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Original Article

Genetic variants of the *XRCC1* gene and susceptibility to esophageal cancer: a meta-analysis

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Abstract: To summarize published data on the role of common genetic variants of the X-ray repair cross-complementing group 1 (*XRCC1*) gene in susceptibility to esophageal cancer (EC), we performed a meta-analysis including 11 eligible publications with 3,306 patients and 6,852 controls for $Arg^{399}Gln$ and 832 patients and 1,418 controls for $Arg^{194}Trp$. Overall, the variant Gln^{399} allele was not associated with EC risk, compared with the Arg^{399} allele in the populations included in the analysis. However, stratified analysis revealed that Gln^{399} allele was associated with an increased EC risk among Chinese populations in a recessive model (OR, 1.33; 95% CI 1.01-1.76; fixed effects) and by homozygote contrast (OR, 1.35; 95% CI 1.01-1.81), particularly for the tumor histology of squamous cell carcinoma (OR, 1.34; 95% CI 1.03-1.73 for the recessive model) and (OR, 1.34; 95% CI 1.02-1.76 for the homozygote contrast). There was no apparent effect of the Trp^{194} allele, compared to the Arg^{194} allele, on the EC risk in all analyses. These results suggest that the *XRCC1* $Arg^{399}Gln$ polymorphism may be a potential biomarker of EC susceptibility in Chinese populations, particularly for squamous cell carcinoma. Further larger studies with multi-ethnic populations are required to further assess the association between *XRCC1* polymorphisms and EC risk.

Key Words: DNA repair gene, esophageal cancer, genetic polymorphism, meta-analysis, molecular epidemiology

Introduction

Esophageal cancer (EC) is one of the most malignant tumors with an estimation of 16,470 new cases and 14,280 deaths in the United States in 2008 [1]. The five-year survival rate was 15.6% from 1996 to 2003, which is comparable to that of lung cancer (15%) but much lower than most of other cancer types [1]. Two histological types account for the majority of EC: adenocarcinoma and squamous cell carcinoma. In the 1960s, squamous cell cancers had comprised over 90% of all EC [2]. However, the incidence of esophageal adenocarcinoma has increased rapidly during the last 30 years, now becoming more prevalent than squamous cell cancer in the United States and Western Europe [3]. Although the overall incidence of squamous cell carcinoma of the esophagus is declining in Western countries, this histological type remains dominant in many other parts of the world.

Previous epidemiological studies have identified a number of environmental factors in the etiology of EC. Tobacco, alcohol and some dietary factors, such as deficiencies of retinol, riboflavin and zinc, have been implicated in the squamous cell carcinoma development [4], whereas gastro-esophageal acid reflux is more important for the adenocarcinoma development [5], and aspirin and NSAID drugs are reported to protect against EC in clinical trials [6]. In addition to those environmental factors, genetic factors are thought also to play an important role in the EC etiology, because only small fractions of those individuals, who have exposed to environmental risk factors, develop EC in their lifetime.

The X-ray repair cross-complementing group 1 (*XRCC1*) gene is located on chromosome 19q13.2~q13.3 [7], and its product, the *XRCC1* protein, is involved in the base-excision repair (BER) pathway, which is responsible for repair of oxidative DNA damage and single strand breaks through interacting with a complex of DNA repair proteins, such as human polynucleotide kinase (PNK), DNA ligase III (LIG3) and DNA polymerase-beta (POLB) [8-10]. Although there are at least 358 single nucleotide polymorphisms (SNPs) in the *XRCC1* gene as reported to date in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP), only eight are nonsynonymous (nsSNPs), three of which are common (minor allele frequency > 0.05) that have amino acid substitutions at codons 194C>T (Arg to Trp), 280G>A (Arg to His) and 399G>A (Arg to Gln) (http://egp.gs.washington.edu). These SNPs may influence the interaction of *XRCC1* with the other BER enzymes and consequently alter DNA repair activity. For example, the *XRCC1* $Arg^{399}Gln$ SNP is associated with higher sister chromatoid exchange frequency induced by tobacco carcinogens [11], higher levels of DNA adducts [12, 13] and prolonged cell-cycle delay in response to ionizing radiation [14]. The *XRCC1* $Arg^{194}Trp$ SNP, which occurs in the nuclear antigen-binding region of the proliferating cell, is suggested to enhance individual DNA repair capability [15]. In addition to those three SNPs, Hao *et al.* reported a new polymorphism (-77T>C), located in the 5' untranslated region (UTR) of the *XRCC1* gene, which may be associated with reduced *XRCC1* protein expression through diminished promoter activity [16]. Therefore, it is likely that the inter-individual variation in DNA repair ability conferred by *XRCC1* variants may modulate esophageal carcinogenesis and influence the individual susceptibility to EC.

Indeed, *XRCC1* SNPs have been shown in previous meta-analyses to be significantly associated with risk of breast and lung cancer, particularly among Asians [17, 18]. However, studies of *XRCC1* SNPs and EC risk produced some mixed results in the literature, and no meta-analysis has been conducted to date. Since single studies may have been underpowered to detect the effect of low-penetrance genes, such as *XRCC1*, particularly their dose-response relationships and interaction with other environmental factors, we selected from all available published articles and performed a quantitative analysis to identify evidence of an association between *XRCC1* SNPs and EC risk.

Materials and Methods

Identification and eligibility of published studies

We searched for papers published before October 2008 by using the electronic MEDLINE database with the following terms "*XRCC1*", "polymorphism" AND "esophageal". We included all the case-control studies of EC with genotyping data for at least one of the three SNPs, $Arg^{399}Gln$, $Arg^{194}Trp$ and $Arg^{280}His$. A total of 12 published studies investigated the association between these *XRCC1* SNPs and EC risk, one of which was excluded [19], because it investigated the same or a subset of population of previous publications [20]. Hence, the final analysis included 11 case-control studies of 3,306 cancer cases and 6,852 controls for $Arg^{399}Gln$, 832 cancer cases and 1,418 controls for $Arg^{194}Trp$ (from only 5 studies) and 520 cancer cases and 744 controls for $Arg^{280}His$ (from two studies only)

Data extraction

We extracted the following information from each manuscript: author, year of publication, country of origin, selection and characteristics of cancer cases and controls, demographics, ethnicity, cancer histological types and genotyping information. For studies including subjects of different ethnicities, data were extracted separately and categorized as Chinese, Caucasians and Indians. However, if the authors did not clearly state the ethnic information or we could not separate them according to the genotype data, the term "mixed" was used.

Meta-analysis

We performed a meta-analysis to estimate the risk (odds ratio, OR) of cancer associated with the *XRCC1* SNPs. In addition to comparisons using all subjects, studies were also categorized into different subgroups according to ethnicity and tumor type. We investigated between-study heterogeneity by using the Cochran's Q test, and the heterogeneity was considered significant for $P < 0.05$ [21]. Values from single studies were combined using the models of fixed effects (Mantel-

Table 1. Studies included in the meta-analysis

First author year	Country	Ethnicity	Cancer type	Cases/Control	Genotype studied	HWE	Method
Doecke 2008 [38]	Australia	Mixed	Adenocarcinoma	263/1337	codon 399	Yes	Other
Ferguson 2008 [39]	Ireland	Caucasian	Adenocarcinoma	248/209	codon 399	Yes	Other
Sobti 2007 [26]	India	Indian	Squamous call	120/160	codon 399	Yes	PCR-RFL
Liu 2007 [40]	U.S.A.	Mixed	Adenocarcinoma	183/336	codon 399	Yes	PCR-RFL
Cai 2006 [23]	China	Chinese	Squamous cell	218/415	codon 399	No	PCR-RFL
Ye 2006 [22]	Sweden	Caucasian	Adeno+Squamous	303/472	codon 399	No	PCR-RFL
Casson 2005 [31]	Canada	Mixed	Adenocarcinoma	56/95	codon 399, 194	Yes	PCR-RFL
Ratnasinghe 2004 [24]	China	Chinese	Squamous cell	131/454	codon 399, 194	Yes	Other
Yu 2004 [27]	China	Chinese	Squamous cell	135/152	codon 399, 194	Yes	PCR-RFL
Hao 2004 [20]	China	Chinese	Squamous cell	419/480	codon 399, 194, 280	Yes	PCR-RFL
Lee 2001 [25]	China	Chinese	Squamous cell	284/122	codon 399, 194, 280	Yes	PCR-RFL

Note: Mixed ethnicity: Doecke 2008, mostly Caucasians; Liu 2007, mostly Caucasians; Casson 2005, unknown. Adeno = adenocarcinoma; squamous cell = squamous cell carcinoma. PCR-RFLP = polymerase chain reaction-restriction fragment length poly-morphism; Other = nucleotide sequencing, MALDI mass spectrometry or TaqMan allelic discrimination assay.

Haenszel). We constructed a funnel plot to examine publication bias. We checked deviation from the Hardy-Weinberg equilibrium among cases and controls by a χ^2-test, with one degree of freedom. All analyses were performed with Statistical Analysis System software (v.8.0; SAS Institute, Cary, NC) and Review Manager (v.5.0; Oxford, England). All the *P* values were two-sided.

Results

Meta-analysis database

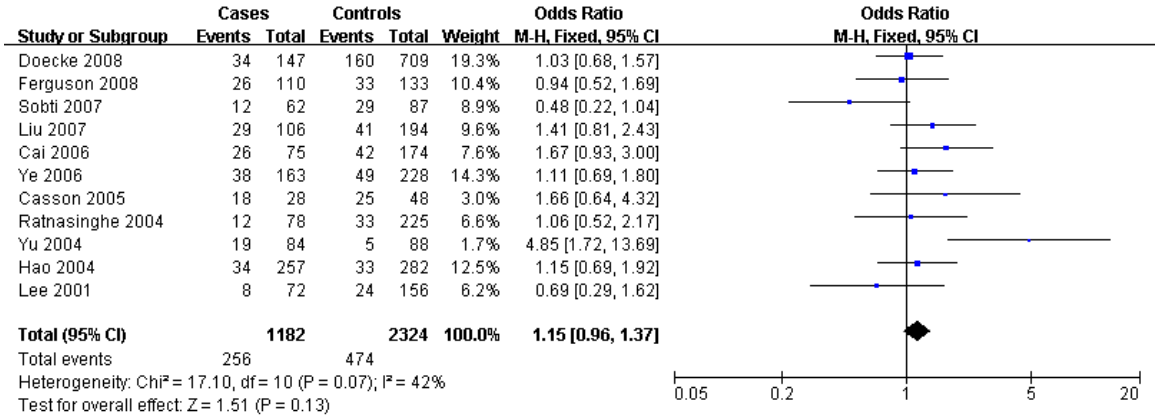
We established a database according to the extracted information from each article. **Table 1** lists the cancer type of the studies, ethnicity of the study populations, and the number of cases and controls for each of the studied *XRCC1* SNPs. All 11 case-control studies had data for Arg^{399}Gln, but only five for Arg^{194}Trp and two for Arg^{280}His. In terms of histology, four studies investigated esophageal adenocarcinoma, six investigated squamous cell carcinoma and one investigated both adenocarcinoma and squamous cell carcinoma [22]. Seven studies indicated that the frequency distributions of genotypes in the cases and controls were consistent with the Hardy-Weinberg equilibrium (HWE), whereas one study from Sweden showed a significant deviation from HWE [22]. Since another three studies did not provide HWE information [23-25], we calculated the expected distribution using the observed data and found one study significantly deviated from HWE (cases: χ^2=16.59, $P < 0.001$; controls: χ^2=11.89, $P < 0.001$) [23]. As for quality control of genotyping, all studies obtained DNA from peripheral blood, a classical polymerase chain reaction-restriction fragment length poly-morphism (PCR-RFLP) assay was used in eight (73%) of the studies, and the rest used other genotyping assays, such as nucleotide sequencing, MALDI mass spectrometry and TaqMan allelic discrimination assay. All studies validated their data by duplicating or partly replicating the genotypes, except for three studies that did not provide this information [23, 26, 27].

Effects of individual alleles on EC risk

For *XRCC1* Arg^{399}Gln, the eligible studies included 3,306 cancer patients and 6,852 control subjects. **Figure 1** shows the cancer risks (ORs) associated with the *XRCC1* Gln/Gln genotype compared with the wild-type homozygote (Arg/Arg). Overall, there was no difference in cancer risk between individuals carrying the *XRCC1* Gln/Gln genotype and those carrying the Arg/Arg genotype (OR, 1.15; 95% CI, 0.96-1.37; $P = 0.07$ for heterogeneity). Similarly, no association with cancer risk was found in the dominant model (Gln/Gln+Arg/Gln versus Arg/Arg: OR, 0.98; 95% CI, 0.88-1.09; $P = 0.06$ for heterogeneity) or in the recessive model (Gln/Gln versus Arg/Arg+Arg/Gln: OR, 1.16; 95% CI 0.98-1. 37; $P = 0.14$ for heterogeneity) (data not shown).

For *XRCC1* Arg^{194}Trp, the eligible studies had 832 cancer patients and 1,418 controls for this locus. Overall, individuals carrying Trp^{194} allele did not have elevated cancer risks, compared with those carrying the wild-type

Comparison: Cancer risk and *XRCC1* SNPs in all subjects
Outcome: *XRCC1* codon 399 Gln/Gln vs. Arg/Arg



Outcome: *XRCC1* codon 194 Trp/Trp vs. Arg/Arg

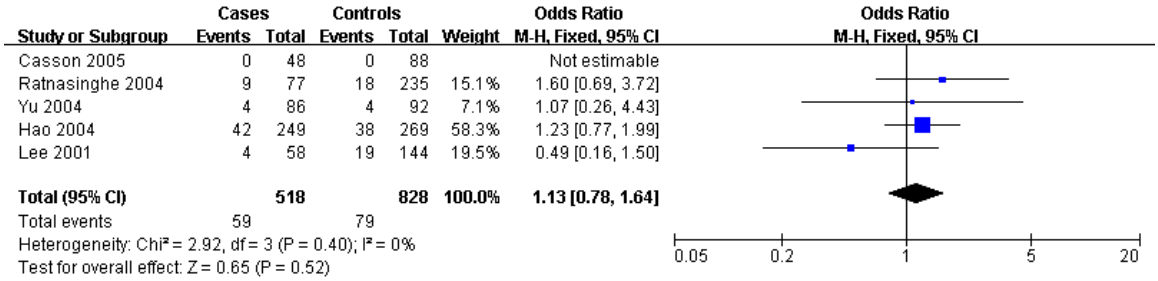


Figure 1. ORs (log scale) of EC associated with *XRCC1* codon 399 and codon 194 genotypes in a homozygote model, respectively. For each study, the estimate of OR and its 95% CI was plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

homozygous genotype (Trp/Trp versus Arg/Arg: OR, 1.13; 95% CI 0.78-1.64; *P* = 0.40 for heterogeneity) (**Figure 1**). Similarly, no association with cancer risk was found under a dominant model (Trp/Trp + Arg/Trp versus Arg/Arg: OR, 0.91; 95% CI 0.76-1.09; *P* = 0.64 for heterogeneity) or a recessive model (Trp/Trp versus Arg/Arg + Arg/Trp: OR, 1.21; 95% CI 0.85-1.74; *P* = 0.35 for heterogeneity) (data not shown).

For *XRCC1* Arg^{280}His, there were only two eligible studies including 520 cancer patients and 744 controls, both of which showed a non-significant association between the *XRCC1* Arg^{280}His SNP and EC risk (data not shown). The meta-analysis was not performed because of the limited data for this genetic variant.

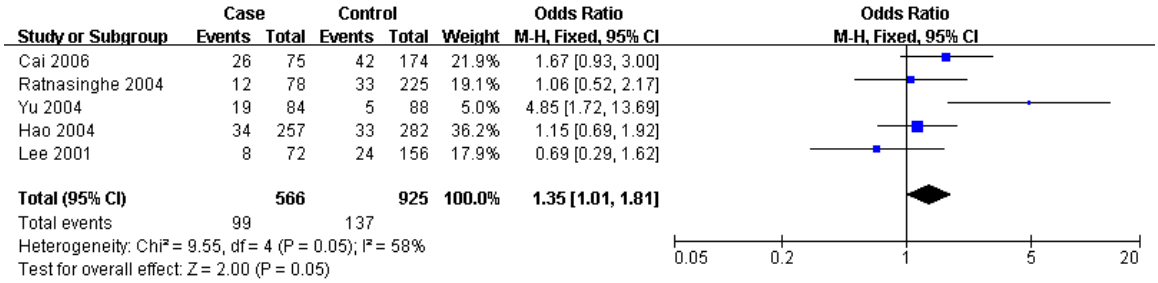
Effect of XRCC1 Arg^{399}Gln in stratified analysis

Because all 11 studies investigated the *XRCC1* codon 399 SNP, the sample size was reasonably large to allow us to perform stratified analysis by ethnicity and tumor type. We noticed that the frequencies of Arg or Gln allele among Asians and Caucasians varied [28]. In addition, esophageal adenocarcinoma and squamous cell carcinoma may differ in the etiology [29].

XRCC1 Arg^{399}Gln and EC risk by ethnicity

Because some studies did not clearly define the ethnicity of their study populations, we assumed the studies conducted in Western countries without ethnic specification as

Comparison: Cancer risk and the *XRCC1* codon 399 SNP in Chinese ethnicity
Outcome: Gln/Gln vs. Arg/Arg



Outcome: Gln/Gln vs Arg/Arg + Arg/Gln

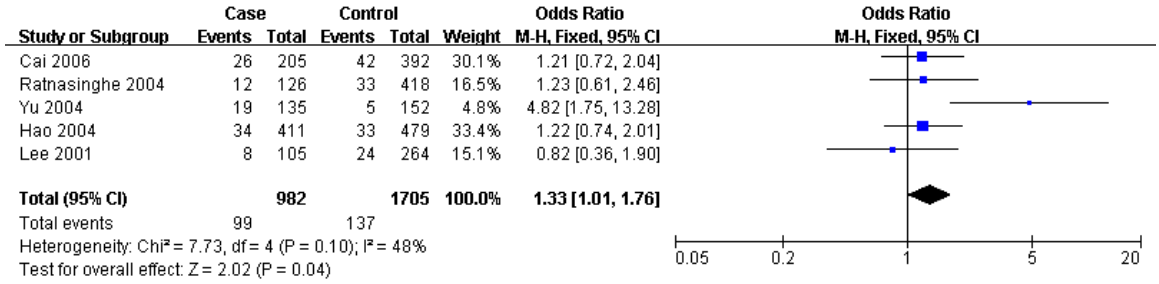


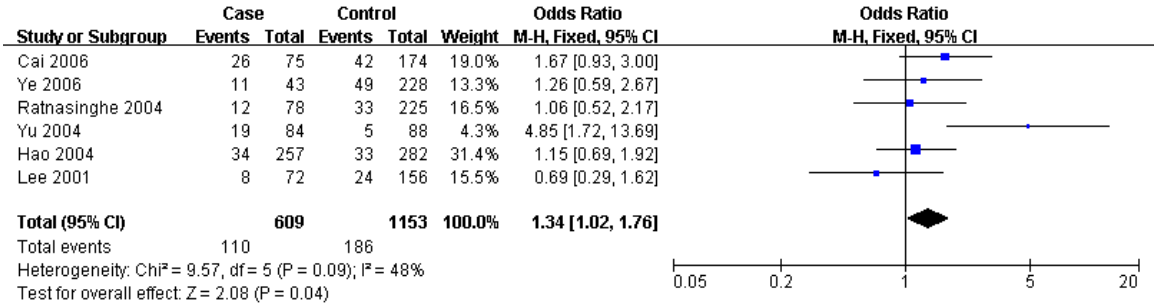
Figure 2. ORs (log scale) of EC associated with *XRCC1* codon 399 genotypes in homozygote and recessive models in Chinese ethnicity. For each study, the estimate of OR and its 95% CI was plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

"Caucasians". We evaluated the association between the *XRCC1* Arg^{399}Gln SNP and EC risk only in Chinese and Caucasian subjects. In Chinese subjects, the *XRCC1* Gln/Gln genotype was marginally associated with an increased risk of EC in a homozygote comparison (Gln/Gln versus Arg/Arg: OR, 1.35; 95% CI 1.01-1.81; *P* = 0.05 for heterogeneity) and in a recessive model (Gln/Gln versus Arg/Arg+Arg/Gln: OR, 1.33; 95% CI 1.01-1.76; *P* = 0.10 for heterogeneity) (**Figure 2**) but not in a dominant model (data not shown). In Caucasians, the *XRCC1* Gln allele was not associated with EC risk in any of the models tested (data not shown).

XRCC1 Arg^{399}Gln and EC risk by cancer histology

We dichotomized the 11 studies by tumor histology: adenocarcinoma and squamous cell carcinoma. A subgroup analysis did not find any association between the *XRCC1* Arg^{399}Gln SNP and EC risk in either squamous cell carcinoma or adenocarcinoma (data not shown) but showed substantial heterogeneity among the 7 studies of squamous cell carcinoma (*P* = 0.02). To identify the source of heterogeneity, we excluded the study by Cai *et al*, which showed a significant HWE deviation of the *XRCC1* Arg^{399}Gln; however, results were not changed (*P* = 0.02). Exclusion of the Sweden study showed an even increased heterogeneity (*P* = 0.009). There was one study from North India that showed some protective effect of the *XRCC1* Gln/Gln genotype among drinkers. After we excluded this Indian study, the heterogeneity decreased, and there appeared a significant association between the *XRCC1* Gln allele and risk of squamous cell carcinoma in either a homozygote comparison (Gln/Gln versus Arg/Arg: OR, 1.34; 95% CI 1.02-1.76; *P* = 0.09 for heterogeneity) or a recessive model

Comparison: Cancer risk and the *XRCC1* codon 399 SNP in squamous cell carcinoma
Outcome: Gln/Gln vs Arg/Arg



Outcome: Gln/Gln vs Arg/Arg+Arg/Gln

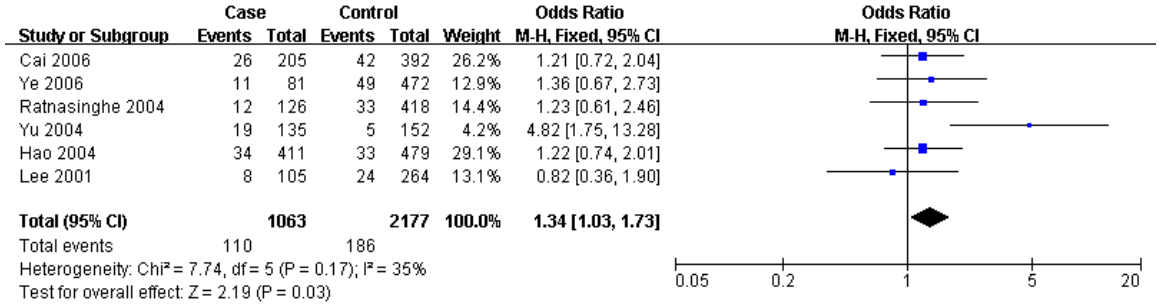


Figure 3. ORs (log scale) of EC associated with *XRCC1* codon 399 genotypes in homozygote and recessive models in squamous cell carcinoma, after excluding the study from India. For each study, the estimate of OR and its 95% CI was plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

(Gln/Gln versus Arg/Arg + Arg/Gln: OR, 1.34; 95% CI 1.03-1.73; *P* = 0.17 for heterogeneity) (**Figure 3**).

Publication bias

Finally, we performed funnel plots and the Egger's test to assess publication bias. In the funnel plot analysis, the shape of the funnel plot seemed symmetrical (**Figure 4**). An Egger's test did not detect any publication bias in comparison of Gln^{399} vs Arg^{399} (t = 0.60, *P* = 0.56) or Trp^{194} vs Arg^{194} (t = 0.71, *P* = 0.55). Therefore, there was no significant publication bias in the studies included in our analyses.

Discussion

In the present meta-analysis, we examined the association between *XRCC1* SNPs and EC risk, by critically reviewing all published studies, from which we selected 11 studies on *XRCC1* $Arg^{399}Gln$ genotypes (a total of 3,306 esophageal cancer patients and 6,852 controls) and five studies on *XRCC1* $Arg^{194}Trp$ genotypes (832 cancer cases and 1,418 controls). Our analysis did not find any association of *XRCC1* of $Arg^{399}Gln$ or $Arg^{194}Trp$ with EC risk in either the overall population or Caucasians for the allelic contrast. However, the $Arg^{399}Gln$ seemed to be associated with susceptibility to EC in Chinese populations, particularly for squamous cell carcinoma.

EC is a multifactorial disease that results from complex interactions between genetic and environmental factors. Therefore, it is of great value to identify high-risk individuals and provide early detection and intervention through population and clinical surveillance. Previous epidemiologic studies have validated a number of genetic variants, such as *ALDH2**1*2 and *CYP1A1* Val allele, that are associated with EC risk [30]. Recent

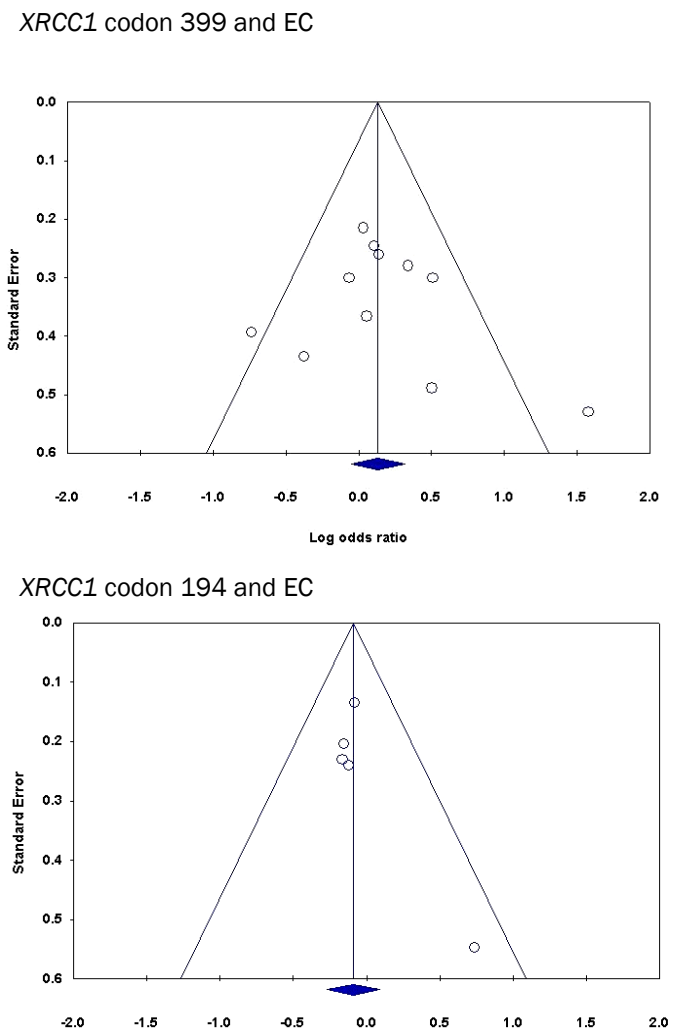


Figure 4. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association.

investigations have also provided some evidence of an association of the *XRCC1* Arg^{399}Gln SNP with increased EC risk, especially among Chinese populations [23, 27]. Studies among Caucasians, however, have consistently found no association, except for one study that showed a protective effect of the homozygous *XRCC1* Gln variant genotype against gastroesophageal reflux disease (GERD) and Barrett esophagus (BE) [31], the precursors of esophageal adenocarcinoma. Differential ethnical cancer susceptibility associated with the *XRCC1* Arg^{399}Gln SNP was also observed in previous meta-analyses of breast cancer, lung cancer and a pooled study of multiple tumor types [18, 28, 32], which suggests that Asians and Africans may be more likely than Caucasians to develop malignancies in the presence of the Gln^{399} allele. Although the underling mechanisms for such an ethnical difference in EC risk have not yet been elucidated, it has been found that the frequency of the variant Gln^{399} allele was significantly different among the three ethnic groups (Caucasian, 34.7%; Asian, 26.5%; African, 15.5%) [28], which is also observed in our current analysis (Caucasian, 36.3% and Chinese, 30.9%). Further large studies are needed to determine if the observed frequency differences in the *XRCC1* alleles by ethnicity have a biological influence or genetic effects on cancer susceptibility. Notably, Wu *et al.* reported that *XRCC1* Arg^{399}Gln SNP was significantly associated with absence of pathological complete response to radiation therapy and poor survival, suggesting that *XRCC1* Arg^{399}Gln polymorphism may be also a valuable biomarker of EC prognosis [33].

EC consists of two major subtypes, adenocarcinoma and squamous cell carcinoma, and each has distinct etiologic and pathologic characteristics [34]. Adenocarcinoma is more prevalent in Western countries, particularly in those who have suffered the gastroesophageal acid reflux, and it is preceded by esophageal metaplasia and induced by N-nitroso compounds through the mixing of salivary nitrates and gastric acid [35, 36]. Esophageal squamous cell cancinoma, however, is more prevalent in Asia and Africa, particularly in those who have the history of long-term smoking and/or heavy alcohol drinking, and it is preceded by esophageal epithelial dysplasia and shown to involve nitrosamine-induced tumorigenesis in rat esophageal tumor models [4]. Our analysis demonstrated that Gln^{399} allele elevated risk of esophageal squamous cell carcinoma in Chinese populations, which is consistent with previous reports indicating reduced DNA repair capacity associated with the *XRCC1* codon 399 Gln/Gln genotype [11-13]. The lack of influence of the *XRCC1* Arg^{399}Gln SNP on esophageal adenocarcinoma might be

explained by different patterns of genetic alterations in the tumors and less dependent on functions of *XRCC1* variants through gene-gene interactions. Our data also suggested that the study from the North Indian population should be considered separately, because it caused significant between-study heterogeneity in the analysis of squamous cell carcinoma. In that study, the *XRCC1* Gln/Gln genotype protected Indian drinkers from EC, but the underlying mechanisms remain unclear [26].

There are some limitations inherent in this kind of meta-analysis. First, selection bias could have influenced our analysis of Caucasian populations since we assumed the subjects were Caucasian in studies conducted in Western countries. In addition, the genotype distribution of the *XRCC1* Arg^{399}Gln SNP also showed a deviation from HWE in two studies [22, 23]. Second, each study had different eligibility criteria for inclusion of subjects and different sources of controls. For example, some studies were population-based, and some were hospital-based. The allele distribution in the hospital control groups might not have been representative of the general population. Third, the study population stratified by ethnicity was almost the same as that stratified by tumor histology, when the two studies from India and Sweden were excluded from the analysis. Therefore, the ethnicity and tumor histology may be mutual confounding factors, which are inseparable in this meta-analysis. Fourth, although an Egger's test did not reveal significant publication bias in current analysis, it is still possible that our findings are biased toward a positive result since negative results are less likely to be published. In addition, many non-English literatures, especially Chinese language literatures, are omitted, which may mask the true association of the *XRCC1* Arg^{399}Gln polymorphism with EC risk in this ethnicity. A time lag bias may also occur because new evidence may have arisen when this manuscript is in press. For example, Tse *et al.* recently presented a new report, showing the *XRCC1* Arg^{399}Gln polymorphism was not associated with esophageal adenocarcinoma risk in Caucasians [37], which was consistent with our conclusions but was not included in our analysis. Considering these limitations inherited from the published studies, our results should always be considered preliminary.

In conclusion, our meta-analysis did not find any evidence for an association between *XRCC1* Arg^{399}Gln and Arg^{194}Trp SNPs and EC risk in the overall populations, whereas there was evidence for an association between the *XRCC1* Gln^{399} variant allele and increased EC risk under the homozygote contrast and a recessive model among Chinese populations, particularly for squamous cell carcinoma. Larger studies with different ethnic populations and tumor histology are needed to clarify possible roles of *XRCC1* polymorphisms in the etiology of EC.

Acknowledgments

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