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Original Article

Association of XRCC3 gene rs861539 polymorphism with gastric cancer risk: evidence from a case-control study and a meta-analysis

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Abstract: The association between the X-ray repair cross-complementing group 3 (XRCC3) gene Thr241Met polymorphism (rs861539) and gastric cancer has been widely evaluated, but a definitive answer is so far lacking. We first conducted a case-control study to assess this association in a large Han Chinese population, and then performed a meta-analysis to further address this issue. Although our case-control association study and the following meta analysis involving 6,520 subjects indicated null association of XRCC3 gene rs861539 polymorphism between gastric cancer patients and controls under both allelic (odds ratio (OR) = 1.02; 95% confidence interval (CI): 0.91-1.14; *P* = 0.739) and dominant (OR = 0.97; 95% CI: 0.78-1.21; *P* = 0.803) models. Stratified analysis by ethnicity demonstrated a significant association in Asians. We conclude that the XRCC3 gene rs861539 polymorphism was associated with the risk for gastric cancer in Asian populations.

Keywords: Gastric cancer, XRCC3, polymorphism, association, meta-analysis

Introduction

According to a recent survey, gastric cancer (GC) is the most frequently occurring cancer in the world with 989,600 new cases diagnosed annually [1]. It is widely accepted that GC is a complex multifactorial disease with masses of genetic and environmental factors contributing to its occurrence [2]. Studies have indicated that different individuals bear different GC risk even under similar environmental conditions [3]. Although great effort has been devoted to uncover the genetic underpinnings of GC, there is no consensus on how many genes and which genetic determinants are actually involved in its development.

The gene encoding X-ray repair cross-complementing group 3 (XRCC3) on chromosome 14q32.3, which functions in the homologous recombination repair of DNA cross-links [4], double-strand break [5] caused by normal metabolic processes and/or exposure to ionizing radiation, has been regarded as one of the most important DNA-repair genes. Inactivation of XRCC3 in human cells leads to two-fold greater sensitivity to DNA cross-linking agents, elevated chromosome aberrations and five to seven-fold increased endo-reduplication [6]. Moreover, a common polymorphism in XRCC3 gene at nucleotide 18607C/T (amino acid Thr241Met, rs861539) has drawn wide attention as its mutation is linked with an increased number of micronuclei in lymphocytes and relatively low DNA repair capacity [7]. Therefore, XRCC3 has been of considerable interest as a candidate susceptibility gene for various cancers. Many studies have attempted to associate XRCC3 gene rs861539 (Thr241Met) polymorphism with GC occurrence, the results, however, are not frequently repeatable. In retrospect, individual studies with small sample sizes that are known to have low statistical power limited the identification of genetic variability and yielded poor replication record [8, 9]. Moreover, this lack of reproducibility might also stem from discrepant genetic linings or lifestyle backgrounds.

To address this issue and derive a more precise estimation, in this study, we first decided to assess the association of rs861539 (Thr-

241Met) polymorphism of XRCC3 gene with GC risk in a large Han Chinese population. Then, given the accumulating data and to shed some light on current uncertain claims, we sought to conduct a comprehensive meta-analysis of this association from all English literature.

Methods

Study population

The study population included 448 unrelated GC patients and 602 cancer-free controls of Chinese Han population had been previously studied [10]. This study was approved by the Ethics Committee of Shanghai Jiaotong University School of Medicine, and was conducted according to the Declaration of Helsinki Principles. All subjects signed the written informed consent.

Genotyping

Blood samples (1 mL) were collected, and genomic DNA was extracted from white blood cells using the TIANamp Blood DNA Kit (Tiangen Biotect [Beijing] Co., LTD). Genotyping was conducted using the PCR-LDR (ligase detection reactions) method by ABI 9600 system (Applied Biosystems, USA) [11]. Cycling parameters were as the following: 94°C for 2 min; 35 cycles of 94°C for 15 s; 60°C for 15 s; 72°C for 30 s; and a final extension step at 72°C for 5 min. Two specific probes to discriminate the specific bases and one common probe were synthesized (available upon request). The common probe was labeled at the 3' end with 6-carboxyfluorescein and phosphorylated at the 5' end. The reacting conditions of LDR were: 94°C for 2 min, 20 cycles of 94°C for 30 s and 60°C for 3 min. After reaction, 1 mL LDR reaction products were mixed with 1 mL ROX passive reference and 1 mL loading buffer, and then denatured at 95°C for 3 min, and chilled rapidly in ice water. The fluorescent products of LDR were differentiated using ABI sequencer 377 (Applied Biosystems, USA).

Statistical analysis

Comparisons between GC patients and controls were conducted by unpaired t-test for continuous variables and by χ^2 test for categorical variables. To avoid gross genotyping error, Thr241Met polymorphism was checked for consistency with Hardy-Weinberg equilibrium by χ^2 test. Genotypes were compared by conditional logistic regression analysis under assumptions of additive, dominant and recessive models of inheritance, respectively. Statistical significance was accepted as $P < 0.05$.

Meta analysis

Search strategy for identification of studies

PubMed and EMBASE databases were screened for articles published before July 20, 2014 using the Boolean combinations of subjects terms (XRCC3 OR rs861539) AND (gastric cancer OR carcinoma OR neoplasm) AND (polymorphism OR allele OR genotype OR variant OR variation). Articles were restricted to English or Chinese-language and human studies. The full text of the retrieved articles was scrutinized to decide whether information on the topic of interest was included. Reference lists of these retrieved articles and systematic reviews were also checked to determine whether citations of articles that were not initially identified. For these articles involving more than one geographic or ethnic heterogeneous groups, each was treated separately.

Articles were included in this meta-analysis if they examined the hypothesis that XRCC3 gene rs861539 polymorphism was associated with GC, if they followed a case-control or cross-sectional study design, and if they provided sufficient information on rs861539 (Thr241Met) genotype counts between GC patients and controls for determining an estimate of odds ratio (OR) and its corresponding 95% confidence interval (95% CI). Where there were multiple articles from the same study population, the most complete and recent results were extracted.

In this meta-analysis, we assessed the association between rs861539 241 Thr allele and GC risk with respect to 241Met (241Thr versus 241Met: allelic model), as well as the homozygous comparison (241Thr/Thr versus 241Met/Met), the dominant genetic model (241Thr/Thr + 241Thr/Met versus 241Met/Met), and the recessive genetic model (241Thr/Thr versus 241Thr/Met + 241Met/Met). Irrespective of between-study heterogeneity, the random-effects model using the DerSimonian & Laird method was implemented to bring the individual effect-size estimates together, and the estimate of heterogeneity was taken from the Mantel-Haenszel model [12]. Unadjusted OR and 95% CI were used to compare genetic contrasts between patients and controls. Satis-

Table 1. Alleles and genotype distributions of XRCC3 gene rs861539 (Thr241Met) polymorphism between cases (n = 440) and controls (n = 602)

Status	Thr241Met genotypes (number)			Thr241Met alleles (%)	
	Thr/Thr	Thr/Met	Met/Met	Thr	Met
Cases	389	50	1	94.09	5.91
Controls	549	52	1	95.52	4.48
	χ^2 = 2.1983; *P* = 0.2987			χ^2 = 2.1356; *P* = 0.1439	
Additive model (a)		Dominant model (a)		Recessive model (a)	
0.74; 0.50-1.10; 0.142		0.73; 0.05-11.71; 0.824		0.74; 0.49-1.10; 0.139	

P-values were calculated using χ^2-test from a series of 3 × 2 contingency tables for genotype data and 2 × 2 contingency tables for allele data. (a) Data are expressed as odds ratio; 95% confidence interval; *P*-values for genetic modes of inheritance.

faction of rs861539 genotypes with Hardy-Weinberg proportions was performed using the χ^2 test or Fisher's exact test in control groups.

Between-study heterogeneity was assessed by the inconsistency index I^2 statistic (ranging from 0 to 100%), which was documented for the percentage of the observed between-study variability due to heterogeneity rather than chance, with higher values suggesting the existence of heterogeneity [13, 14]. In the case of between-study heterogeneity, we examined the study characteristics that can stratified the studies into subgroups with homogeneous effects. In addition, to estimate the extent to which one or more covariates explain heterogeneity, meta-regression, as an extension to random-effects meta-analysis, was employed.

The funnel plots and Egger regression asymmetry test were used to assess publication bias. Egger's test can detect funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision.

Probability less than 0.05 was judged significant with the exception of the I^2 statistic and Egger's test, where a significance level of less than 0.1 was chosen. Data management and statistical analyses were conducted using STATA version 11.0 for Windows.

Results

Single-locus analysis

The success rates of genotyping for Thr-241Met polymorphism were 98.21% and 100% in patients and controls, respectively. Genotype distributions of examined polymorphism respected Hardy-Weinberg equilibrium in controls ($P > 0.05$). There was no significant difference in the genotype and allele distributions of Thr241Met polymorphism between GC and controls, and this non-significance was also mirrored under assumptions of the additive (OR = 0.74; 95% CI: 0.50-1.10; P = 0.142), dominant (OR = 0.73; 95% CI: 0.05-11.71; *P* = 0.824) and recessive (OR = 0.74; 95% CI: 0.49-1.10; *P* = 0.139) models (**Table 1**).

Search results

Based on our search strategy, the primary screening produced 18 potentially relevant articles, of which 9 met the inclusion criteria in an attempt to evaluate the association of XRCC3 gene rs861539 polymorphism with GC [15-23]. Therefore, 9 separate studies plus the present study encompassing a total of 2649 patients with GC and 3871 controls were finally meta-analyzed. Of these 10 study populations, 5 populations were conducted in Caucasians, 4 in Asians and one in Brazilians.

Study characteristics

The baseline characteristics of qualified studies are presented in **Table 2**. The overall rs861539 241Thr allele frequency was 73.94%/84.83% (patients/controls) in Asians, which was exceedingly higher than that in Caucasians (63.42%/62.30%) and Brazilians (69.06%/64.67%). Taking into account only the controls, genotype distributions were in Hardy-Weinberg equilibrium for all qualified studies.

Overall analysis

After combining all qualified studies, we found null association of XRCC3 gene Thr241Met polymorphism with GC under both allelic (OR = 0.89; 95% CI: 0.65-1.24; *P* = 0.504) and dominant (OR = 0.89; 95% CI: 0.57-1.39; *P* = 0.600)

Table 2. The baseline characteristics of all eligible studies

References	Ethnicity	Country	Sources of Con.	Number of Ca.	Number of Con.	Thr/Thr Ca./Con.	Thr/Met Ca./Con	Met/Met Ca./Con	MAF (%) Ca/Con	HWE
Duarte MC (2005)	Others	Brazil	HCC	160	150	84/67	53/60	23/23	69.06/64.67	> 0.05
Huang WY (2005)	Caucasian	Poland	PCC	281	390	128/174	128/163	25/53	68.33/65.51	> 0.05
Huang GP (2006)	Asian	China	HCC	309	188	149/112	135/66	25/10	70.06/77.13	> 0.05
Ye W (2006)	Caucasian	Sweden	PCC	126	472	52/203	63/218	11/51	66.27/66.10	> 0.05
Ruzzo A (2007)	Caucasian	Italy	PCC	90	121	35/36	44/66	11/19	63.33/57.02	> 0.05
Palli D (2010)	Caucasian	Italy	PCC	294	546	95/189	148/268	51/89	57.48/59.16	> 0.05
Canbay E (2010)	Caucasian	Turkey	HCC	40	247	16/74	19/146	5/27	63.75/59.51	> 0.05
Zhao L (2011)	Asian	China	HCC	721	989	257/635	321/274	143/80	57.91/78.06	> 0.05
Hu WG (the present study)	Asian	China	HCC	440	602	389/549	50/52	1/1	94.09/95.52	> 0.05

Abbreviations: HCC = Hospital-based case-control study; PCC = Population-based case-control study; Ca = Case; Con = Control; HW = Hardy-Weinberg equilibrium in the control group; MAF = minor allele frequency.

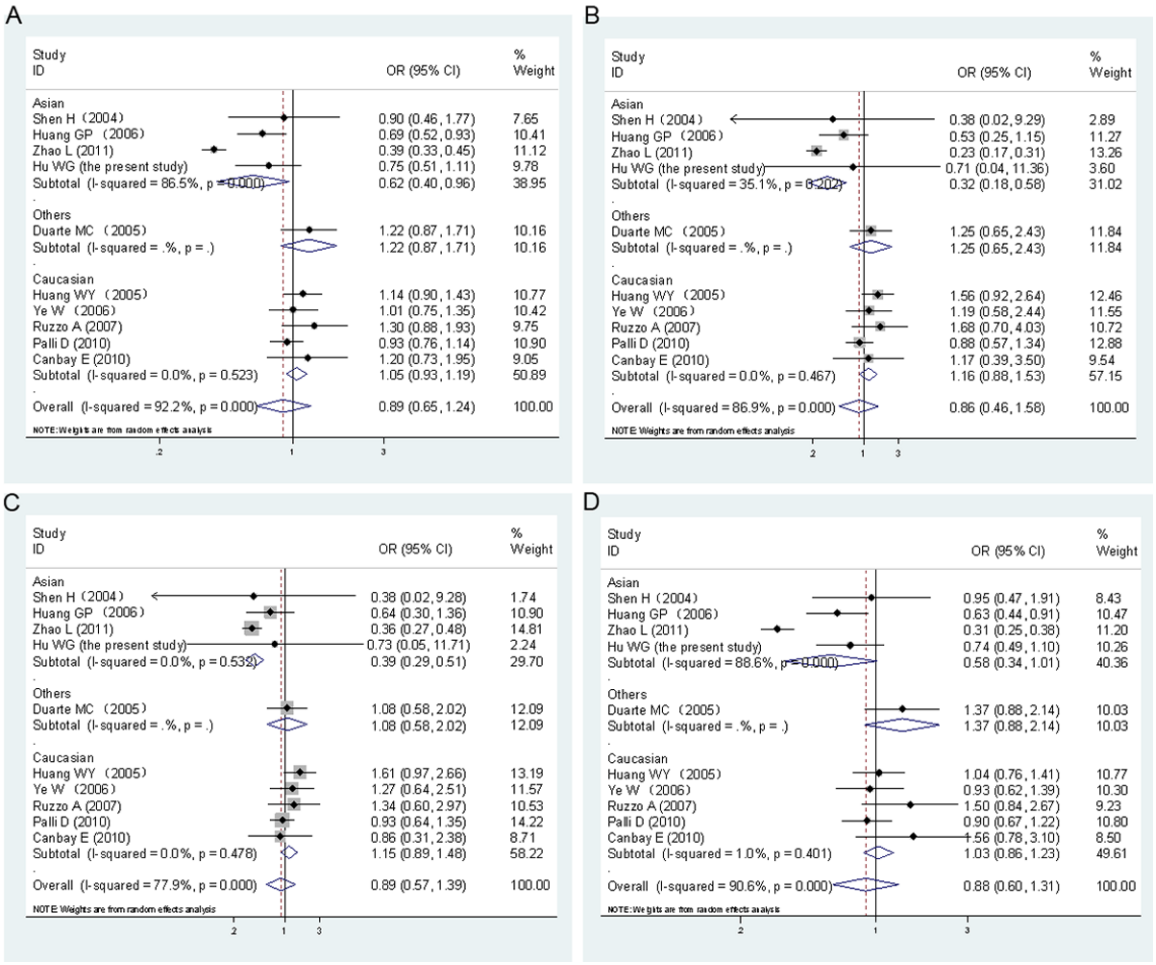

Figure 1. Subgroup analysis of XRCC3 gene rs861539 polymorphism for gastric cancer by ethnicity in the allelic (A), homozygous (B), dominant (C) and recessive (D) models.

models, and this association suffered from significant evidence of heterogeneity between studies (allelic and dominant models: I^2 = 92.2% and 77.9%). However, there was low probability of publication bias for both models (P_{Egger} = 0.055 and 0.184).

Subgroup analysis

To evaluate the possible effect of study design on the variability of overall estimates, the studies were divided into population-based and hospital-based studies. The magnitude of asso-

Table 3. Overall and subgroup analysis of XRCC3 gene rs861539 (Thr241Met) polymorphism and gastric cancer

Subgroup	Study number	Thr vs Met				Thr/Thr vs Met/Met				Dominant				Recessive			
		OR (95% CI)	*P*	I^2 (%)	phetero-geneity	OR (95% CI)	*P*	I^2 (%)	phetero-geneity	OR (95% CI)	*P*	I^2 (%)	phetero-geneity	OR (95% CI)	*P*	I^2 (%)	phetero-geneity
Total	10	0.89 (0.65, 1.24)	0.504	92.2	0.08	0.86 (0.46, 1.58)	0.624	86.9	< 0.001	0.89 (0.57, 1.39)	0.600	77.9	< 0.001	0.88 (0.60, 1.31)	0.538	90.6	< 0.001
Ethnicity																	
Asians	4	0.62 (0.40, 0.96)	0.033	86.5	< 0.001	0.32 (0.18, 0.58)	< 0.001	35.1	0.202	0.39 (0.29, 0.51)	< 0.001	0	0.532	0.58 (0.34, 1.01)	0.054	88.6	< 0.001
Caucasians	5	1.05 (0.93, 1.19)	0.432	0	0.523	1.16 (0.88, 1.53)	0.281	0	0.467	1.15 (0.89, 1.48)	0.280	0	0.478	1.03 (0.86,1.23)	0.735	1.0	0.401
Others	1	1.22 (0.87, 1.71)	0.245	/	/	1.25 (0.65, 2.43)	0.503	/	/	1.08 (0.58, 2.02)	0.813	/	/	1.37 (0.88, 2.14)	0.168	/	/
Study design																	
HCC	5	0.77 (0.46, 1.28)	0.307	93.0	< 0.001	0.62 (0.25, 1.56)	0.309	85.7	< 0.001	0.64 (0.36, 1.14)	0.132	67.5	0.015	0.76 (0.40, 1.44)	0.404	93.0	< 0.001
PCC	5	1.04 (0.91, 1.18)	0.578	0	0.542	1.15 (0.87, 1.54)	0.324	1.1	0.400	1.16 (0.90, 1.51)	0.256	0	0.457	1.00 (0.84, 1.19)	0.981	0	0.631

Abbreviations: HCC = Hospital-based case-control study; PCC = Population-based case-control study; OR = odds ratio; CI = confidence interval.

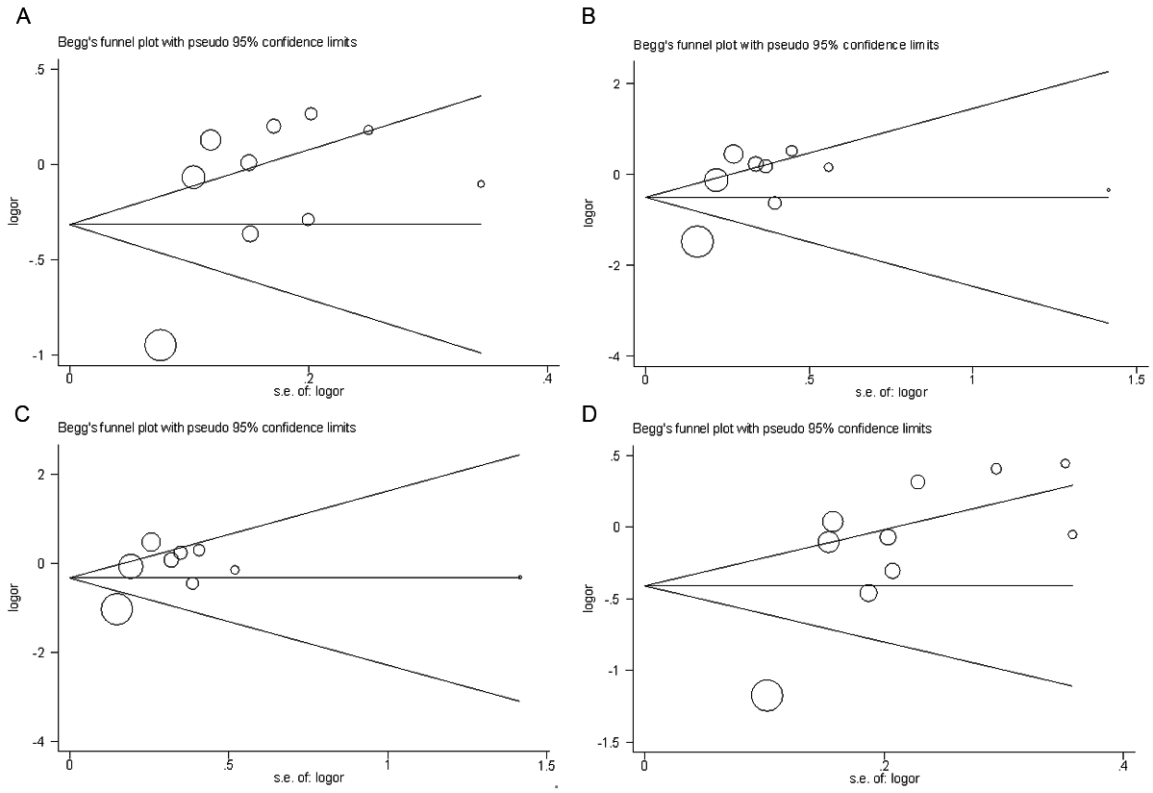

Figure 2. Funnel plots for studies investigating the effect of XRCC3 gene rs861539 polymorphism on gastric cancer risk across the allelic (A), homozygous (B), dominant (C) and recessive (D) models.

ciation in population-based studies was higher than the overall estimate for rs861539 polymorphism across all genetic models. Contrastingly, the magnitude of association in hospital-based studies was consistently weakened across all genetic models (**Table 3**). However, no significant association was detected in the comparison between hospital-based group and population-based group.

Further stratification by ethnicity supported the protective profiles of rs861539 241Thr allele and Thr/Thr genotype on GC in Asians in all genetic models, but a weak and nonsignificant risk tendency was identified in Caucasians (**Figure 1**).

Publication bias

As reflected by the funnel plots (**Figure 2**) and the corresponding Egger's test, there was a low probability of publication bias for the polymorphism examined.

Discussion

XRCC3, coding the key protein of DNA double-strand break/ recombination repair pathway, is the crucial gene involved in the homologous recombination repair mechanism. With respect to the important roles of XRCC3 in the DNA repair, it is biologically plausible that XRCC3 genetic polymorphism may modulate the risk of various cancers. As for the XRCC3 rs861539 polymorphism with cancer risk, Yu et al. [24] conducted a meta-analysis to confirm that XRCC3 Thr241Met polymorphism contributes to the risk of thyroid cancer, A meta-analysis of nine case-control studies suggested that the XRCC3 Thr241Met polymorphism was significantly associated with the risk of gliomas [25]. A meta-analysis of five case-control studies suggested h XRCC3 Thr241Met polymorphism is associated with cervical cancer risk among East Asians [26]. Although numerous studies have regarded XRCC3 gene rs861539 polymorphism as a promising candidate for GC, our case-control study in Han Chinese population, along with the meta-analysis, failed to confirm this relation. This non-significance was also in accordance with previous meta result, although the previous analysis only included six studies with small study samples [27]. To our knowledge, this is the most comprehensive meta-

analysis investigating the genetic susceptibility of XRCC3 gene rs861539 polymorphism to GC.

Some aspects of the current meta-analysis need to be considered to appreciate the findings. First, this is to date the largest synthesis exploring the association of XRCC3 gene rs861539 polymorphism with GC. Second, the results of the present case-control study were in line with that of the corresponding meta-analysis. Third, our results are less prone to selection bias in view of low probability of publication bias.

In addition, ethnicity was regarded as a potential source of between-study heterogeneity by subgroup analysis. After stratifying studies into Caucasians, Asians and other population studies, we observed that polymorphism rs861539 displayed reverse association with GC across all genetic models between Asians and non-Asians. Moreover, we noticed striking differences in terms of rs861539 241Thr allele frequency between Asians (73.94%/84.83% in patients/controls) and non-Asians, with the former exceedingly higher than that in Caucasians (63.42%/62.30%) and Brazilians (69.06%/64.67%), suggesting that different genetic backgrounds may cause this discrepancy or different populations may have different linkage disequilibrium patterns. However, the situation is not rare. We have found similar phenomenon in previous studies in inflammatory disease [28] and cancerous disease [10]. A polymorphism may be in close linkage with another nearby causal variant in one ethnic population but not in another [29]. The XRCC3 gene rs861539 polymorphism may be in close linkage with different nearby causal variants in different populations. It is therefore reasonable to speculate that if involved, rs861539 polymorphism may have pleiotropic effects on the etiology of gastric carcinogenesis cross different races or ethnic groups. In view of the divergent genetic backgrounds, it is necessary to construct a database of polymorphisms related to GC in each ethnic group.

Despite the clear strengths of our study including large sample sizes, and low possibility of publication bias across all genetic models, interpretation of our current study, however, should be viewed in light of several technical limitations. First, all of the studies in this meta-analysis were case-control studies, which are susceptible to selection bias by including only nonfatal cases. Second, because only published studies were retrieved in this meta-analysis and the "grey" literature (articles in languages other than English or Chinese) was not included, publication bias might be possible, even though our funnel plots and statistical tests did not show it. Third, the single-locus-based nature of meta-analysis precluded the possibility of gene-gene and gene-environment interactions, as well as haplotype-based effects, suggesting that additional studies assessing these aspects will be necessary. Furthermore, we only centered on XRCC3 gene rs861539 polymorphism, and did not covered other candidate genes or polymorphisms. It seems likely that the polymorphism rs861539 individually makes a moderate contribution to risk prediction in GC patients, but whether this polymorphism integrated with other risk factors will enhance the prediction requires additional research. Moreover, due to the relative small number of some studies or lack of necessary information, we were unable to perform further subgroup analyses upon various confounding factors such as smoking and drinking. Thus, the jury must refrain from drawing a conclusion until large, well-performed studies confirm or refuse our results.

Taken together, we expand previous single studies on GC by suggesting that XRCC3 gene rs861539 polymorphism might contribute to the occurrence of GC in Asians but not in other populations. Also our observations leave open the question regarding the pleiotropic effects of rs861539 in different ethnic populations. Further studies should investigate XRCC3 gene adjacent markers to confirm whether the present association is causal or due to linkage disequilibrium.

Disclosure of conflict of interest

None.

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References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.

[2] Lochhead P and El-Omar EM. Gastric cancer. Br Med Bull 2008; 85: 87-100.
[3] Zabaleta J. Multifactorial etiology of gastric cancer. Methods Mol Biol 2012; 863: 411-435.
[4] Risch N and Merikangas K. The future of genetic studies of complex human diseases. Sci 1996; 273: 1516-1517.
[5] Khanna KK and Jackson SP. DNA double-strand breaks: signaling, repair and the cancer connection. Nat Genet 2001; 27: 247-254.
[6] Griffin CS. Aneuploidy, centrosome activity and chromosome instability in cells deficient in homologous recombination repair. Mutat Res 2002; 504: 149-155.
[7] Aka P, Mateuca R, Buchet JP, Thierens H and Kirsch-Volders M. Are genetic polymorphisms in OGG1, XRCC1 and XRCC3 genes predictive for the DNA strand break repair phenotype and genotoxicity in workers exposed to low dose ionising radiations? Mutat Res 2004; 556: 169-181.
[8] Wang Z, Hu J and Zhong J. Meta-analysis of the NAD(P)H: quinine oxidoreductase 1 gene 609 C > T polymorphism with esophageal cancer risk. DNA Cell Biol 2012; 31: 560-567.
[9] Wang Z, Hu J, Fan R, Zhou J and Zhong J. Association between CD14 gene C-260T polymorphism and inflammatory bowel disease: a meta-analysis. PLoS One 2012; 7: e45144.
[10] Hu WG, Hu JJ, Cai W, Zheng MH, Zang L, Wang ZT and Zhu ZG. The NAD(P)H: quinine oxidoreductase 1 (NQO1) gene 609 C > T polymorphism is associated with gastric cancer risk: evidence from a case-control study and a meta-analysis. Asian Pac J Cancer Prev 2014; 15: 2363-2367.
[11] Wang ZT, Hu JJ, Fan R, Zhou J and Zhong J. RAGE gene three polymorphisms with Crohn's disease susceptibility in Chinese Han population. World J Gastroenterol 2014; 20: 2397-2402.
[12] Cohn LD and Becker BJ. How meta-analysis increases statistical power. Psychol Methods 2003; 8: 243-253.
[13] Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
[14] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[15] Shen H, Wang X, Hu Z, Zhang Z, Xu Y, Hu X, Guo J and Wei Q. Polymorphisms of DNA repair gene XRCC3 Thr241Met and risk of gastric cancer in a Chinese population. Cancer Lett 2004; 206: 51-58.
[16] Huang WY, Chow WH, Rothman N, Lissowska J, Llaca V, Yeager M, Zatonski W and Hayes RB. Selected DNA repair polymorphisms and gastric cancer in Poland. Carcinogenesis 2005; 26: 1354-1359.
[17] Duarte MC, Colombo J, Rossit AR, Caetano A, Borim AA, Wornrath D and Silva AE. Polymorphisms of DNA repair genes XRCC1 and XRCC3, interaction with environmental exposure and risk of chronic gastritis and gastric cancer. World J Gastroenterol 2005; 11: 6593-6600.
[18] Ye W, Kumar R, Bacova G, Lagergren J, Hemminki K, Nyrén O. The XPD 751GIn allele is associated with an increased risk for esophageal adenocarcinoma: a population-based case-control study in Sweden. Carcinogenesis 2006; 27: 1835-1841.
[19] Huang GP, Zheng ZL and Cai L. DNA repair gene XRCC3 Thr241Met polymorphism and susceptibility to cardia and non-cardia gastric cancer: a case-control study. Zhonghua Liu Xing Bing Xue Za Zhi 2006; 27: 420-423.
[20] Ruzzo A, Canestrari E, Maltese P, Pizzagalli F, Graziano F, Santini D, Catalano V, Ficarelli R, Mari D, Bisonni R, Giordani P, Giustini L, Lippe P, Silva R, Mattioli R, Torresi U, Latini L and Magnani M. Polymorphisms in genes involved in DNA repair and metabolism of xenobiotics in individual susceptibility to sporadic diffuse gastric cancer. Clin Chem Lab Med 2007; 45: 822-828.
[21] Canbay E, Agachan B, Gulluoglu M, Isbir T, Balik E, Yamaner S, Bulut T, Cacina C, Eraltan IY, Yilmaz A and Bugra D. Possible associations of APE1 polymorphism with susceptibility and HOGG1 polymorphism with prognosis in gastric cancer. Anticancer Res 2010; 30: 1359-1364.
[22] Palli D, Polidoro S, D'Errico M, Saieva C, Guarrera S, Calcagnile AS, Sera F, Allione A, Gemma S, Zanna I, Filomena A, Testai E, Caini S, Moretti R, Gomez-Miguel MJ, Nesi G, Luzzi I, Ottini L, Masala G, Matullo G and Dogliotti E. Polymorphic DNA repair and metabolic genes: a multigenic study on gastric cancer. Mutagenesis 2010; 25: 569-575.
[23] Zhao L, Long XD, Yao JG, Wang C, Ma Y, Huang YZ, Li YQ, Wang MF and Fu GH. Genetic polymorphism of XRCC3 codon 241 and Helicobacter pylori infection-related gastric antrum adenocarcinoma in Guangxi Population, China: a hospital-based case-control study. Cancer Epidemiol 2011; 35: 564-568.
[24] Yu XL, Liu H, Wang B, Fu ZJ, Yuan Y, Yan SL, Zhao WJ, Wang YG and Cai J. Significant associations between X-ray repair cross-complementing group 3 genetic polymorphisms and thyroid cancer risk. Tumour Biol 2014; 35: 2009-2015.
[25] Liang HJ, Yan YL, Liu ZM, Chen X, Peng QL, Wang J, Mo CJ, Sui JZ, Wu JR, Zhai LM, Yang S,

Li TJ, Li RL, Li S and Qin X. Association of XRCC3 Thr241Met polymorphisms and gliomas risk: evidence from a meta-analysis. Asian Pac J Cancer Prev 2013; 14: 4243-4247.

[26] Qin LY, Chen X, Li P, Yang Z and Mo WN. Association between the XRCC3 Thr241Met polymorphism and cervical cancer risk: a meta-analysis. Asian Pac J Cancer Prev 2013; 14: 6703-6707.

[27] Fang F, Wang J, Yao L, Yu XJ, Yu L and Yu L. Relationship between XRCC3 T241M polymorphism and gastric cancer risk: a meta-analysis. Med Oncol 2011; 28: 999-1003.

[28] Wang L, Wang ZT, Hu JJ, Fan R, Zhou J and Zhong J. Polymorphisms of the vitamin D receptor gene and the risk of inflammatory bowel disease: a meta-analysis. Genet Mol Res 2014; 13: 2598-2610.

[29] Yu K, Zhang J, Zhang J, Dou C, Gu S, Xie Y, Mao Y and Ji C. Methionine synthase A2756G polymorphism and cancer risk: a meta-analysis. Eur J Hum Genet 2010; 18: 370-378.