; XRCC1, x-ray repair cross-complementing group 1.

Editor’s note: This article also appears on the Web site of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/default.htm).

While gastric cancer incidence and mortality have both shown decreasing trends in recent decades, gastric cancer still ranks fourth in incidence and second in mortality universally (1). In China, particularly in the midwestern rural areas (2), gastric cancer still constitutes one of the most lethal malignancies in terms of mortality. It is widely known that infectious, dietary, environmental, and genetic factors are implicated in gastric carcinogenesis, yet only a minority of persons who have been exposed to risk factors such as Helicobacter pylori infection ultimately develop gastric cancer (3), which implies that host genetic susceptibility to gastric cancer could play a role. Susceptibility could be partially explained by genetic variations like single nucleotide polymorphisms (SNPs) in susceptible genes.

DNA bearing indispensable inheritance information must remain stable in order to undertake its crucial physiologic functions, but it is persistently vulnerable to many types of endogenous and/or exogenous damage; thus, mutations could accumulate and carcinogenesis may occur because of the damaged DNA. The DNA repair system plays a pivotal role in maintaining the functions of normal cells and genome

363 Am J Epidemiol 2011;173:363–375
Table 1. Study Characteristics and Genotypes of Gastric Cancer Cases and Controls in an Analysis of the X-Ray Repair Cross-Complementing Group 1 Gene (XRCC1) Arg399Gln Polymorphism and Gastric Cancer, 2000–2009

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Year of Publication</th>
<th>Quality Assessment Score</th>
<th>Genotyping Method</th>
<th>Total Sample Size</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>Study Location</th>
<th>Ethnic Group</th>
<th>No. of Controls, by Genotype</th>
<th>No. of Cases, by Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>GA</td>
</tr>
<tr>
<td>Shen, 2000 (11) a</td>
<td>2000</td>
<td>8</td>
<td>RFLP</td>
<td>354</td>
<td>166</td>
<td>188</td>
<td>China</td>
<td>Asian</td>
<td>94</td>
<td>59</td>
</tr>
<tr>
<td>Lee, 2002 (12)</td>
<td>2002</td>
<td>5.5</td>
<td>RFLP</td>
<td>362</td>
<td>172</td>
<td>190</td>
<td>South Korea</td>
<td>Asian</td>
<td>94</td>
<td>69</td>
</tr>
<tr>
<td>Ratnasinghe, 2004 (13) ab</td>
<td>2004</td>
<td>3</td>
<td>RT1</td>
<td>544</td>
<td>454</td>
<td>90</td>
<td>China</td>
<td>Asian</td>
<td>192</td>
<td>193</td>
</tr>
<tr>
<td>Duarte, 2005 (14)</td>
<td>2005</td>
<td>4</td>
<td>RFLP</td>
<td>310</td>
<td>150</td>
<td>160</td>
<td>Brazil</td>
<td>Hispanic</td>
<td>70</td>
<td>57</td>
</tr>
<tr>
<td>Huang, 2005 (15)</td>
<td>2005</td>
<td>7</td>
<td>MALDI-TOF</td>
<td>671</td>
<td>390</td>
<td>281</td>
<td>Poland</td>
<td>Caucasian</td>
<td>166</td>
<td>179</td>
</tr>
<tr>
<td>Miao, 2006 (16)</td>
<td>2006</td>
<td>5</td>
<td>RFLP</td>
<td>1,500</td>
<td>1,000</td>
<td>500</td>
<td>China</td>
<td>Asian</td>
<td>532</td>
<td>402</td>
</tr>
<tr>
<td>Song, 2006 (17)</td>
<td>2006</td>
<td>2.5</td>
<td>DHPLC c</td>
<td>203</td>
<td>101</td>
<td>102</td>
<td>China</td>
<td>Asian</td>
<td>54</td>
<td>44</td>
</tr>
<tr>
<td>Zhang, 2006 (18)</td>
<td>2006</td>
<td>4</td>
<td>RFLP</td>
<td>944</td>
<td>708</td>
<td>236</td>
<td>China</td>
<td>Asian</td>
<td>369</td>
<td>275</td>
</tr>
<tr>
<td>Ruzzo, 2007 (19)</td>
<td>2007</td>
<td>5</td>
<td>RFLP</td>
<td>270</td>
<td>144</td>
<td>126</td>
<td>Italy</td>
<td>Caucasian</td>
<td>50</td>
<td>59</td>
</tr>
<tr>
<td>Capellá, 2008 (20) a,e</td>
<td>2008</td>
<td>6.5</td>
<td>RT2</td>
<td>1,418</td>
<td>1,173</td>
<td>245</td>
<td>European countries</td>
<td>Caucasian</td>
<td>473</td>
<td>545</td>
</tr>
<tr>
<td>Yan, 2009 (21)</td>
<td>2009</td>
<td>4.5</td>
<td>RFLP</td>
<td>1,105</td>
<td>650</td>
<td>455</td>
<td>China</td>
<td>Asian</td>
<td>345</td>
<td>270</td>
</tr>
<tr>
<td>Liu, 2009 (22)</td>
<td>2009</td>
<td>2.5</td>
<td>RFLP</td>
<td>214</td>
<td>107</td>
<td>107</td>
<td>China</td>
<td>Asian</td>
<td>57</td>
<td>46</td>
</tr>
</tbody>
</table>

Abbreviations: DHPLC, denaturing high-performance liquid chromatography; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphism; RT1, real-time TaqMan analysis; RT2, fluorescently labeled real-time sensor probe.

a Data on the cardia type of gastric cancer were accessible.

b Case-cohort study; otherwise a case-control study.

c Based on polymerase chain reaction.

D Data on the diffuse type of gastric cancer were accessible.

a Nested case-control study.
integrity through the reversal of DNA damage. The repair of damaged DNA is a complicated process involving various enzymes and proteins. However, if the accumulated mutations occur in corresponding DNA repair genes, their repair or reversal capacity could be jeopardized, possibly increasing the risk of cancer (4). SNPs in common DNA repair genes have been identified (5), and these SNPs have been demonstrated to be linked to sporadic carcinogenesis (6, 7). Recently, SNPs in 1 susceptible gene, x-ray repair cross-complementing group 1 (XRCC1), have been increasingly emphasized on the grounds that XRCC1 is considered a crucial scaffold protein closely associated with the base excision repair pathway (8, 9), which has been thought of as the predominant DNA-damage repair pathway for the processing of small base lesions derived from oxidation and alkylation damage (10). The XRCC1 gene is located on chromosome 19q13.2-13.3, with a length of 33 kilobases. Although there are more than 300 validated SNPs in the XRCC1 gene in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), only 3 have been extensively studied: Arg194Trp (a change from arginine to tryptophan at codon 194; C/T substitution at position 26304 on exon 6), Arg280His (a change from arginine to histidine at codon 280; G/A substitution at position 27466 on exon 9), and Arg399Gln (a change from arginine to glutamine at codon 399; G/A substitution at position 28152 on exon 10). Those alterations may affect DNA repair capability by changing interactions between XRCC1-coded proteins and other base excision repair gene (BER)-coded proteins.

In 2000, Shen et al. (11) published the first study indicating that 2 of those XRCC1 SNPs, the Arg194Trp CC and Arg399Gln GA/AA genotypes, may contribute to the increased risk of developing gastric cancer, particularly that of the cardia type. Since then, researchers have consecutively reported associations between at least 1 of those 3 SNPs and gastric cancer risk, but with mixed or even conflicting results (12–22). In 2008, Geng et al. (23) published findings from a meta-analysis of the Arg399Gln SNP and gastric cancer risk. No associations were found on the basis of either a recessive genetic model or a dominant one, although some of the extracted data (revealed in Geng et al.’s Table 1), to our knowledge, were incorrect. Accordingly, we aimed to conduct a meta-analysis to shed more light on the role of these 3 SNPs in susceptibility to gastric cancer and to identify possible sources of heterogeneity among the eligible studies.

MATERIALS AND METHODS

Search strategy

We performed a systematic literature search for published articles on at least 1 of the 3 SNPs associated with risk of gastric cancer. The MEDLINE, EMBASE, and Chinese National Knowledge Infrastructure databases were used simultaneously with the combination of the English and/or Chinese key terms “x-ray repair cross-complementing 1,” “XRCC1,” “BER,” “gene,” “polymorphism,” or “SNP” and “gastric cancer,” “gastric carcinoma,” “cardia gastric cancer,” or “stomach cancer” for the period January 2000–December 2009. The scope of the computerized literature search strategy included articles published in peer-reviewed journals, with no language restriction.

Table 2. Study Characteristics and Genotypes of Gastric Cancer Cases and Controls in an Analysis of the X-Ray Repair Cross-Complementing Group 1 Gene (XRCC1) Arg194Trp Polymorphism and Gastric Cancer, 2000–2009

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Year of Publication</th>
<th>Quality Assessment Score</th>
<th>No. of Controls</th>
<th>No. of Cases</th>
<th>No. of Controls, by Genotype</th>
<th>No. of Cases, by Genotype</th>
<th>Study Location</th>
<th>Ethnic Group</th>
<th>Genotyping Method</th>
<th>Genotyping Sample Size</th>
<th>Total Sample Size</th>
<th>Genotyping Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen, 2000 (11a)</td>
<td>2000</td>
<td>8</td>
<td>354</td>
<td>166</td>
<td>70 CT 19 CT 19 TT TT</td>
<td>168 CT 19 CT 19 TT TT</td>
<td>China</td>
<td>Asian</td>
<td>RFLP</td>
<td>354</td>
<td>354</td>
<td>RFLP</td>
</tr>
<tr>
<td>Lee, 2002 (12)</td>
<td>2002</td>
<td>5.5</td>
<td>362</td>
<td>172</td>
<td>72 CT 172 CT 172 TT TT</td>
<td>160 CT 172 CT 172 TT TT</td>
<td>South Korea</td>
<td>Asian</td>
<td>RFLP</td>
<td>362</td>
<td>362</td>
<td>RFLP</td>
</tr>
<tr>
<td>Ratnasighe, 2004 (13b,c)</td>
<td>2004</td>
<td>4.5</td>
<td>544</td>
<td>454</td>
<td>217 CT 454 CT 454 TT TT</td>
<td>231 CT 454 CT 454 TT TT</td>
<td>China</td>
<td>Asian</td>
<td>RT1</td>
<td>544</td>
<td>544</td>
<td>RT1</td>
</tr>
<tr>
<td>Duarte, 2005 (14)</td>
<td>2005</td>
<td>4</td>
<td>310</td>
<td>150</td>
<td>130 CT 150 CT 150 TT TT</td>
<td>20 TT 130 CT 150 CT 150 TT</td>
<td>Brazil</td>
<td>Hispanic</td>
<td>RFLP</td>
<td>310</td>
<td>310</td>
<td>RFLP</td>
</tr>
<tr>
<td>Capella, 2008 (15a,c)</td>
<td>2008</td>
<td>7</td>
<td>1,418</td>
<td>1,173</td>
<td>1,039 CT 1,173 CT 1,173 TT</td>
<td>245 CT 1,173 CT 1,173 TT</td>
<td>European countries</td>
<td>Caucasian</td>
<td>RT1, real-time TaqMan analysis</td>
<td>1,418</td>
<td>1,418</td>
<td>RT1, real-time TaqMan analysis</td>
</tr>
<tr>
<td>Liu, 2009 (22)</td>
<td>2009</td>
<td>2.5</td>
<td>214</td>
<td>107</td>
<td>60 CT 43 CT 43 TT TT</td>
<td>47 CT 43 CT 43 TT TT</td>
<td>China</td>
<td>Asian</td>
<td>RFLP</td>
<td>214</td>
<td>214</td>
<td>RFLP</td>
</tr>
</tbody>
</table>

Abbreviations: HWE, Hardy-Weinberg equilibrium; RFLP, restriction fragment length polymorphism; RT1, real-time TaqMan analysis; RT2, fluorescently labeled real-time sensor probe.

a Data on the cardia type of gastric cancer were accessible.

b Case-cohort study; otherwise a case-control study.

c Nested case-control study.
search was expanded on the basis of the reference lists of retrieved articles. Published original articles concerning at least 1 of the 3 SNPs associated with the risk of gastric cancer were also sought manually.

**Study selection**

Studies testing at least 1 of the 3 SNPs associated with the risk of gastric cancer were included if all of the following conditions were met: 1) results were reported in English or Chinese; 2) numbers of both controls and gastric cancer cases pertaining to at least 1 of the 3 SNPs were reported; 3) results were expressed as odds ratios; 4) 95% confidence intervals for the odds ratios were provided; and 5) the study had a case-control or nested case-control design.

**Methodological quality appraisal**

To identify high-quality studies, we further refined predefined criteria for quality appraisal originally proposed by Thakkinstian et al. (24) and adapted by Camargo et al. (25). The revised criteria (see Web Table 1 (http://aje.oxfordjournals.org/)) cover the credibility of controls, the representativeness of cases, consolidation of gastric cancer, genotyping examination, and association assessment. Methodological quality was independently appraised by 2 of the present authors (B. Lin, H. Xu). Disagreements were resolved through discussion. Scores ranged from 0 (lowest) to 9 (highest). Articles with scores less than 5 were considered “low- or moderate-quality” studies, whereas those with scores equal to or higher than 5 were considered “high-quality” studies.

**Data extraction**

The following data were abstracted from each article: author(s), year of publication, country, predominant ethnicity of participants (Caucasian, Hispanic, Asian, etc.), study design, source of controls, numbers of cases and controls, genotyping method, age and gender distribution of the subjects, Lauren’s histopathologic classification (intestinal, diffuse, or mixed), and anatomic type (cardia or noncardia). The data were extracted and independently entered into 2 databases by 2 of the authors (B. Lin, H. Xu), who were blind to journal names, institutions, and funding grants. Any discrepancy between these 2 investigators was resolved by a third author (H. Xu).

**Statistical analysis**

All statistical analyses were performed using STATA statistical software (version 10.1; Stata Corporation, College Station, Texas). Two-sided $P$ values less than 0.05 were considered statistically significant. Hardy-Weinberg equilibrium in controls was calculated again in our meta-analysis. The chi-squared goodness-of-fit test was used to test deviation from Hardy-Weinberg equilibrium (significant at the 0.05 level).

Odds ratios and 95% confidence intervals were employed to assess the strength of associations between SNPs in Arg194Trp, Arg280His, and Arg399Gln and gastric cancer risk. Odds ratios 1, 2, and 3 (OR1, OR2, and OR3) were
calculated for the genotypes 1) TT (Trp/Trp) versus CC (Arg/Arg), 2) CT (Arg/Trp) versus CT (Arg/Trp) for Arg194Trp; 1) AA (His/His) versus GG (Arg/Arg), 2) GA (Arg/His) versus GG (Arg/Arg), and 3) AA (His/His) versus GA (Arg/His) for Arg280His; and 1) AA (Gln/Gln) versus GG (Arg/Arg), 2) GA (Arg/Gln) versus GG (Arg/Arg), and 3) AA (Gln/Gln) versus GA (Arg/Gln) for Arg399Gln, respectively.

The above pairwise differences were used to determine the most appropriate genetic model. If \( \text{OR}_1 = \text{OR}_3 \neq 1 \) and \( \text{OR}_2 = 1 \), a recessive model is suggested. If \( \text{OR}_1 = \text{OR}_2 \neq 1 \) and \( \text{OR}_3 = 1 \), a dominant model is implied. If \( \text{OR}_2 = 1 / \text{OR}_3 \neq 1 \) and \( \text{OR}_1 = 1 \), then a complete overdominant model is suggested. If \( \text{OR}_1 > \text{OR}_2 > 1 \) and \( \text{OR}_1 > \text{OR}_3 > 1 \), or if \( \text{OR}_1 < \text{OR}_2 < 1 \) and \( \text{OR}_1 < \text{OR}_3 < 1 \), then a codominant model is indicated (26). Take the Arg399Gln SNP as an example. If a dominant model was indicated, the original grouping was collapsed and the new group of A carriers (AA + GA) was compared with the GG genotype group; if a recessive model was suggested, the AA group was compared with the GG-plus-GA group; if a complete overdominant model was implied, the AA-plus-GG group was compared with the GA group; and if a codominant model was suggested, the AA group was compared with the GA and GG groups, respectively.

The \( Q \) statistic was used to test for heterogeneity among the studies included in the meta-analysis. A fixed-effects model, using the Mantel-Haenszel method, was used to
**Figure 2.** Odds ratios (ORs) for associations between 3 single nucleotide polymorphisms (Arg399Gln, Arg194Trp, and Arg280His) in the x-ray repair cross-complementing group 1 gene (XRCC1) and gastric cancer risk, in order of increasing publication year, 2000–2009. Studies were...
calculate the pooled odds ratios when homogeneity existed on the basis of a Q-test $P$ value no less than 0.1. By contrast, a random-effects model, using the DerSimonian and Laird method, was utilized if there was heterogeneity based on a $Q$-test $P$ value less than 0.1. The $I^2$ statistic was then used to estimate heterogeneity quantitatively. Heterogeneity was deemed apparent if $I^2$ was greater than 50%. The significance of pooled odds ratios was tested by $Z$ test ($P < 0.05$ was considered significant).

Overall meta-analyses for the 3 SNPs were initially performed. Then we conducted stratification analysis, if feasible, according to sample size, quality appraisal score, publication time, participant ethnicity, anatomic classification (noncardia or cardia), histopathologic classification (intestinal, diffuse, or mixed), and genotyping technique (polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) or another genotyping method). Additionally, 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 both publication time and sample size. Finally, publication bias was assessed qualitatively by performance of funnel plots and quantitatively by means of Begg’s and Egger’s tests ($P < 0.05$ was considered significant).

RESULTS

Literature search and study selection

After comprehensive searching, 26 articles in English and 7 articles in Chinese were retrieved, among which 1 article (18) had been registered in both English and Chinese databases. Our meta-analysis initially included 12 studies (11–22) which met the inclusion criteria. Those 12 studies were preliminarily appropriate for meta-analysis of the associations with gastric cancer regarding Arg399Gln; 6 articles (11–14, 20, 22) were relevant to the association with Arg194Trp, and 3 articles (12, 21, 22) were relevant to the association with Arg280His. Tables 1–3 show the characteristics of the studies and the corresponding genotype distributions among cases and controls. The literature search and study selection procedures are shown in Figure 1.

The studies regarding the SNPs Arg399Gln and Arg280His were both in Hardy-Weinberg equilibrium, while 2 studies regarding the Arg194Trp SNP (13, 20) deviated from Hardy-Weinberg equilibrium. Generally speaking, studies that deviated from Hardy-Weinberg equilibrium through our calculation should have been removed; however, considering that these were the 2 largest studies of Arg194Trp and given that sensitivity analyses would be conducted, we kept them in our meta-analysis. Thus, 12 studies (11–22) with a total of 2,680 cases and 5,215 controls were ultimately eligible for the meta-analysis of the Arg399Gln SNP, 6 studies (11–14, 20, 22) with 976 cases and 2,199 controls were eligible for the meta-analysis of the Arg194Trp SNP, and 3 studies (12, 21–22) with 752 cases and 929 controls were eligible for the meta-analysis of the Arg280His SNP.

Overall meta-analysis

For the Arg399Gln SNP, OR$_1$, OR$_3$, and OR$_3$ were 1.07 ($P = 0.475$), 1.05 ($P = 0.320$), and 1.00 ($P = 0.984$), respectively, suggesting a dominant effect of the putative susceptibility allele A. Thus, the original grouping was collapsed, and AA and GA were combined, in accordance with a dominant model, into an A carrier group, the latter of which was compared with the GG genotype group.

For the Arg194Trp SNP, OR$_1$, OR$_2$, and OR$_3$ were 0.81 ($P = 0.339$), 0.83 ($P = 0.075$), and 1.04 ($P = 0.869$), respectively, strongly suggesting a dominant effect of the putative susceptibility allele T. Likewise, the group of T carriers (TT plus CT) was compared with the CC genotype group.

For the Arg280His SNP, OR$_1$, OR$_2$, and OR$_3$ were 1.34 ($P = 0.586$), 1.17 ($P = 0.216$), and 1.08 ($P = 0.885$), respectively, also strongly suggesting a dominant effect of the putative susceptibility allele A. Thus, the group of A carriers (AA plus GA) was compared with the GG genotype group.

Parts A–C of Figure 2 show the pooled odds ratios and 95% confidence intervals for the associations between Arg399Gln, Arg194Trp, and Arg280His and gastric cancer risk, respectively. Part A shows the associations between Arg399Gln AA-plus-GA genotypes (A carrier group), as compared with the GG genotype, and gastric cancer risk. Part B shows the associations between Arg194Trp TT-plus-CT genotypes (T carrier group), as compared with the CC genotype, and gastric cancer risk; and part C shows the associations for Arg280His AA-plus-GA genotypes (A carrier group), as compared with the GG genotype. For overall gastric cancer, there were no statistically significant findings. The pooled odds ratio associated with the Arg399Gln A allele versus the GG genotype was 1.04 (95% confidence interval (CI): 0.90, 1.20; $P = 0.572$); the pooled odds ratio associated with the Arg194Trp T allele versus the CC genotype was 0.83 (95% CI: 0.68, 1.01; $P = 0.059$); and the pooled odds ratio associated with the Arg280His A allele versus the GG genotype was 1.18 (95% CI: 0.92, 1.50; $P = 0.194$).

Stratification analysis

Because of the limited numbers of ultimately eligible studies regarding the Arg194Trp and Arg280His SNPs, stratification analysis was performed only for the Arg399Gln SNP. As Table 4 shows, specific data for the Arg399Gln SNP were stratified, on the basis of sample size, into 2 subgroups: the large-sample-size subgroup (numbers of both cases and controls $\geq 150$) and the small- or moderate-sample-size subgroup (numbers of
both cases and controls <150). No statistically significant results were found in either the large-sample-size subgroup or the small- and moderate-sample-size subgroup; the pooled odds ratios for the former and the latter were 1.04 (95% CI: 0.89, 1.22; \( P = 0.602 \)) and 1.03 (95% CI: 0.79, 1.33; \( P = 0.854 \)), respectively.

The data were also stratified, in accordance with the quality appraisal scores, into high-quality (scores \( \geq 6 \)) and low- and moderate-quality (scores <6) subgroups. No statistically significant findings were observed in either the low- and moderate-quality subgroup or the high-quality counterpart, with one exception: A very fragile statistically significant finding was seen when the Mantel-Haenszel method was employed to calculate the pooled odds ratio for the latter subgroup (pooled OR = 1.15, 95% CI: 1.01, 1.31; \( P = 0.037 \)), while the pooled odds ratio calculated by means of the DerSimonian and Laird method was 1.11 (95% CI: 0.92, 1.34; \( P = 0.262 \)), probably indicating no statistically significant finding.

The data were additionally stratified by publication time into subgroups of articles published after 2005 and articles published prior to or during 2005. No statistically significant findings were observed in either subgroup.

### Table 4. Results From Stratified Analysis of the X-Ray Repair Cross-Complementing Group 1 Gene (XRCC1) Arg399Gln Polymorphism and Gastric Cancer Risk, 2000–2009

<table>
<thead>
<tr>
<th>Stratification Factor</th>
<th>( \chi^2 ) df</th>
<th>( P ) Value</th>
<th>( I^2, % )</th>
<th>Odds Ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% Confidence Interval&lt;sup&gt;b&lt;/sup&gt;</th>
<th>( P ) Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>20.34</td>
<td>11</td>
<td>0.041</td>
<td>1.04</td>
<td>0.90, 1.20</td>
<td>0.572</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>14.27</td>
<td>7</td>
<td>0.047</td>
<td>1.04</td>
<td>0.89, 1.22</td>
<td>0.602</td>
</tr>
<tr>
<td>Small or moderate</td>
<td>6.00</td>
<td>3</td>
<td>0.111</td>
<td>1.03&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.79, 1.33&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.854</td>
</tr>
<tr>
<td>Study quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9.24</td>
<td>5</td>
<td>0.100</td>
<td>1.15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.01, 1.31&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.037</td>
</tr>
<tr>
<td>Low or moderate</td>
<td>7.70</td>
<td>5</td>
<td>0.174</td>
<td>0.95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.82, 1.11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.518</td>
</tr>
<tr>
<td>Date of publication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before or during 2005</td>
<td>5.85</td>
<td>4</td>
<td>0.210</td>
<td>0.95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.80, 1.14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.601</td>
</tr>
<tr>
<td>After 2005</td>
<td>4.76</td>
<td>5</td>
<td>0.446</td>
<td>0.99&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.87, 1.14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.933</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.26</td>
<td>2</td>
<td>0.878</td>
<td>0.98&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.81, 1.19&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.820</td>
</tr>
<tr>
<td>Hispanic&lt;sup&gt;d&lt;/sup&gt;</td>
<td>19.17</td>
<td>7</td>
<td>0.008</td>
<td>1.06</td>
<td>0.86, 1.31</td>
<td>0.583</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anatomic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardia</td>
<td>13.01</td>
<td>4</td>
<td>0.011</td>
<td>1.07</td>
<td>0.84, 1.37</td>
<td>0.568</td>
</tr>
<tr>
<td>Cardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histopathologic type&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal</td>
<td>13.49</td>
<td>7</td>
<td>0.061</td>
<td>1.10</td>
<td>0.92, 1.30</td>
<td>0.308</td>
</tr>
<tr>
<td>Diffuse</td>
<td>4.45</td>
<td>3</td>
<td>0.217</td>
<td>0.94&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.79, 1.12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.497</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyping technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR-RFLP</td>
<td>13.49</td>
<td>7</td>
<td>0.061</td>
<td>1.10</td>
<td>0.92, 1.30</td>
<td>0.308</td>
</tr>
<tr>
<td>Other</td>
<td>4.45</td>
<td>3</td>
<td>0.217</td>
<td>0.94&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.79, 1.12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.497</td>
</tr>
</tbody>
</table>

Abbreviations: df, degrees of freedom; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

<sup>a</sup> Test for heterogeneity in Arg399Gln A carriers (AA + GA) versus persons with the GG genotype, based on a dominant model.

<sup>b</sup> Odds ratios and 95% confidence intervals were estimated by means of the Mantel-Haenszel method unless otherwise indicated.

<sup>c</sup> Estimated using the DerSimonian and Laird method.

<sup>d</sup> Insufficient data for analysis.
findings were observed; the pooled odds ratios were 0.99 (95% CI: 0.87, 1.14; \(P = 0.933\)) in the former subgroup and 0.95 (95% CI: 0.80, 1.14; \(P = 0.601\)) in the latter, respectively.

The data were further stratified by the ethnicity of participants, into Caucasians, Asians, and Hispanics. No statistically significant results were found in Caucasians or Asians. The pooled odds ratios in the former and the latter were 0.98 (95% CI: 0.81, 1.19; \(P = 0.820\)) and 1.06 (95% CI: 0.86, 1.31; \(P = 0.583\)), respectively. The pooled odds ratio could not be appraised in Hispanics because only 1 study (14) was conducted among Hispanics.

When gastric cancer was classified into noncardia (or distal) and cardia subtypes, no statistically significant findings were seen among persons with the cardia type (pooled OR = 1.07, 95% CI: 0.84, 1.37; \(P = 0.568\)). The pooled odds ratio could not be calculated among persons with the noncardia type because of a lack of specific data.

In terms of pathology, gastric cancer can be classified into intestinal, diffuse, or mixed subtypes, but only 1 study (19) dealt with the diffuse subtype; none of the other studies offered such classification data. Thus, the pooled odds ratios specific to pathologic types could not be estimated.

When genotyping techniques were considered, no statistically significant findings were obtained for either PCR-RFLP or other genotyping techniques. Pooled odds ratios were 1.10 (95% CI: 0.92, 1.30; \(P = 0.308\)) for the former and 0.94 (95% CI: 0.79, 1.12; \(P = 0.497\)) for the latter.

**Sensitivity analysis**

Firstly, both fixed-effects models and random-effects models, if homogeneity was indicated (\(Q\)-test \(P \geq 0.1\)), were employed, and their results were compared simultaneously because of the need for sensitivity analysis (Table 4). With the exception that 95% confidence intervals were slightly narrower using the fixed-effects models and that 1 significantly different result was noted above, the other findings from both models were perfectly similar in the sense that the \(Q\)-test \(P\) value was no less than 0.1, indicating robust stability of the outcomes theoretically in the absence of heterogeneity. The \(I^2\) statistic suggested different degrees of variation in the meta-analyses (ranging from 0% to 69.2%). Secondly, meta-analyses were conducted repeatedly after removal of each particular study. Fixed-effects estimates and/or random-effects estimates before and after the deletion of each study were similar, suggesting high stability of the meta-analysis results. As for the association of the Arg399Gln SNP with gastric cancer risk, the study that had the most influence on the overall pooled estimates (Figure 3) seemed to be the one conducted by Miao et al. (16); however, the sensitivity analysis showed that the odds ratios were 1.04 (95% CI: 0.90, 1.20; \(P = 0.572\)) and 0.98 (95% CI: 0.88, 1.09; \(P = 0.697\)) before and after the removal of that study, respectively, indicating high stability of the results.

**Cumulative meta-analysis**

Cumulative meta-analyses of the 3 associations were also conducted via the assortment of studies by both publication time and sample size. Figure 3 shows results from the cumulative meta-analysis of the association of the Arg399Gln SNP with overall gastric carcinoma in chronologic order.
Inclinations toward null significant associations were evident with each accumulation of more data over time, although associations were initially strong (Figure 4, part A). 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 (Figure 4, part B). Results for the other 2 SNPs are not shown but are available upon request.

Publication bias analysis

For each of the 3 SNPs, publication bias was preliminarily examined by funnel plots qualitatively and estimated by Begg’s and Egger’s tests quantitatively. All 3 SNPs showed consistent results, indicating no publication biases. Take the Arg399Gln SNP as an example. In its funnel plot (Figure 5), the dots were nearly symmetrically distributed,
DNA repair pathways aimed at damaged DNA, and each pathway is involved in numerous molecules. *BER* is only 1 of such repair pathways, operating merely on small lesions (4, 35). Accordingly, it is more rational to measure SNPs in various involved genes together so as to discern more clearly the probable association with gastric cancer risk in terms of DNA repair pathways.

Additionally, the overwhelming majority of eligible studies regarding the Arg399Gln SNP in our meta-analysis dealt with gastric cancer overall, with no further discrimination anatomically or pathologically. It is widely known that the cardia type of gastric cancer differs from the noncardia type in terms of etiology, pathology, carcinogenesis, and/or prognosis (36–38); so does the intestinal type versus the diffuse type. It could be said that the indiscriminate combination of intestinal and diffuse types of gastric cancer, or cardia and noncardia types, may mask or produce underestimation of the strength of the authentic associations.

In the stratification analysis carried out according to the quality appraisal scores for the Arg399Gln SNP, a statistically significant finding was seen in the high-quality group when the Mantel-Haenszel method was used to calculate the pooled odds ratio. Although its significance was very weak and disappeared when the DerSimonian and Laird method was used instead, it indicates that high-quality studies may offer quite different outcomes than average or mediocre studies. We strongly recommend that researchers design genetic polymorphism association studies more rigorously and uniformly in the future.

As for ethnicity, our meta-analysis did not find any significant difference between Caucasians and Asians regarding the Arg399Gln SNP. Studies on the association of Arg399Gln with gastric cancer were predominantly conducted in East Asian countries; only a few were conducted in Western countries. Thus, possible ethnic differences in the association of Arg399Gln with gastric cancer should be investigated further and confirmed as more studies are conducted in Western countries.

With the advent of sophisticated genotyping technologies like seminested PCR, the TaqMan allelic discrimination test, or real-time PCR, we may witness a surge of genetic association studies in the future. In our meta-analysis, no significant findings regarding Arg399Gln could be found regardless of genotyping technique. We propose that the sensitivity and specificity of genotyping techniques be further explored so as to seek out optimal approaches which could minimize genotyping errors.

The strengths of our meta-analysis could be summarized as follows. We sought to find as many publications as we could by means of various searching approaches. We placed more emphasis on assessing biases across studies and pinpointing the potential sources of heterogeneity via stratification and sensitivity analyses. We comprehensively assessed publication biases using several methods such as Begg’s and Egger’s tests, as well as funnel plot tests. In view of this, we are convinced that the results of our meta-analysis, in essence, are sound and reliable.

In conclusion, SNPs in Arg399Gln, Arg194Trp, and Arg280His are not associated with the risk of gastric cancer. In addition, Arg399Gln is not associated with the cardia...
type of gastric cancer. Evidently, neither ethnicity nor genotyping technique, sample size, or article publication date constitutes the source of heterogeneity across studies regarding the Arg399Gln SNP, and no publication biases regarding the 3 SNPs evaluated were found in our meta-analysis.

ACKNOWLEDGMENTS

Author affiliations: Department of Gastroenterology, Renji Hospital, Shanghai Institute of Gastrointestinal Diseases, School of Medicine, Shanghai Jiaotong University, Shanghai, People’s Republic of China (Huiping Xue); Faculty of Laboratory Medicine, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, People’s Republic of China (Peihua Ni); Division of Nutrition, Zhongshan Hospital, School of Medicine, Fudan University, Shanghai, People’s Republic of China (Bing Lin); Division of Biochemistry, School of Medicine, Shanghai Jiaotong University, Shanghai, People’s Republic of China (Hong Xu); and Department of Nuclear Medicine, Renji Hospital, School of Medicine, Shanghai Jiaotong University, People’s Republic of China (Gang Huang).

Drs. Huiping Xue, Peihua Ni, Bing Lin, and Hong Xu contributed equally to this work.

This research was sponsored by the National Natural Science Foundation of China (grants 30830308, 30970842, and 81071180); the Key Project of Science and Technology Commission of Shanghai Municipality (grants 10JC1410000, 08JC1415000, and 08410702000); and the Shanghai Leading Academic Discipline Project (grant S30203).

Conflict of interest: none declared.

REFERENCES


