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ORIGINAL ARTICLE

Lack of associations between XPC polymorphisms and colorectal cancer: a meta-analysis

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Summary

Purpose: *The relationships between XPC polymorphisms (Lys939Gln and Ala499Val) and the susceptibility to colorectal cancer (CRC) have been studied by several researchers, but the results were inconclusive. To get a more precise estimation of the relationships, we conducted this meta-analysis.*

Methods: *A total of 9 case-control studies, including 3679 cases and 33551 controls for Lys939Gln and 1327 cases and 30438 controls for Ala499Val, were selected. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association in the additive, dominant and recessive models.*

Results: *When all the studies were pooled into the meta-analysis, no evidence showing a significant association between XPC polymorphisms and CRC risk was noticed. In the subgroup analysis by ethnicity and study design, no significant association was also found.*

Conclusion: *In conclusion, this meta-analysis indicated that the XPC polymorphisms were not risk factors for the development of CRC.*

Key words: *colorectal cancer, meta-analysis, polymorphism, susceptibility, XPC*

Introduction

CRC is one of the leading cause of cancer morbidity and mortality in the world. Studies had suggested that genetic factors can explain about a third of the trait variance [1]. The development of CRC is a complex, gradual, multistep process, in which many factors are known to be implicated. Colorectal carcinogenesis is characterized by several alterations in DNA sequences involved in numerous molecular pathways, such as tumor suppressors, oncogenes and genes involved in the DNA repair process, such as APC (Adenomatous Polyposis Coli), K-ras (Kirsten-ras), DCC (Deleted in Colorectal Cancer) and mismatch repair (MMR) [2].

In addition to the genes mentioned above, much attention had been focused on xeroderma pigmentosum group C (XPC) gene, a DNA repair gene involved in the nucleotide excision repair (NER) mechanism which repairs bulky DNA lesions such as pyrimidine dimers, ultraviolet light-induced damage, photoproducts, intrastrand cross links, larger chemical adducts and other genotoxic agents [3]. Genetic variations in the XPC gene have been reported to modulate an individual's susceptibility to developing cancer .

A number of studies had been conducted to investigate the associations of XPC polymorphisms

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and colorectal cancer risks. The most informative polymorphism among XPC gene are Ala499Val (rs2228000) and Lys939Gln (rs2228001).Numerous studies have focused on the association between these polymorphisms and CRC risk; however, the conclusions were controversial. This inconsistency could be due to the relatively small sample size of each study and weak effect that the polymorphisms may have on CRC risk. So, we performed this meta-analysis based on all the published studies to draw a more precise estimation of this association.

Methods

Studies identification

We carried out a search in the PubMed and Chinese National Knowledge Infrastructure (CNKI) without language limitation, covering all papers published up to August 2014, with the following keywords: "*XPC or Xeroderma pigmentosum group C*", "polymorphism or variant" and "colorectal cancer or tumor or carcinoma or neoplasm". We evaluated the potentially associated publications by checking their titles and abstracts and then procured the most relevant publications for a closer examination. Moreover, the reference lists of the selected papers were also screened for other potential articles that could have been missed in the initial search.

Selection criteria

The following criteria were used for the literature selection of studies for further analysis: (a) studies concerning the association between XPC polymorphism and CRC; (b) case-control studies; (c) papers showing clear CRC diagnosis and the sources of cases and controls; (d) sufficient information to estimate ORs and their 95 % CIs. After searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data extraction

Data were carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria mentioned above. For conflicting evaluations, agreement was reached by discussion. If a consensus could not be reached, another author was consulted to resolve the dispute and then a final decision was made by the majority of the votes. The following data was collected from each study: first author's name, year of publication, country of origin, ethnicity, control source (hospital-based or population-based), genotyping methods, and numbers of cases and controls with the *XPC* different genotypes plus with their corresponding total number. The stratification analysis was conducted by ethnicity and study design [4-6].

Statistics

The ORs of XPC polymorphisms and CRC risk were estimated for each study. The effect of association was indicated as OR and the corresponding 95% CI. The pooled ORs were performed for additive model, dominant model and recessive model, respectively. A x^2-based Q statistic test was performed to assess heterogeneity. A p value >0.05 for the Q-test indicated lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (Mantel–Haenszel method) [7]. Otherwise, the random-effects model (DerSimonian and Laird method) [8] was used. The Hardy–Weinberg equilibrium (HWE) was assessed via Fisher's exact test. Publication bias was assessed by visual inspection of funnel plots [9], in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot indicated possible publication bias. The symmetry of the funnel plot was further evaluated by Egger's linear regression test ($p<0.05$ was considered representative of statistically significant publication bias) [10]. Statistical analyses were performed using the program STATA version 11.0 (Stata Corporation, College Station, TX). All statistical analyses were two sided and $p<0.05$ was considered significant.

Results

Study characteristics

Through literature search and the selection methodology described above, a total of 12 published studies were retrieved. By rigorous assessment of abstracts and contents, 9 publications met the inclusion criteria and were subjected to further examination [6,11-18]. The details are listed in Table 1. Lys939Gln and Ala499Val were reported in 9 studies (3679 cases and 33551 controls) [6,11-18], and in 3 studies (1327 cases and 30438 controls) [11,15,17], respectively. The genotype distribution of the Lys939Gln polymorphism was in compliance with HWE in the controls of all studies, whereas the distributions of genotypes for Ala499Val in one study were deviated from HWE [11]. Since the distribution of Lys939Gln polymorphism followed HWE (HWE=0.77) in the same study, we decided to include it in the final analysis. All of the cases were pathologically confirmed. Controls were mainly healthy people matched by age, sex and ethnicity.

Meta-analysis results

The overall results indicated that there were no significant associations between the two studied XPC polymorphisms and the risk of CRC (Table 2). For Lys939Gln, the overall data showed that

Table 1. Main characteristics of all studies included in the meta-analysis

First author [Ref.no.]	Year	Country	Ethnicity	Design	Method	Cases	Control	Cases			Controls		
								AA	AC	CC	AA	AC	CC
Lys939Gln													
Aizat [6]	2013	Malaysia	Asian	hospital-based	PCR-RFLP	255	255	108	106	41	129	100	26
Berndt [11]	2006	USA	Caucasian	population-based	TaqMan	244	29236	81	110	53	9791	14277	5168
Engin [12]	2010	Turkey	Caucasian	hospital-based	PCR-RFLP	110	116	22	63	25	25	55	36
Gil [13]	2012	Poland	Caucasian	hospital-based	PCR-RFLP	133	100	48	71	14	43	46	11
Hansen [14]	2007	Denmark	Caucasian	population-based	TaqMan	395	797	141	204	50	307	392	98
Huang [15]	2006	USA	Mixed	population-based	Not available	665	667	253	300	112	241	312	114
Liu [16]	2012	China	Asian	hospital-based	PCR-RFLP	1028	1085	360	565	103	453	500	132
Wu [17]	2011	China	Asian	population-based	PCR-RFLP	421	845	155	204	61	363	375	104
Yue [18]	2013	China	Asian	hospital-based	PCR-RFLP	428	450	174	212	64	142	225	61
Ala499Val													
Berndt [11]	2006	USA	Caucasian	population-based	TaqMan	219	28897	123	85	11	16983	10515	1399
Huang [15]	2006	USA	Mixed	population-based	Not available	689	703	397	261	31	403	259	41
Wu [17]	2011	China	Asian	population-based	PCR-RFLP	419	838	172	195	52	315	406	117

Table 2. Summary of OR for XPC polymorphisms and colorectal cancer risk

Variables	Number of studies	Homozygous OR (95%CI)	P_h	Recessive OR (95%CI)	P_h	Dominant OR (95%CI)	P_h
Lys939Gln		AA vs CC		(AC+AA) vs CC		AA vs (AC+CC)	
Total	9	0.92 (0.8-1.05)	0.33	0.97 (0.86-1.10)	0.16	0.9 (0.78-1.03)	0.03
Ethnicity							
Caucasian	4	0.88 (0.70-1.12)	0.77	0.93 (0.75-1.15)	0.24	0.91 (0.77-1.08)	0.82
Asian	4	0.89 (0.74-1.07)	0.07	0.98 (0.83-1.17)	0.06	0.85 (0.67-1.09)	0.01
Design							
Hospital-based	5	0.97 (0.79-1.19)	0.2	1.08 (0.90-1.31)	0.11	0.86 (0.67-1.12)	0.03
Population-based	4	0.88 (0.74-1.05)	0.43	0.90 (0.76-1.05)	0.56	0.93 (0.80-1.08)	0.21
Ala499Val		CC vs TT		(CC+CT) vs TT		CC vs (CT+TT)	
Total	3	1.19 (0.91-1.56)	0.665	1.16 (0.89-1.50)	0.73	1.02 (0.89-1.18)	0.39

P_h: P value of Q test for heterogeneity test

the individuals who carried the AA genotype did not have a significantly increased CRC risk compared with those who carried the CC genotype (additive model, OR=0.92, 95% CI=0.8-1.05); no significant association was found in the dominant model (OR=0.92, 95% CI=0.78-1.03) or the recessive model (OR=0.97, 95% CI=0.86-1.10). The subgroup analysis based on the ethnicity and study design showed no obvious associations; details are listed in Table 2. In the case of Ala499Val, there was no significant association between this polymorphism and CRC risk.

Heterogeneity analysis

No obvious heterogeneities were observed in the overall analysis evaluating the association between XPC Lys939Gln and CRC risk in the homozygous model (p=0.33) and the recessive model (p=0.16), except the dominant model (p=0.03). For the Ala499Val polymorphism, all inheritance models did not show significant heterogeneity (homozygous model, p=0.67; recessive model, p=0.73; dominant model, p=0.39).

Sensitivity analyses

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not substantially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Begg's funnel plots and Egger's test were performed to assess publication bias. The shapes of the funnel plots revealed no obvious asymmetry. The Egger's test was then used to statistically assess funnel plot symmetry. There was no evidence of publication bias in reporting the association between Ala499Val and risk of CRC for all statistical models (p=0.48 for the additive model, p=0.75 for the dominant model, and p=0.77 for the recessive model). In the case of Lys939Gln, no publication bias was found in all statistic models (p=0.67 for the additive model, p=0.86 for the dominant model, and p=0.86 for the recessive model). The results indicated that the meta-analysis was relatively stable and that publication bias was unlikely to affect the results of the meta-analysis.

Discussion

The XPC gene encodes a protein of 940 amino acids which is involved in the genome repair. XPC Lys939Gln polymorphism, which leads to an amino acid change from lysine to glutamine at codon 939, is the most common SNP studied in the XPC gene and has been shown to be associated with increased risk of several cancers, such as cancers of the skin [19], breast [20] and bladder [21]. For CRC, previous studies have reported conflicting results about the association between XPC polymorphisms and the risk of CRC, which might have been influenced by the relatively small sample sizes and different genetic backgrounds. Meta-analysis is a powerful method for resolving inconsistent findings with a relatively large number of subjects. In this meta-analysis, we included a total of 3679 cases and 33551 controls for Lys939Gln and 1327 cases and 30438 controls for Ala499Val to investigate the associations between these polymorphisms and CRC risk. Our results indicated that these two polymorphisms were not significantly associated with CRC risk. And, in the subgroup analysis by ethnicity and study design, we did not find any association between these polymorphisms and CRC risk.

Cigarette smoking is a major risk factor for CRC. In an attempt to distinguish CRC risk between smokers and nonsmokers, we tried to assess the association between these polymorphisms and CRC risk, but there were very few studies providing detailed information on smoking status for Lys939Gln (2 studies), Ala499Val (no study). Not surprisingly, due to the limited number of studies as well as little information, we did not find any statistically significant difference in the risk of CRC among different smoking statuses based on Lys939Gln (data not shown).

There are some limitations in this meta-analysis. First, our results were based on unadjusted estimates and a more precise analysis could be conducted if individual data were available; this would allow for adjustment by other covariates such as age, environmental factors and lifestyle. And second, in the stratified analyses, the number of subgroups was relatively small, not having enough statistical power to investigate the association of the polymorphism with CRC susceptibility.

In conclusion, this meta-analysis indicates that the two polymorphisms of XPC were not risk factors for the development of CRC. However, it is necessary to conduct large studies using standardized unbiased genotyping methods, homogeneous CRC patients and well-matched controls.

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