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Original Article

Association between three *XRCC1* polymorphisms and susceptibility to pancreatic cancer

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Abstract: The X-ray repair cross-complementing 1 gene (*XRCC1*) is involved in the repair of single-strand breaks in DNA, induced by ionizing radiation and alkylating agents. Association between *XRCC1* polymorphisms and susceptibility to pancreatic cancer has been inconsistent. To address this, the present updated meta-analysis was conducted. The maximum range of databases were searched for studies reporting on the association between susceptibility to pancreatic cancer and three *XRCC1* polymorphisms, published from January 1, 2006, to August 1, 2017. The strength of associations was applied to calculate odds ratios with 95% confidence intervals. Based on present search criteria, nine reports, including 11 case-control studies, were identified as acceptable. Results of the *Q*-test revealed a positive association between the *rs1799782 C/G* polymorphism and susceptibility to pancreatic cancer in both the total population and population of European descent. However, results of the *H*-test did not show any association. Furthermore, both *rs139599857 G/A* and *rs72554204 T/C* polymorphisms were found to be negatively associated with susceptibility to pancreatic cancer. The current study suggests that two *XRCC1* polymorphisms are potentially associated with pancreatic cancer risk. Further studies, with larger sample sizes and gene-environment interactions, should be conducted to confirm present results.

Keywords: X-ray repair cross-complementing 1, pancreatic cancer, polymorphism, meta-analysis, susceptibility

Introduction

Pancreatic cancer (PC) is a common malignant cancer, with high mortality rates, worldwide, and a relative 5-year survival rate of less than 10% [1, 2]. It was estimated that 53,670 new cases of PC were diagnosed, with 43,090 PC-related deaths reported in the USA in 2017 [3]. These numbers are in line with statistics for China in 2015 ($90.1/10^5$ incidence and $79.4/10^5$ mortality) [4]. However, there remains a lack of clear understanding of the risk factors for development of PC. Sex, age, drinking, smoking, obesity, and diabetes mellitus may be possible risk factors for PC development [5-7]. In addition, a family history of PC has also been reported, suggesting that genetic factors may be involved in incidence of PC [8, 9]. Functional polymorphisms, such as *ERCC2 Lys751Gln*, *CLPTM1L-TERT rs401681*, and *OGG1 Ser326Cys*, have been confirmed to be associated with susceptibility to PC [10-12]. The present analysis focused on assessing polymorphisms in the X-ray repair cross-complementing 1 gene (*XRCC1*) and their association with susceptibility to PC.

XRCC1, also known as RCC or SCAR26 (Gene ID: 7515), located on chromosome 19, NC_000019.10 (43543312.43575578, complement) [13, 14], plays a role in base-excision repair (BER) pathways, which are responsible for repairing oxidative DNA damage. It is also involved in the single-strand break repair (SSBR) mechanism through its interaction with a complex of DNA repair proteins, such as DNA ligase III, polynucleotide kinase, and DNA polymerase β [15, 16]. Various *XRCC1* single nucleotide polymorphisms (SNPs), including *Arg194Trp, Arg280His, Arg399Gln, c.1254C > T, c.1517G > C, c.1471G > A, C310T, 539del542,* and *T1915C*, have been reported [17, 18]. Duell et al. (2008) [19] reported that the *XRCC1* allele, *Arg399Gln,* is a potentially important determinant of susceptibility to smoking-induced PC. Several reports with similar findings have been published. In addition, two meta-analyses [20, 21] of the *Arg194Trp* site (also called *rs1799782* or *R194W*) have been pub-

lished. However, neither established a positive association between the polymorphism and susceptibility to PC. Moreover, two large-scale case-control studies focusing on *Arg194Trp* in PC were conducted in 2016 [17, 22]. Association between *XRCC1* polymorphisms and susceptibility to PC remains unclear, however, warranting a meta-analysis of all available publications to analyze factors associated with susceptibility to PC. For two *XRCC1* SNPs, *-1517 C/G* (also called *rs139599857*) and *1471 T/C* (also called *rs72554204*), combined analysis of published studies has not yet been conducted.

Therefore, to determine the association between *XRCC1* polymorphisms *rs1799782, rs139599857*, and *rs72554204* and susceptibility to PC, the present meta-analysis of nine different studies was conducted, including 11 case-control studies [17, 22-29].

Methods

Search strategy

PubMed, Embase, Web of Science, Scopus, VIP Periodical, Cochrane Library, Google Scholar, and SinoMed (Chinese National Knowledge Infrastructure and China Biological Medicine Database-disc) databases were searched for studies published from 2006 to August 1, 2017. The following keywords were used: 'X-ray repair cross-complementing group 1' or 'XRCC1'; 'pancreatic cancer', 'carcinoma', or 'tumor'; and 'polymorphism' or 'variant'.

Inclusion and exclusion criteria

Inclusion criteria: (1) About the correlation between susceptibility to PC and each of the three *XRCC1* polymorphisms; (2) Involve case-control studies; and (3) Include a sufficient number of genotypes (TT + TC + CC for *rs1799782*, GG + GC + CC for *rs139599857*, and CC + TC + TT for *rs72554204*) both in cases and in controls. Exclusion criteria: (1) No control population; (2) Insufficient genotype frequency data; and/or (3) Duplications.

Data extraction

Extracted data included the name of the first author, year of publication, country of publication, ethnicity, total number of samples in case/control groups, number of each genotype in both case and control groups, HWE of the control group, and genotyping methods. Ethnicity was classified as 'European' or 'Asian'. Control groups were classified as population-based (PB) or hospital-based (HB) and the genotypes were classified as PCR-RFLP-based or non-PCR-RFLP-based. Based on the country of origin, all samples were categorized into 'China' and 'non-China' groups.

Statistical analysis

PolyPhen-2 and SIFT bioinformatic tools were used to predict the effects of *XRCC1* SNPs on translated proteins. For PolyPhen-2 analysis, scores could range from 0 to 1, with a score of zero indicating 'benign' and a score of one indicating 'probably damaging'. For SIFT analysis, scores of <0.05 indicated that an SNP could influence protein function. Based on genotype frequencies for the cases and controls, crude ORs with 95% CIs were used to measure the strength of association between each of the three *XRCC1* SNPs and susceptibility to PC. Statistical significance of the ORs was determined by the *Z*-test. Heterogeneity among the studies was evaluated with a χ^2-based *Q*-test. A *P*-value of > 0.10 in the *Q*-test indicates that there was no heterogeneity among studies. When significant heterogeneity was detected, a random-effects model was used for analysis. When there was no significant heterogeneity, a fixed-effects model was used for analysis [30, 31]. It is worth noting that the *Q*-test is easily affected by sample size, while the *H* and I^2 tests are not. They are adjusted to the degrees of freedom. Therefore, heterogeneity results obtained using these tests are relatively stable and powerful. In addition, these tests have been frequently applied in recent years. Therefore, this study used these two methods to compare differences between the studies. As a guide, an I^2 value of zero was considered as 'no heterogeneity', an I^2 value of < 25% was considered as 'low heterogeneity', an I^2 value of 25-50% was considered as 'moderate heterogeneity', and an I^2 value of > 75% was considered as 'high heterogeneity' [32]. On the other hand, H > 1.5 was considered as 'heterogeneity', H<1.2 was considered as 'homogeneity', while 1.2<H<1.5 and H = 1, at a 95% CI (α<0.05), may or may not be considered as 'heterogeneity' [33]. Furthermore, the *galbr*

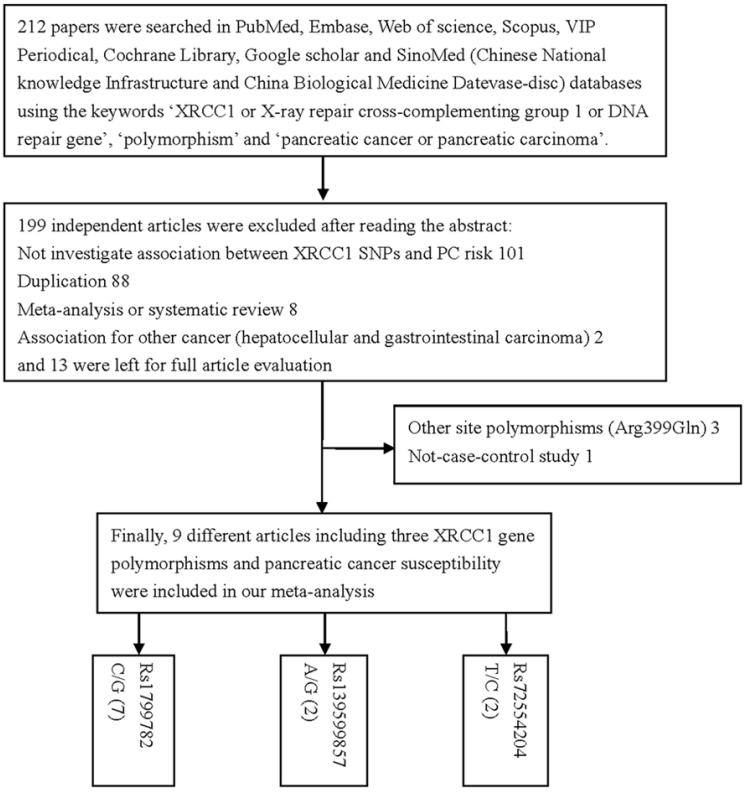

Figure 1. Flowchart illustrating the search strategy used to identify association studies for *XRCC1* gene polymorphisms and PC risk.

command was applied for plotting a Galbraith graph to identify studies that influenced heterogeneity [34]. This study assessed the association between *XRCC1* polymorphisms and susceptibility to PC using the allelic contrast, heterozygote comparison, and dominant genetic models. Sensitivity analysis was performed by excluding individual studies, one after another, to assess the stability of results. HWE for the controls was evaluated with Pearson's χ^2 test and $P<0.05$ indicates significance [35]. Publication bias was investigated using Egger's linear regression method and funnel plots. In addition to Egger's test, publication bias was assessed with Begg's test, wherein $P<0.05$ indicates significance [36]. All statistical tests for this meta-analysis were performed using version 10.0 of Stata software (StataCorp LP, College Station, TX, USA).

Results

Study characteristics

Using various combinations of key terms, a total of 212 publications were identified from public databases. As shown in **Figure 1**, after screening the abstracts, 199 publications were excluded from analysis for the following reasons: Duplications (88), meta-analyses or systematic reviews (8), publications exploring the association between PC and other types of cancer (2), and publications not investigating the association between *XRCC1* SNPs and susceptibility to PC (101). Full texts of the remaining publications were then evaluated. Four additional publications were then excluded. Three dealt with other *XRCC1* polymorphisms and one did not have a case-control group. Finally, nine publications [17, 22-29] were chosen for the meta-analysis, consisting of seven studies on *rs1799782*, two on *rs139599857*, and two on *rs72554204* (**Table 1**). Data was extracted from these publications and a systematic meta-analysis of the data was performed, aiming to explore the association between three *XRCC1* polymorphisms, *rs1799782, rs139599857*, and *rs72554204*, and susceptibility to PC.

For the *rs1799782 C/T* site, 1,594 cases and 3,517 healthy controls were evaluated. To evaluate the quality of data, the minor allele frequency (MAF) was assessed for *XRCC1* in the five main world populations in the 1000 Genomes Browser: East Asian (EAS), 0.2817; European (EUR), 0.0517; African (AFR), 0.0719; American (AMR), 0.1167; and South Asian (SAS), 0.1104 (**Figure 2A**). MAF values were 0.1916 and 0.2263 in the case and control groups, respectively, both of which were lower than results obtained from the 1000 Genomes Browser database. For the *rs139599857 G/A* site, 688 cases and 690 controls were evaluated. For the *rs72554204 T/C* site, 626 cases and 648 controls were evaluated. MAF values for these two SNPs, obtained from the 1000 Genomes Browser database, are shown in **Figure 2B** and **2C**. Apart from the control groups of two of the studies [17, 22], the distribution of

Table 1. Basic information for included studies of the association between three polymorphisms in *XRCC1* gene and pancreatic cancer susceptibility

Author/SNP	Year	Country (1)	Country (2)	Ethnicity	Case	Control	SOC	Case			Control				Genotype (1)	Genotype (2)
rs1799782								TT	TC	CC	TT	TC	CC	HWE		
Yan	2013	China	China	Asian	210	213	HB	12	83	115	7	63	143	0.984	SNaPshot	Non-PCR-RFLP
Wang	2006	China	China	Asian	101	337	HB	8	47	46	27	154	156	0.193	PCR-RFLP	PCR-RFLP
Wang	2016	China	China	Asian	152	264	HB	10	33	109	10	54	200	0.014	PCR-RFLP	PCR-RFLP
Nakao	2012	Japan	Non-China	Asian	185	1465	HB	17	80	88	152	636	677	0.884	TaqMan	Non-PCR-RFLP
Jiao	2006	USA	Non-China	European	182	338	HB	3	49	130	3	34	301	0.076	PCR-SSCP	Non-PCR-RFLP
McWilliams	2008	USA	Non-China	European	466	602	HB	2	64	400	2	80	520	0.559	SNP stream/Pyrosequencing	Non-PCR-RFLP
Hou	2016	China	China	Asian	298	298	HB	18	115	165	17	135	146	0.047	PCR-RFLP	PCR-RFLP
rs139599857								GG	GC	CC	GG	GC	CC			
Hou	2016	China	China	Asian	298	298	HB	25	125	148	29	137	132	0.445	PCR-RFLP	PCR-RFLP
Zhao	2014	China	China	Asian	390	392	HB	51	152	187	23	164	205	0.187	PCR-RFLP	PCR-RFLP
rs72554204								CC	CT	TT	CC	CT	TT			
Hou	2016	China	China	Asian	298	298	HB	28	130	140	18	119	161	0.516	PCR-RFLP	PCR-RFLP
Chen	2013	China	China	Asian	328	350	HB	30	127	171	59	148	143	0.055	CRS-PCR/PCR-RFLP	Non-PCR-RFLP

HWE: Hardy-Weinberg equilibrium; HB: hospital-based; SOC: source of control; PCR-FLIP: polymerase chain reaction and restrictive fragment length polymorphism; PCR-SSCP: polymerase chain reaction and single-strand conformation polymorphism, CRS-PCR: created restriction site and polymerase chain reaction.

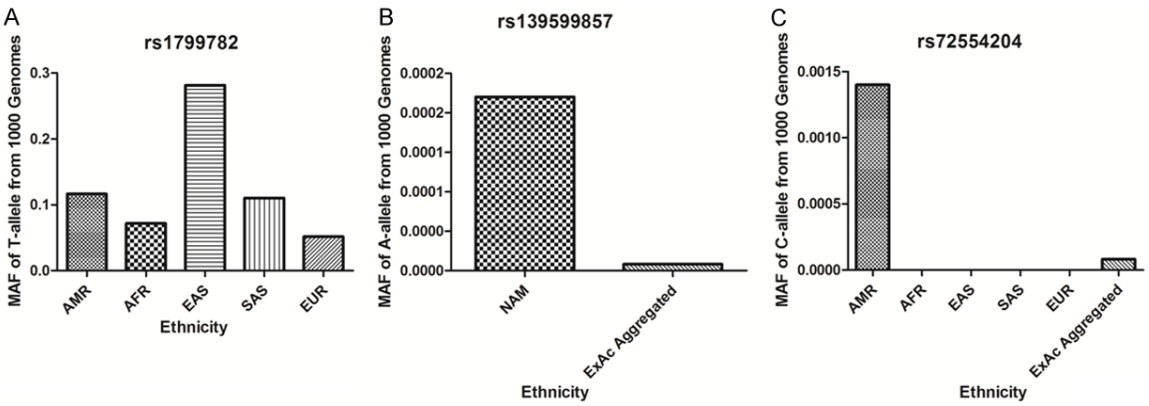

Figure 2. The MAF of minor-allele (mutant-allele) for each polymorphism in the *XRCC1* gene from the 1000 Genomes online database. EAS: East Asian; EUR: European; AFR: African; AMR: American; SAS: South Asian; NAM: north American.

genotypes in all control groups was consistent with Hardy-Weinberg equilibrium (HWE).

The following genotyping methods were used in the studies included in this meta-analysis: 1) Polymerase chain reaction-restrictive fragment length polymorphism (PCR-FLIP); 2) Polymerase chain reaction and single-strand conformation polymorphism (PCR-SSCP); and 3) Created restriction site and polymerase chain reaction (CRS-PCR).

Quantitative synthesis

rs1799782 C/T: Results of the overall meta-analysis revealed a marginally significant positive association between the *rs1799782 C/T* polymorphism and susceptibility to PC in the dominant model (OR: 1.16, 95% CI: 1.00-1.33, *P* (heterogeneity) <0.001, *P* = 0.043, **Figure 3A**) and the allelic comparison (OR: 1.12, 95% CI: 1.00-1.26, *P* (heterogeneity) <0.001, *P* = 0.048) (**Table 2**). Subgroup analysis based on ethnicity showed a significant association in the population of European-descent (dominant model, OR: 1.56, 95% CI: 1.18-2.05, *P* (heterogeneity) <0.001, *P* = 0.002; heterozygote comparison, OR: 1.55, 95% CI: 1.17-2.05, *P* (heterogeneity) <0.001, *P* = 0.002; allelic comparison, OR: 1.51, 95% CI: 1.17-1.96, *P* (heterogeneity) <0.001, *P* = 0.002; **Figure 3B**; **Table 2**). Similar results, with a significantly higher risk of PC, were detected for this SNP in the non-China and non-PCR-RFLP subgroups (**Figure 3C**, **3D**; **Table 2**). When *H* and I^2 statistics were applied to evaluate heterogeneity, regardless of the model chosen, there was no significant association between this SNP and susceptibility to PC. This result was taken as the definitive conclusion of the study (**Table 2**). Furthermore, the *galbr* command was applied to plot a Galbraith graph, aiming to identify studies that influenced heterogeneity. Detected heterogeneity was a result of the study by Jiao et al. [23] (**Figure 4**), though this did not affect present results.

rs139599857 G/A and *rs72554204 T/C*: Because the degrees of freedom for these two SNPs were less than two, *H* and I^2 statistics were not applicable. Thus, the *Q*-test was used to evaluate heterogeneity. Overall meta-analysis revealed a positive, but weak, association between these two SNPs and susceptibi= lity to PC (allelic comparison, OR: 0.66, 95% CI: 0.46-0.94, *P* (heterogeneity) = 0.020, *P* = 0.023 for *rs139599857* and OR: 0.62, 95% CI: 0.39-0.98, *P* (heterogeneity) = 0.004, *P* = 0.040 for *rs72554204*; **Figure 5A**, **5B**; **Table 2**).

The present meta-analysis combined data from 2,908 patients with PC and 4,855 controls, revealing that two *XRCC1* SNPs, *rs139599857* and *rs72554204*, are associated with susceptibility to PC and that both are protective SNPs.

Bias diagnosis and sensitivity analysis

Egger's and Begg's tests were performed to assess publication bias. No publication bias was found, except in the analyses of allelic comparisons. The following values were obtained: *z* = 1.8 and *P* = 0.072 with Begg's test and *t* = 2.38 and *P* = 0.063 with Egger's test for the dominant model (TT + TC vs. CC) (**Fi-**

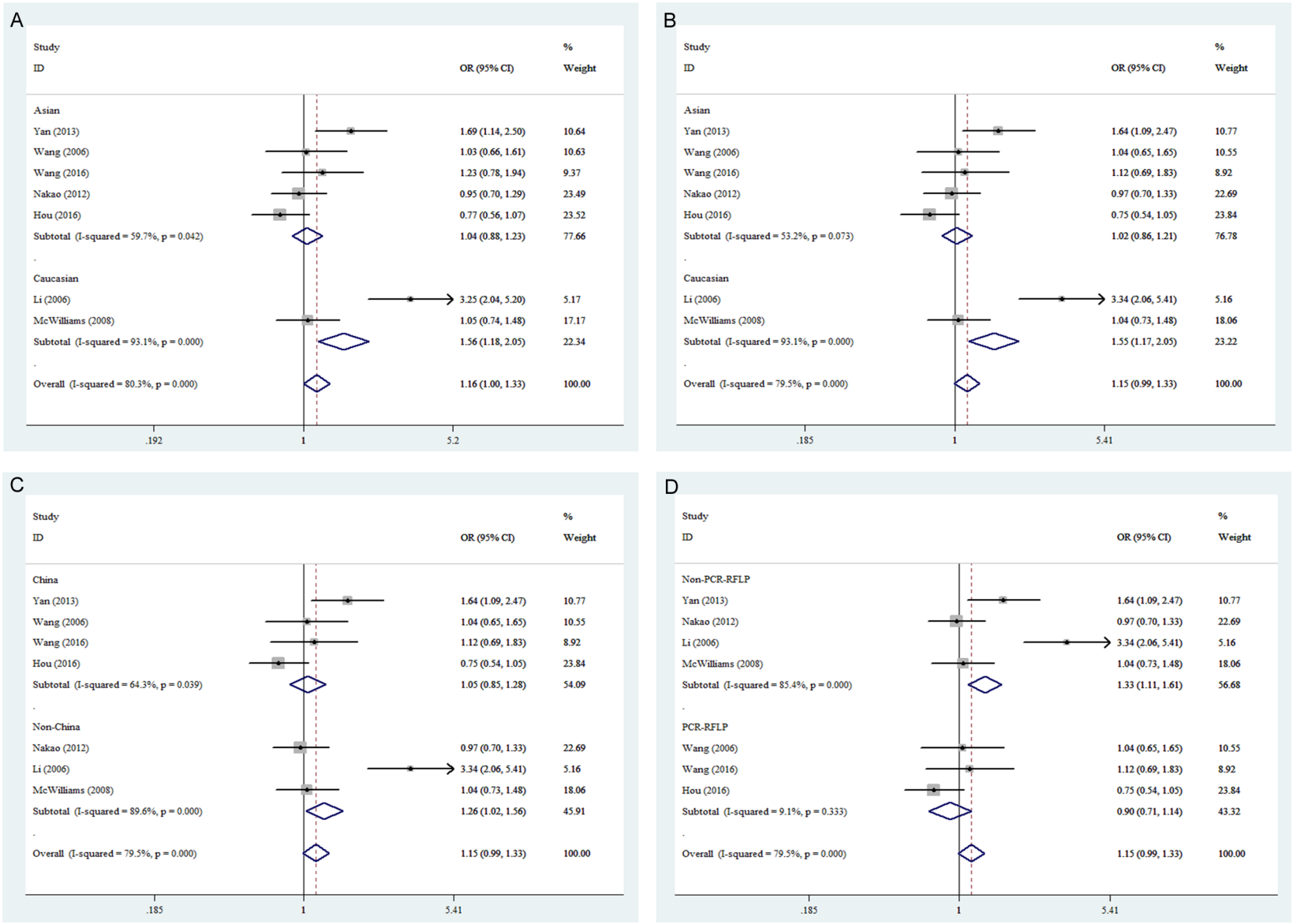

Figure 3. Forest plot of PC risk associated with *rs1799782 C/G* polymorphism (*Q*-test). Squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of variance). The diamond represents the summary OR and 95% CI. (A: CC + CG vs. GG for total; B: CG vs. GG for ethnicity; C: CG vs. GG for country of origin; D: CG vs. GG for genotype methods).

Table 2. Total and stratified subgroup analysis for *XRCC1 gene* polymorphism sites and pancreatic cancer susceptibility

Variables	N	Case/ Control	C-allele vs. G-allele					CG vs. GG					CC + CG vs. GG				
			OR (95% CI)	P_h	*P*	*H* (95% CI)	I^2	OR (95% CI)	P_h	*P*	*H* (95% CI)	I^2	OR (95% CI)	P_h	*P*	*H* (95% CI)	I^2
rs1799782																	
Total	7	1594/3517	1.22 (0.94-1.59)	<0.001	0.136	2.19 (1.53-3.14)	79.2	1.23 (0.88-1.71)	<0.001	0.225	2.21 (1.54-3.16)	79.5	1.25 (0.90-1.73)	<0.001	0.184	2.25 (1.58-3.21)	80.3
Ethnicity																	
Asian	5	946/2577	1.08 (0.87-1.33)	0.045	0.475	1.56 (1.00-2.55)	58.8	1.05 (0.81-1.36)	0.073	0.723	1.46 (1.00-2.41)	53.2	1.07 (0.82-1.40)	0.042	0.595	1.57 (1.00-2.58)	59.6
European	2	648/940	1.71 (0.65-4.51)	<0.001	0.281	-		1.84 (0.59-5.77)	<0.001	0.295	-		1.82 (0.60-5.55)	<0.001	0.289	-	
Source of country																	
China	4	761/814	1.13 (0.86-1.49)	0.034	0.374	1.70 (1.00-2.91)	65.3	1.08 (0.76-1.54)	0.039	0.664	1.67 (1.00-2.87)	64.2	1.12 (0.79-1.60)	0.025	0.522	1.77 (1.04-3.02)	68.0
Non-China	3	833/2405	1.38 (0.76-2.49)	<0.001	0.289	3.16 (1.93-5.16)	90.0	1.46 (0.74-2.89)	<0.001	0.273	3.11 (1.89-5.10)	89.6	1.45 (0.74-2.84)	<0.001	0.284	3.17 (1.94-5.18)	90.1
Genotype methods																	
PCR-RFLP	3	551/899	1.01 (0.80-1.27)	0.212	0.964	1.24 (1.00-2.19)	35.4	0.90 (0.71-1.14)	0.333	0.374	1.05 (1.00-3.25)	9.1	0.96 (0.72-1.27)	0.230	0.757	1.21 (1.00-3.76)	31.97
Non-PCR-RFLP	4	1043/2618	1.41 (0.91-2.18)	<0.001	0.124	2.71 (1.75-4.24)	22.1	1.50 (0.90-2.48)	<0.001	0.117	2.62 (1.66-4.11)	85.3	1.49 (0.90-2.47)	<0.001	0.119	2.70 (1.73-4.22)	86.3
			OR (95% CI)	P_h	*P* (*Q*-test)			OR (95% CI)	P_h	*P* (*Q*-test)			OR (95% CI)	P_h	*P* (*Q*-test)		
Total	7	1594/3517	1.12 (1.00-1.26)	<0.001	0.048			1.15 (0.99-1.33)	<0.001	0.070			1.16 (1.00-1.33)	<0.001	0.043		
Ethnicity																	
Asian	5	946/2577	1.04 (0.92-1.19)	0.045	0.522			1.02 (0.86-1.21)	0.073	0.801			1.04 (0.88-1.23)	0.042	0.624		
European	2	648/940	1.51 (1.17-1.96)	<0.001	0.002			1.55 (1.17-2.05)	<0.001	0.002			1.56 (1.18-2.05)	<0.001	0.002		
Source of country																	
China	4	761/814	1.13 (0.86-1.49)	0.034	0.374			1.05 (0.85-1.28)	0.039	0.670			1.08 (0.89-1.32)	0.025	0.422		
Non-China	3	833/2405	1.38 (0.76-2.49)	<0.001	0.289			1.26 (1.02-1.56)	<0.001	0.030			1.24 (1.01-1.53)	<0.001	0.036		
Genotype methods																	
PCR-RFLP	3	551/899	0.98 (0.82-1.18)	0.212	0.861			0.90 (0.71-1.14)	0.333	0.374			0.94 (0.75-1.17)	0.230	0.563		
Non-PCR-RFLP	4	1043/2618	1.24 (1.06-1.44)	<0.001	0.006			1.33 (1.11-1.61)	<0.001	0.003			1.33 (1.11-1.59)	<0.001	0.002		
			A-allele vs. G-allele (*Q*-test)					AG vs. GG (*Q*-test)					AA + AG vs. GG (*Q*-test)				
rs139599857	2	688/690	0.66 (0.46-0.94)	0.020	0.023			0.92 (0.74-1.15)	0.333	0.476			0.99 (0.67-1.45)	0.074	0.949		
			C-allele vs. T-allele (*Q*-test)					CT vs. TT (*Q*-test)					CC + CT vs. TT (*Q*-test)				
rs72554204	2	626/648	0.62 (0.39-0.98)	0.004	0.040			0.95 (0.55-1.64)	0.019	0.848			0.92 (0.44-1.89)	0.001	0.810		

P_h: value of *Q*-test for heterogeneity test; *P*: *Z*-test for the statistical significance of the OR; the red mark: statistical differences by Stata software. H > 1.5 may be considered 'heterogeneous'; if H<1.2 may be considered 'homogeneity'; if 1.2<H<1.5, and the 95% CI including 1 (α<0.05), may not be considered, otherwise, may be consider 'heterogeneous'. Heterogeneous for random-effects model, homogeneity for fixed-effects model.

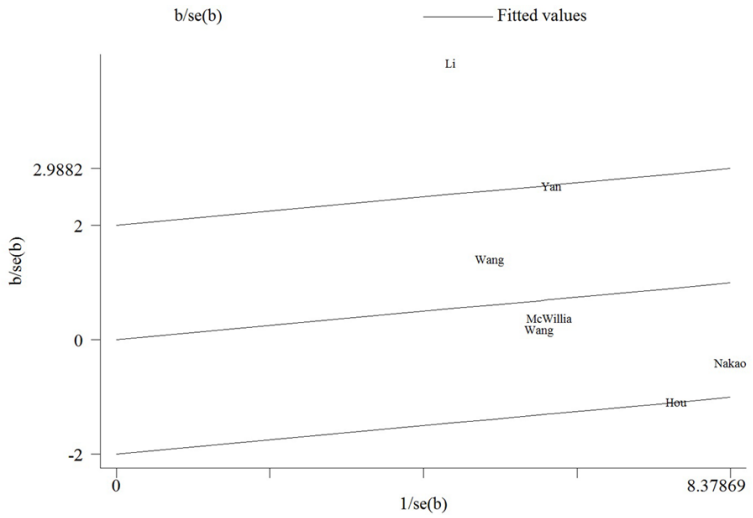

Figure 4. The Galbraith graph shows which included studies may have influenced heterogeneity. If studies showing the first author are outside two parallel lines, heterogeneity may come from these studies.

gure 6A, **6B**, **Table 3**). For sensitivity analysis, the overall OR was not significantly altered by inclusion/exclusion of any individual study of the *rs1799782 C/T* polymorphism (**Figure 7**).

PolyPhen-2 and SIFT analysis

To verify this association, the PolyPhen-2 tool was used to analyze the features of the *rs1799782* mutant. A score of 0.899 was obtained from analysis, suggesting the possibility of *rs1799782* being a damaging mutation (**Figure 8**). In addition, analysis with the SIFT tool, which can predict the effects of an SNP on protein function, showed that the *rs1799782* SNP could affect the function of XRCC1 proteins. This suggests that the mutation may be in a functional site.

Discussion

XRCC1 plays vital roles in several DNA damage recovery pathways, including BER and SSBR pathways. In addition, it is involved in the repair of DNA damage induced by exposure to various DNA-damaging agents, such as ionizing radiation, endogenous reactive oxygen species, and alkylating agents [37, 38]. XRCC1 can bind directly to both gapped and nicked DNA, as well as gapped DNA associated with DNA polymerase β, suggesting that it is independently involved in DNA-damage recognition and can be considered an anti-cancer agent [39].

SNPs can influence expression of a gene and the function of its translated protein [40, 41] *XRCC1* is no exception. There are several SNPs that may influence its expression and its anti-cancer role. Therefore, it is necessary to identify functional SNPs that could contribute to PC susceptibility, better predicting the risk to individuals for development of PC and understanding the pathogenesis of PC.

Meta-analyses can effectively increase sample sizes by collecting data from individual correlation studies, thereby adding to the statistical power of genetic analyses [42]. Although two studies exploring the association between the *Arg194Trp* (*rs1799782*) polymorphism and susceptibility to PC [20, 21] have been published, neither detected a positive association. Shen et al. [21] included four studies, with 1,343 cases and 2,302 controls, to evaluate three *XRCC1* SNPs, *rs1799782*, *rs25489*, and *rs25487*. However, no association was found between the three SNPs and susceptibility to PC. He et al. [20] conducted an updated meta-analysis, including five eligible studies with 1,144 PC cases and 2,925 controls, but did not detect any positive association between *rs1799782* and susceptibility to PC in people of Asian or European descent. Following these studies, two more studies with larger sample sizes were published [17, 22]. These indicated that the *rs1799782* polymorphism may have a significant association with susceptibility to PC. Afterwards, Chen et al. [43] performed an updated meta-analysis, but the results did not show any significant association between three polymorphisms, *Arg399Gln*, *rs1799782*, and *rs72554204*, and susceptibility to PC. However, *Arg280His* and *rs139599857* were found to be associated with susceptibility to PC. All three of these meta-analyses used the *Q*-test, which is easily affected by sample size, because they included studies with small sample sizes. In view of these results, it was necessary to re-analyze the correlation between *XRCC1* polymorphisms and susceptibility to PC using *H* and I^2 statistics [32, 33]. These are unaffected by sample size. Therefore, three polymorphisms were selected for meta-analysis, *rs1799782*, *rs139599857*,

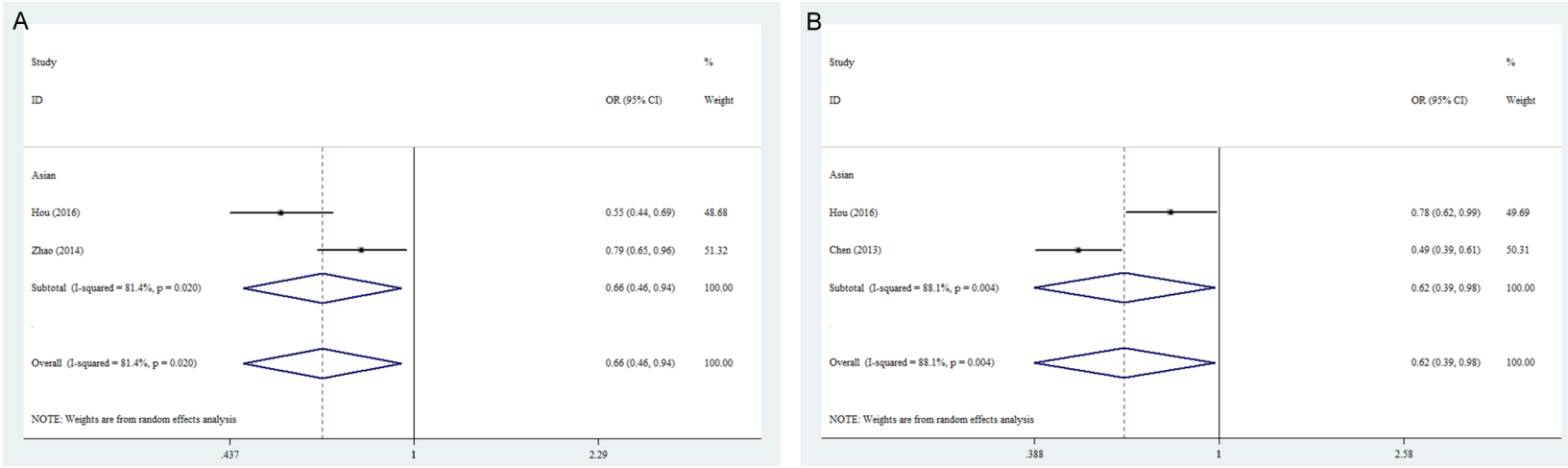

Figure 5. Forest plot of PC risk associated with *rs139599857* (A) and *rs72554204* (B) polymorphisms for total analysis. Squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of variance). The diamond represents the summary OR and 95% CI.

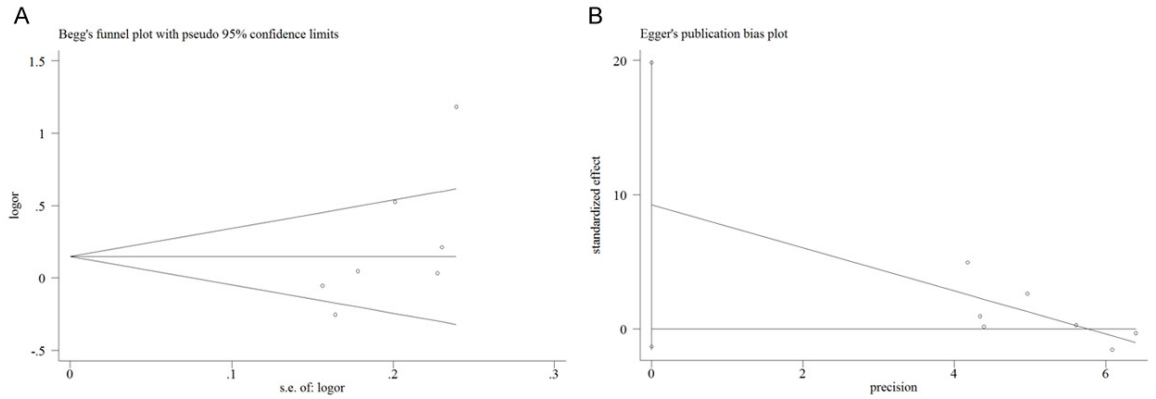

Figure 6. A: Begg's funnel plot for publication bias test in analyses involving the *rs1799782 C/G* polymorphism (G-allele vs. C-allele). Each point represents a separate study for the indicated association. Log [OR] represents the natural logarithm of OR. The horizontal line indicates mean effect size. B: Egger's publication bias plot for the *rs1799782 C/G* polymorphism (G-allele vs. C-allele).

Table 3. Publication bias tests (Begg's funnel plot and Egger's test for publication bias test) for *XRCC1 rs1799782* polymorphism

Genetic type	Egger's test					Begg's test	
	Coefficient	Standard error	*t*	*P*-value	95% CI of intercept	*z*	*P*-value
G-allele vs. C-allele	8.147	2.742	2.97	0.031	(1.099, 15.196)	1.5	0.133
GC vs. CC	7.291	3.308	2.2	0.079	(-1.232, 15.773)	1.8	0.072
GG vs. CC	1.189	0.58	2.05	0.096	(-0.302, 2.681)	1.8	0.072
GG + CG vs. CC	8.079	3.393	2.38	0.063	(-0.644, 16.802)	1.8	0.072
GG vs. CG + CC	1.181	0.566	2.09	0.091	(-0.273, 2.635)	1.8	0.072

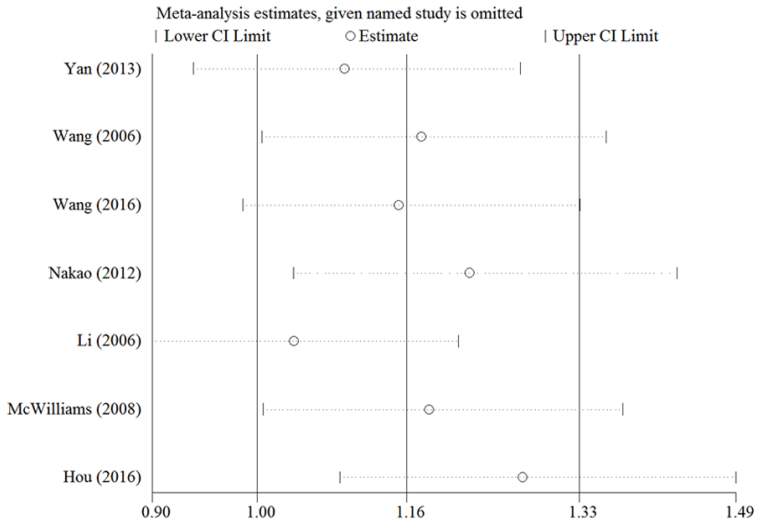

Figure 7. Sensitivity analysis between *rs1799782 C/G* polymorphism and PC risk (G-allele vs. C-allele).

and *rs72554204*. Findings regarding their association with susceptibility to PC have been controversial.

For *rs1799782*, in the 1000 Genomes browser, it was found that the frequency of the C-mutant allele was highest in the East Asian population, including China and Japan. It was the lowest in the population of European descent. In this study, seven studies were conducted in East Asian populations and two were conducted in populations of European descent. A positive association between *rs1799782* and susceptibility to PC was found in East Asian populations, which was easy to understand. However, no such association was observed in the two studies conducted on populations of European descent [23, 24]. Results of the *Q*-test revealed a marginally significant positive association between *rs1799782 C/G* and susceptibility to PC, both in the

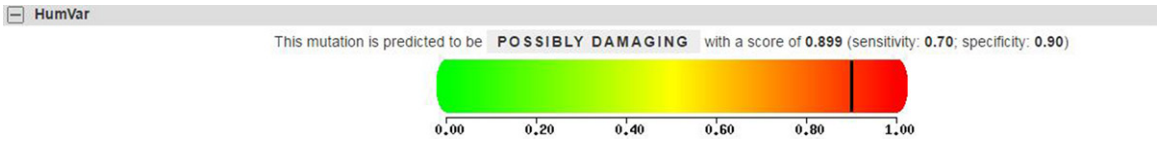

Figure 8. Analysis of the effects of the *rs1799782 C/G* polymorphism on XRCC1 protein using the Polyphen-2 bioinformatics tool. The position of the black line represents the score, a measure of how damaging the mutation could be to protein function.

total population and in the population of European descent. On the other hand, results of the H-test did not show an association. Finally, results of the *H* and I^2 tests showed no association between *rs1799782* and susceptibility to PC.

Based on present analyses, it was hypothesized that these two SNPs may increase *XRCC1* function and enhance the ability of cells to repair methylation, oxidation, or reduce damage induced by ionizing radiation or oxidizing agents. Present results could be explained well by the suggested effects of these two SNPs. However, other factors, such as gene-gene or gene-environment interactions, may also affect the relationship between the *XRCC1* polymorphisms and susceptibility to PC.

There were some limitations to this study. First, although data was collected from as many eligible studies as possible, the combined data pool was not large, especially for *rs139599-857* and *rs72554204* SNPs. Therefore, there was not only an increased likelihood of type I/II error but also insufficient statistical power to evaluate the association. Further studies focusing on populations of European and African descent are necessary. Second, specific environmental and lifestyle factors, such as age, diabetes, smoking, drinking, and family history, may have altered results. Therefore, information on environmental and lifestyle factors should be included in future analysis. Third, none of the included studies considered epigenetic factors, only focusing on sequence polymorphisms. However, the clinical relevance of PC, such as different stages of PC progression and a survival curve, were missing. These should also be included in future analysis. Results of such analysis could better explain how the functional changes caused by *XRCC1* polymorphisms affect susceptibility to PC.

In summary, the current meta-analysis suggests that *XRCC1* polymorphisms *rs1395998-57 G/A* and *rs72554204 T/C*, but not *rs1799782 G/C*, may be associated with susceptibility to PC. Further studies including larger sample sizes and factors accounting for gene-environment interactions should be considered.

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Disclosure of conflict of interest

None.

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