

Review Article

XRCC1 Polymorphisms and Pancreatic Cancer: A Meta-Analysis

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ABSTRACT

Objective: To assess the association between X-ray repair cross-complementating group 1 (XRCC1) polymorphisms and pancreatic cancer.

Methods: We searched MEDLINE, Web of Science and HuGE Navigator at June 2010, and then quantitatively summarized associations of the XRCC1 polymorphisms with pancreatic cancer risk using meta-analysis.

Results: Four studies with 1343 cases and 2302 controls were included. Our analysis found: at codon 194, the Trp allele did not decrease pancreatic cancer risk (Arg/Arg versus Trp/Trp: OR=0.97; 95% CI: 0.48-1.96; *P*=0.97; Arg/Arg versus Arg/Trp: OR=0.89; 95% CI: 0.70-1.13; *P*=0.55; Arg/Trp versus Trp/Trp: OR=1.06; 95% CI: 0.52-2.16; *P*=0.90); at codon 280, only a study showed a nonsignificant association between single nucleotide polymorphism with pancreatic cancer risk; at codon 399, the Gln allele also showed no significant effect on pancreatic cancer compared to Arg allele (Arg/Arg versus Gln/Gln: OR=0.94; 95% CI: 0.74-1.18; Arg/Arg versus Arg/Gln: OR=0.97; 95% CI: 0.83-1.13; Arg/Gln versus Gln/Gln: OR=0.97; 95% CI: 0.77-1.22). The shape of the funnel plot and the Egger's test did not detect any publication bias.

Conclusion: There is no evidence that XRCC1 polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) are associated with pancreatic cancer risk.

Key words: Pancreatic cancer; X-ray repair cross-complementating group 1; Gene polymorphism; Meta-analysis; Molecular epidemiology

INTRODUCTION

Pancreatic cancer, although infrequent, has an exceptionally high mortality rate, making it one of the four or five most common causes of cancer mortality in developed countries^[1]. In 2008, the estimated incidence of pancreatic cancer in the United States was 37,700 cases, and an estimated 34,300 patients died from the disease. The overall 5-year survival rate among patients with pancreatic cancer is <5%^[2]. According to etiological studies, several environmental factors have been implicated. Tobacco smoking and alcohol drinking are two important potential risk factors for pancreatic cancer^[3, 4]. Exposure to tobacco smoke has been associated with DNA damage in human tissues^[5]. Alcohol abuse may also induce mitochondria DNA damage^[6]. Damaged DNA can be removed and recovered which are critical for the genome protection and cancer prevention.

Some important pathways in DNA repair have been described: base-excision repair (BER), nucleotide excision repair, and double-strand break repair^[7]. The X-ray repair cross-complementating group 1 (XRCC1) gene is involved in the 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, DNA ligase III and DNA polymerase-beta^[8]. The human XRCC1 gene is 33 kb in length, and is located on chromosome 19q13.2-13.3^[9]. There are several single nucleotide polymorphisms (SNP) in the XRCC1 gene as reported to date in the dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP/>). Three of these SNP are common that have amino acid substitutions at codons 194 (db SNP rs. 1799782; Arg to Trp), 280 (db SNP rs. 25489; Arg to His) and 399 (db SNP rs. 25487; Arg to Gln)^[10]. These SNPs in XRCC1 that causes amino acid substitutions may impair the interaction of XRCC1 with the other enzymatic proteins, and consequently alter DNA repair activity. Although SNP in XRCC1 are associated with a variety of ethnic backgrounds, they are also relevant to cancer^[11].

Indeed, some previous studies have investigated the relationship between SNP in XRCC1 and human cancers, and some meta-analyses have been shown that XRCC1 SNPs are significantly associated with risk of breast cancer^[12], lung cancer^[13], and colorectal cancer^[14]. However, studies of XRCC1 SNP and pancreatic cancer risk produced some mixed results in the literature, and no meta-analysis has been conducted to date. In this study, we carried out a meta-analysis focusing on SNP Arg194Trp, Arg280His and Arg399Gln, and pooled the results to identify evidence of an association between XRCC1 SNP and pancreatic cancer risk.

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MATERIALS AND METHODS

Publication Search

Relevant studies were identified by searching MEDLINE, Web of Science and the HuGE Navigator (<http://www.hugenavigator.net>, version 1.4)^[15]. We used retrieval strategy of "Pancreatic Neoplasms" [MeSH Terms] and ("XRCC1" [title/abstract] or "XRCC1" [text]) for MEDLINE, "[Ts= (cancer same pancrea*) or Ts= (carcinoma same pancrea*)]" and Ts= (XRCC1)" for Web of Science. And the similar strategy of "pancreatic cancer (Text+MeSH)>>XRCC1 (Gene)" was performed in searching the HuGE Navigator, which means "human genome epidemiology". All the searches were performed at June 2010.

Eligible Studies

To be included in the meta-analysis, studies had to meet the following criteria: (1) Distribution of XRCC1 genotypes in pancreatic cancer patients and in the controls should be determined; (2) There had to be at least two comparison groups (pancreatic cancer groups vs. control groups), which included odds ratio (OR) or adjusted OR by Logistic regression; (3) The studied population should be composed of unrelated individuals; (4) Genotype distribution of the pancreatic cancer patients and the controls must be in Hardy-Weinberg equilibrium (HWE).

Data Extraction

Genotypes of XRCC1, which including three single nucleotide polymorphisms of Arg194Trp, Arg280His, and Arg399Gln, were collected on both patients and controls. The other information was also extracted from each study: first author, years of publication, ethnicity (country) of study population, and other variables that may be sources of bias. Two authors of the present study had collected the data independently and reached a consensus on all classified items.

Statistical Analysis

We analyzed the data by the following processes: First, We assessed the departure from the HWE in each study by the chi-square test for goodness of fit using a web-based program (<http://ihg2.helmholtz-muenchen.de/cgi-bin/h/hwa1.pl>). Second, the risks [ORs and their 95% confidence interval (95% CIs)] of pancreatic cancer associated with the XRCC1 polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) were calculated directly from the data given in the eligible studies. We estimated the risks of the combined variant genotypes (i.e. Arg/Trp and Trp/Trp for Arg194Trp, Arg/His and His/His for Arg280His, and Arg/Gln and Gln/Gln for Arg399Gln) versus their wild genotypes. Third, a chi-square-based Q-statistic test^[16] and an I²-test^[17] were performed to assess the between-study heterogeneity. Heterogeneity was considered significant if the P-value of Q-statistic test is <0.10. Then fourth, we pooled data. If there was no heterogeneity, fixed effects model was used; otherwise, a random effect model based on the DerSimonian and Laird estimator was used^[18]. The significance of the pooled OR was determined by the Z-test; a P-value of <0.05 was considered significant. And last, we checked the

publication bias by inverted funnel plots and the Egger's test^[19]. An asymmetric plot suggested possible publication bias. The funnel plot asymmetry was assessed by Egger's linear regression test, a P-value <0.05 was considered a significant publication bias. We used the computer programs Review Manager (version 4.2.8, The Cochrane Collaboration) for Meta analysis and the inverted funnel plots, Stata (version 11.0, Stata Corporation) for the Egger's test. All the tests were two-sided.

RESULTS

Eligible Studies

A total of 8 papers were included from the initially retrieved, 1 paper were excluded because of review, 2 papers were excluded because of study of XRCC1 gene polymorphisms for pancreatic cancer survival, and 1 paper for XRCC1 gene downregulated in pancreatic adenocarcinomas were also excluded. Finally, 4 study papers^[20-23] were included for analysis.

In the 4 eligible reports, 3 studies were hospital based case-control studies, 1 study was population-based study. A total of 1343 cases and 2302 controls enrolled. The number of studies with Arg194Trp, Arg280His, and Arg399Gln was 3, 1, and 4, respectively. The populations selected in those studies come from the United States or China. And genotype distributions in all studies were consistent with HWE. The information details of eligible studies are showed in Table 1.

Meta-analysis Databases

XRCC1 Arg194Trp

The Trp/Trp genotype carriers did not have a decreased pancreatic cancer risk compared with those with the Arg/Arg genotype (Arg/Arg versus Trp/Trp: OR=0.97; 95% CI: 0.48-1.96; P=0.97, I²=0% for heterogeneity). Similarly, no association with cancer risk was found in a model (Arg/Arg versus Arg/Trp: OR=0.89; 95% CI: 0.70-1.13; P=0.55, I²=0% for heterogeneity) or a mode (Arg/Trp versus Trp/Trp: OR=1.06; 95% CI: 0.52-2.16; P=0.90, I²=0% for heterogeneity). The results are showed in Figure 1.

XRCC1 Arg280His

There was only one eligible study^[20] associated between the XRCC1 Arg280His SNP and cancer risk. The meta-analysis was not performed because of the limited data. Therefore, the study showed a nonsignificant association between the XRCC1 Arg280His SNP and pancreatic cancer risk (His/His versus Arg/His: OR=1.428 95% CI: 0.901-2.290; His/His versus Arg/Arg: OR=0.411 95% CI: 0.007-7.935; Arg/His versus Arg/Arg: OR=0.288 95% CI: 0.005-5.803) (Table 1).

XRCC1 Arg399Gln

The Gln/Gln genotype carriers did not have a decreased pancreatic cancer risk compared with those with the Arg/Arg genotype (Arg/Arg versus Gln/Gln: OR=0.94; 95% CI: 0.74-1.18; P=0.57, I²=0% for heterogeneity). Similarly, no association was found in the model (Arg/Arg versus Arg/Gln: OR=0.97; 95% CI: 0.83-1.13; P=0.57, I²=0% for

Table 1. Studies included in the meta-analysis

SNPs	Research	Setting	Design	Race	Method	Case genotypes				Control genotypes				OR (95% CI)		HWE	
						AA	AT	TT	AA	AT	TT	AA/AT	AA/TT	AT/TT	Goodness of fit χ^2	P value	
Arg194Trp	McWilliams RR, 2008	USA	Hospital-based	98% white	PCR	400	64	2	520	80	2	0.962 (0.665-1.393)	0.769 (0.056-10.657)	0.800 (0.057-11.334)	0.08	0.77363	
	Wang L, 2006	China	Hospital-based	Chinese	PCR	46	47	8	156	154	27	0.945 (0.577-1.547)	0.973 (0.395-2.656)	1.030 (0.419-2.804)	0.01	0.92685	
	Jiao L, 2006	USA	Hospital-based	85% Non-Hispanic	PCR	308	49	3	301	34	3	0.710 (0.432-1.158)	1.023 (0.136-7.699)	1.441 (0.181-11.370)	1.53	0.21555	
Arg280His	McWilliams RR, 2008	USA	Hospital-based	98% white	PCR	432	34	2	525	59	1	1.428 (0.901-2.290)	0.411 (0.007-7.935)	0.288 (0.005-5.803)	1.52	0.21707	
	Wang L, 2006	China	Hospital-based	Chinese	PCR	59	37	5	177	135	25	1.216 (0.743-2.003)	1.667 (0.589-5.818)	1.370 (0.470-4.893)	1.41	0.23553	
Arg399Gln	Jiao L, 2006	USA	Hospital-based	85% Non-Hispanic	PCR	130	197	53	135	172	47	0.841 (0.605-1.168)	0.854 (0.524-1.389)	1.016 (0.636-1.620)	0.87	0.35195	
	Duell EJ, 2002	USA	Population-based	86% Caucasians	PCR	137	119	37	452	365	102	0.903 (0.695-1.245)	0.836 (0.539-1.314)	0.899 (0.575-1.424)	0.75	0.38617	

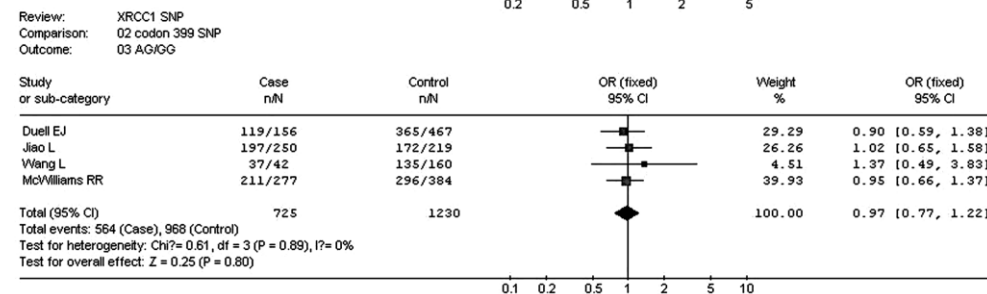
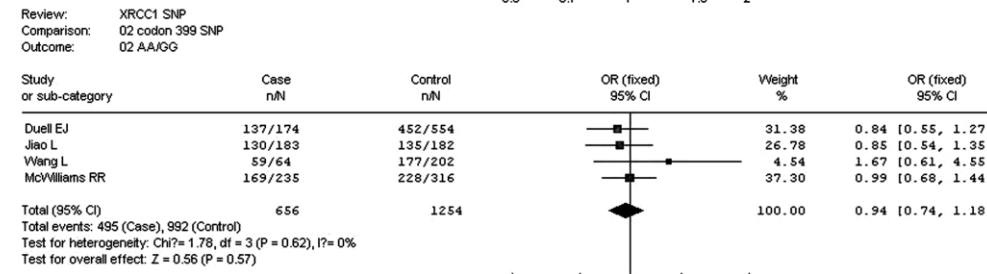
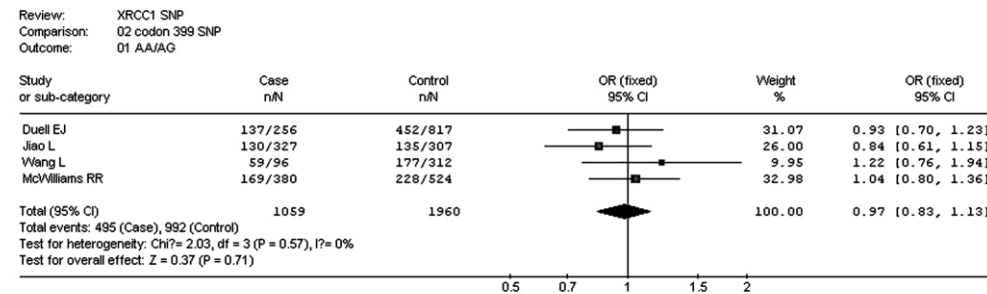
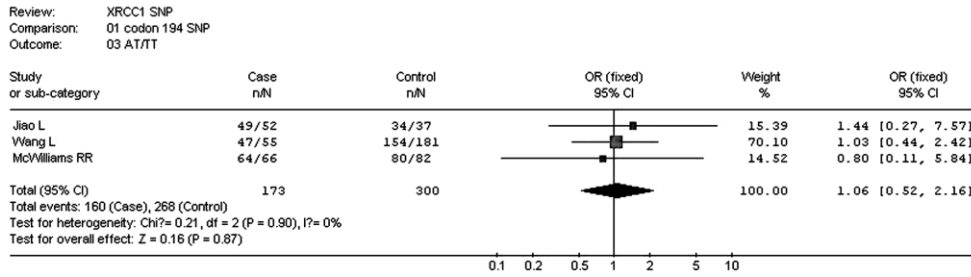
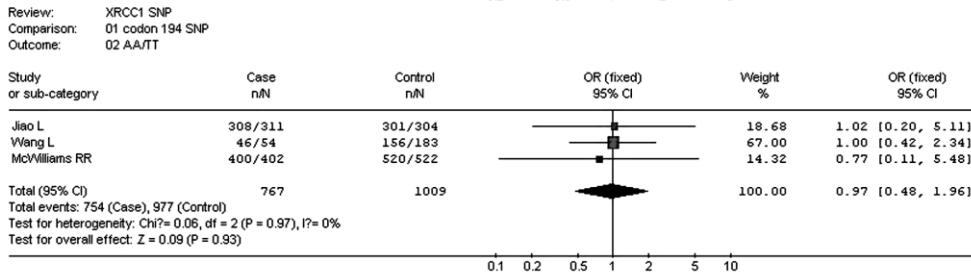
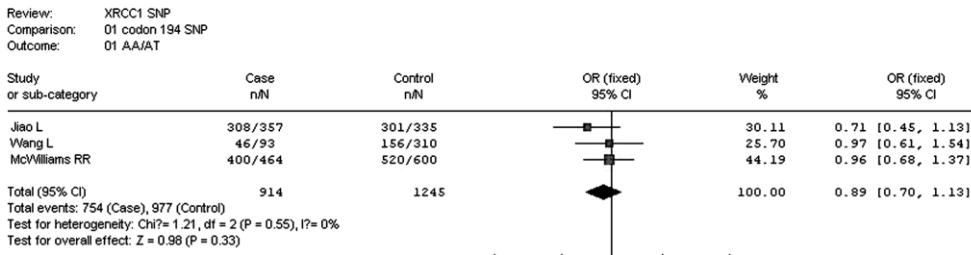


Figure 1. Forest plots of ORs with 95% CI for XRCC1 Arg194Trp SNP and risk for pancreatic cancer. The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. The summary OR is represented by the diamond, where the center of the diamond indicates the OR and the ends of the diamond correspond to the 95% CI. The meta-analysis was in a fixed effects model.

Figure 2. Forest plots of ORs with 95% CI for XRCC1 Arg399Gln SNP and risk for pancreatic cancer. The center of each square represents the OR, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95% CI. The summary OR is represented by the diamond, where the center of the diamond indicates the OR and the ends of the diamond correspond to the 95% CI. The meta-analysis was in a fixed effects model.

heterogeneity) or a mode (Arg/Gln versus Gln/Gln: OR=0.97; 95% CI: 0.77-1.22; $P=0.89$, $I^2=0\%$ for heterogeneity). The results are showed in Figure 2.

Publication Bias

An Egger's test did not detect any publication bias in comparison of Arg/Arg versus Arg/Trp at codon 194 ($t=0.09$, $P=0.942$), Arg/Arg versus Trp/Trp at codon 194 ($t=0.44$, $P=0.738$), Arg/Trp versus Trp/Trp at codon 194 ($t=1.48$, $P=0.378$), Arg/Arg versus Arg/Gln at codon 399 ($t=0.22$, $P=0.843$), Arg/Arg versus Gln/Gln at codon 399 ($t=0.62$, $P=0.599$), Arg/Gln versus Gln/Gln at codon 399 ($t=1.74$, $P=0.224$), respectively.

DISCUSSION

In the present meta-analysis, we examined the association between XRCC1 SNP and pancreatic cancer risk, by critically reviewing all published studies, from which we selected 3 studies on XRCC1 Arg194Trp genotypes (914 cancer cases and 1,245 controls), a study on XRCC1 Arg280His genotypes (468 cancer cases and 585 controls), and 4 studies on XRCC1 Arg399Gln genotypes (1,059 cancer cases and 1,960 controls).

Our current pooled data suggested no evidence for a major role of variants in pancreatic cancer risk for XRCC1 Arg194Trp SNP. Studies of Arg194Trp showed no association with the indicators of DNA repair capacity, such as DNA-adduct levels, frequency of mutations in glycoprotein A, or sensitivity to ionizing radiation^[24]. Arg194Trp SNP have no relationship with most cancers, such as breast cancer^[12], colorectal cancer^[14], esophageal cancer^[25] and bladder cancer^[26]. Arg194Trp SNP may affect the susceptibility only in lung cancer risk^[13]. But in our meta-analysis, Arg194Trp SNP showed no association with pancreatic cancer risk. However, a previous study^[22] showed that Arg194Trp SNP has a significant interaction with APE1 or MGMT genes polymorphism in modifying the risk of pancreatic cancer, suggesting that in combination with other genes polymorphism, XRCC1 Arg194Trp SNP may increase the risk of pancreatic cancer. Another meta-analysis may be conducted on this topic.

Only one study^[20] investigated relationship between Arg280His SNP and pancreatic cancer risk. We cannot perform the meta-analysis because of the limited data. Therefore, the study showed a nonsignificant association between the XRCC1 Arg280His SNP and pancreatic cancer risk. Biologically, Arg280His is located in the proliferating cell nuclear antigen-binding region and was suggested to be associated with higher bleomycin sensitivity, which resulted in a reduced DNA repair capacity produced by bleomycin^[27]. As studies of Arg280His are currently limited, further studies should be carried out to confirm whether this XRCC1 variant can alter pancreatic cancer risk.

Previous studies showed the cancer risk of XRCC1 SNP were mostly at Arg399Gln genotypes^[12-14]. Arg399Gln is located at the carboxylic acid terminal side of the poly adenosine diphosphate-ribose polymerase interacting domain and has been shown to reduce DNA repair capacity, and somatic glycoprotein a mutations were significantly

higher in Arg399Gln homozygotes than in heterozygotes^[27]. But in this meta-analysis, the Arg399Gln SNP was not associated with pancreatic cancer risk.

Cigarette smoke is important potential factor for pancreatic cancer risk^[3]. In these four enrolled studies, two studies^[20, 23] included stratified analysis by cigarette smoke, another two studies^[21, 22] adjusted pancreatic cancer risk OR by cigarette smoke. And Duell et al^[23] found: among men, ORs for current active smoking and heavy smoking (≥ 41 pack-years or >40 years) were greater among Arg399Gln variant genotypes (Gln/Gln or Arg/Gln) than among nonvariant genotypes. But we can not conduct a stratified analysis for cigarette smoke because of not enough data and different stratified standard.

XRCC1 polymorphisms are affected by the race. In these four included studies, three studies^[20, 22, 23] were in the United States, and one study^[21] was in China. The enrolled people mostly were White, African Americans, and Asians. Only one study^[23] included stratified analysis by ethnic group and found no difference of XRCC1 SNP for pancreatic cancer risk in different ethnic group. And we also can not conduct a stratified analysis by ethnicity.

There are some limitations inherent in this kind of meta-analysis. First, only 4 eligible reports, with 1343 cases and 2302 controls enrolled in this meta-analysis. The number of studies included in this study was limited. Second, each study had different eligibility criteria for inclusion of subjects and different sources of controls. For example, three studies^[20-22] were hospital-based, and one^[23] was population-based. The allele distribution in the hospital control groups might not have been representative of the general population. Third, although an Egger's test did not reveal significant publication bias in current analysis, it is still possible that our findings are biased for many non-English literatures are not included.

Larger studies with different ethnic populations are needed to clarify possible roles of XRCC1 polymorphisms in the etiology of pancreatic cancer. We will follow closely the progress of relevant research, regularly updated on the meta-analysis, to draw more reliable conclusions for XRCC1 gene polymorphism and pancreatic cancer risk.

In conclusion, the present study shows no evidence that XRCC1 polymorphisms (Arg194Trp, Arg280His, and Arg399Gln) are associated with pancreatic cancer risk.

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