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Association of xeroderma pigmentosum complementation group G Asp1104His polymorphism with breast cancer risk: A cumulative meta-analysis

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Abstract. The xeroderma pigmentosum complementation group G (XPG) gene plays an important role in the DNA nucleotide excision repair (NER) pathway. Several studies have investigated the association between the XPG Asp1104His polymorphism and breast cancer; however, the results have been inconsistent. Therefore, we conducted a meta-analysis of 8 published articles (10 case-control studies) including a total of 5,235 patients with breast cancer and 5,685 healthy controls. The results demonstrated that the XPG Asp1104His polymorphism was not associated with breast cancer in the overall population [His vs. Asp, odds ratio (OR)=1.00, 95% confidence interval (CI): 0.91-1.08; His/His vs. Asp/Asp, OR=0.96, 95% CI: 0.83-1.11; Asp/His vs. Asp/Asp, OR=1.02, 95% CI: 0.94-1.11; His/His+Asp/His vs. Asp/Asp, OR=1.03, 95% CI: 0.92-1.15; and His/His vs. Asp/Asp+Asp/His, OR=0.93, 95% CI: 0.81-1.06]. In the subgroup analysis by ethnicity, no significant association was observed in European subjects. In conclusion, this meta-analysis suggested that the XPG Asp1104His polymorphism is not associated with breast cancer risk.

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related mortality among women worldwide, accounting for 1.38 million new cancer cases and 458,400 deaths in 2008 (1). Over the last few years, the incidence rates of breast cancer have increased in most countries. Several studies have found that the development of breast cancer is possibly associated with tobacco, alcohol consumption and other environmental factors (2,3). Furthermore, interindividual differences, including single-nucleotide polymorphisms, may affect protein activity and alter the susceptibility to developing breast cancer. The nucleotide excision repair (NER) system plays an important role in DNA repair; this system recognizes the DNA damage and incises the DNA strand on both sides of the lesion, removes the oligonucleotide containing the damage and reconstructs the corrected fragment.

The xeroderma pigmentosum complementation group G (XPG) gene is an important component of the NER system and is also referred to as excision repair cross-complementation group 5 (ERCC5). The fundamental structure of the human ERCC5 protein contains N- and I-nuclease domains that are highly conserved and collectively form the nuclease core. The N- and I-nuclease domains are separated by 600 amino acids that constitute a critical region for protein-protein interactions, including with transcription factor IIH (TFIIH) and replication protein A (RPA) and combine ERCC5 with the sites of NER (4).

The mutation of nucleotides may alter gene function and affect protein construction, which in turn alters the mechanical interactions and the function of the NER system during cellular DNA repair. The Asp1104His (G>C) polymorphism (rs17655) results in an aspartic acid to histidine transition at position 1104 in exon 15, which may affect protein activity and interaction with TFIIH, affect the NER system and alter genetic susceptibility to cancer (5,6).

It was previously demonstrated that the variant genotype may affect susceptibility to different diseases, such as lung cancer (7) and bladder cancer (8), in different ethnicities and increase the risk of progression from HIV infection to AIDS (9). In 2003, Kumar *et al* (10) reported the first study on the association between the XPG Asp1104His polymorphism and breast cancer risk. To date, several studies on the XPG Asp1104His polymorphism and breast cancer have been conducted. However, the results of those studies have been

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Table I. Characteristics of case-control studies on XPG Asp1104His polymorphism and breast cancer risk included in the meta-analysis.

First author	Year	Country	Racial descent	Source of controls	Cases	Controls	Genotype distribution						P for HWE[a]	(Refs.)
							Cases			Controls				
							Asp/Asp	Asp/His	His/His	Asp/Asp	Asp/His	His/His		
Kumar	2003	Finland	Caucasian	PB	220	308	108	96	16	182	107	19	0.54	(10)
Mechanic	2006	America	Caucasian	PB	1,249	1,133	771	409	69	661	412	60	0.69	(16)
Mechanic	2006	America	African	PB	757	674	231	387	139	231	320	123	0.51	(16)
Shen	2006	America	Caucasian	Sisters	154	151	83	63	8	82	62	7	0.27	(17)
Crew	2007	America	Caucasian	PB	999	1,051	562	371	66	571	409	71	0.85	(18)
Jorgensen	2007	America	Caucasian	PB	264	275	159	93	12	165	95	15	0.78	(19)
Rajaraman	2008	America	Mixed	PB	819	1,079	482	288	49	674	352	53	0.42	(20)
Smith	2008	America	Caucasian	HB	320	408	195	113	12	256	124	28	0.02	(21)
Smith	2008	America	African	HB	52	75	13	32	7	18	37	20	0.91	(21)
Ming-Shiean	2010	China	Asian	HB	401	531	134	191	76	159	243	129	0.06	(22)

[a]Hardy-Weinberg equilibrium in controls. XPG, xeroderma pigmentosum complementation group G; PB, population-based; HB, hospital-based.

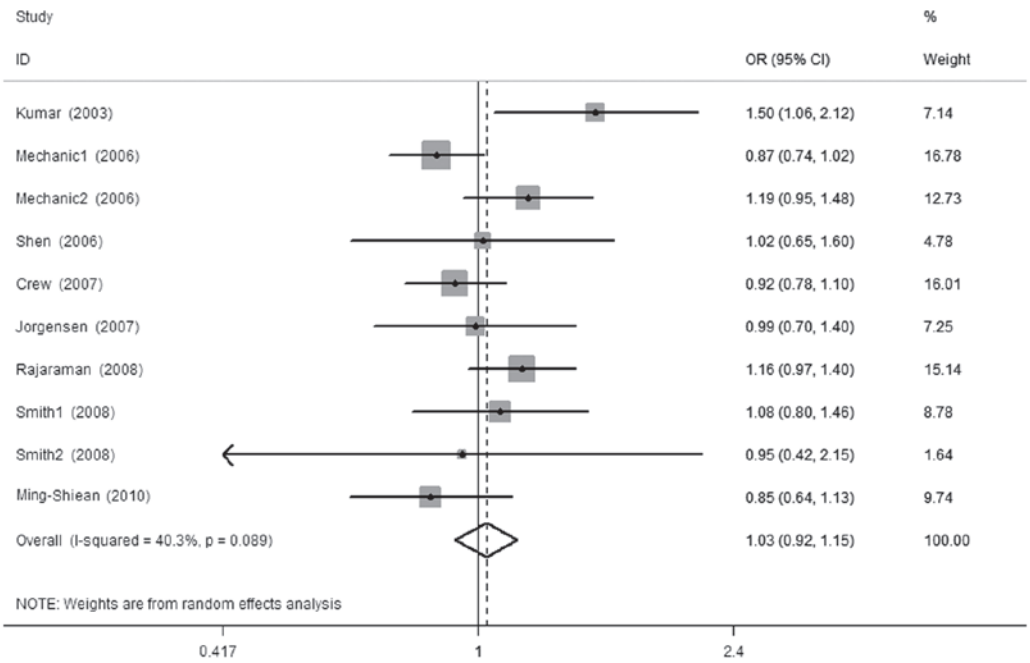

Figure 1. OR of breast cancer associated with XPG Asp1104His polymorphism for the His/His+Asp/His vs. Asp/Asp model in total. OR, odds ratio; CI, confidence interval; XPG, xeroderma pigmentosum complementation group G.

inconsistent or even contradictory. Therefore, we performed the meta-analysis to assess the association between the XPG Asp1104His polymorphism and breast cancer risk based on the currently available published studies.

Materials and methods

Search strategy. The US National Library of Medicine's PubMed database was searched using the terms 'breast cancer', 'XPG', 'ERCC5', 'polymorphism' and their combinations for all genetic studies on the association between Asp1104His polymorphism and breast cancer risk during the time period from 2003, when the first study was reported by Kumar *et al* (10), to May, 2014. The 'Related Articles' application was used to identify additional studies on the same subject. All the studies were selected using the following three criteria: i) case-control study of the XPG Asp1104His polymorphism and breast cancer; ii) sufficient published data for estimating

Table II. Summary ORs and 95% CIs of XPG Asp1104His polymorphism and breast cancer risk.

Variables	No.[a]	His vs. Asp				His/His vs. Asp/Asp				Asp/His vs. Asp/Asp				His/His+Asp/His vs. Asp/Asp				His/His vs. Asp/Asp+Asp/His			
		OR	95% CI	P	P_h[b]	OR	95% CI	P	P_h[b]	OR	95% CI	P	P_h[b]	OR	95% CI	P	P_h[b]	OR	95% CI	P	P_h[b]
Total	10	1.00	0.91-1.08	0.92	0.082	0.96	0.83-1.11	0.62	0.265	1.02	0.94-1.11	0.57	0.098	1.03	0.92-1.15	0.62	0.089	0.93	0.81-1.06	0.29	0.286
HWE	9	1.00	0.91-1.10	0.98	0.054	0.99	0.85-1.15	0.88	0.362	1.04	0.92-1.17	0.57	0.088	1.02	0.91-1.16	-	0.061	0.95	0.83-1.09	0.48	0.420
Ethnicity																					
Caucasian	7	1.00	0.94-1.08	0.90	0.148	1.01	0.84-1.22	0.94	0.491	1.01	0.92-1.10	0.90	0.058	1.03	0.91-1.18	0.63	0.072	1.01	0.84-1.21	0.95	0.556
African	2	1.05	0.91-1.21	0.50	0.173	1.06	0.79-1.42	0.68	0.152	1.21	0.96-1.52	0.10	0.983	1.17	0.94-1.45	0.15	0.603	0.74	0.33-1.66	0.47	0.088
Design																					
Population-based	6	1.04	0.94-1.15	0.49	0.074	1.08	0.91-1.27	0.38	0.756	1.02	0.93-1.11	0.68	0.021	1.06	0.91-1.23	0.45	0.021	1.04	0.89-1.22	0.62	0.928
Hospital-based	3	0.87	0.15-1.00	0.05	0.573	0.65[c]	0.48-0.89[c]	0.006[c]	0.748[c]	1.06	0.86-1.30	0.61	0.509	0.95	0.78-1.16	0.61	0.526	0.66[c]	0.50-0.87[c]	0.003[c]	0.456[c]

[a]Number of comparisons. [b]Test for heterogeneity. [c]Statistical significance. Bold print denotes statistical significance. OR, odds ratio; CI, confidence interval; XPG, xeroderma pigmentosum complementation group G; HWE, Hardy-Weinberg equilibrium.

Figure 2. Funnel plot analysis for the detection of publication bias for the His/His+Asp/His vs. Asp/Asp model. Each point represents a separate study. OR, odds ratio; SE, standard error.

Figure 3. Sensitivity analysis through sequentially deleting each of the studies to determine the effect of the individual dataset on the pooled ORs in the His/His+Asp/His vs. Asp/Asp model of XPG Asp1104His polymorphism. OR, odds ratio; CI, confidence interval; XPG, xeroderma pigmentosum complementation group G.

odds ratios (ORs) with 95% confidence intervals (CIs); and iii) when multiple publications reported similar or overlapping data, we selected the largest or most recent publication, as recommended by Little *et al* (11) The characteristics of the studies are summarized in Table I.

Data extraction. Two investigators (Xu and Xie) independently extracted the following data from the 8 publications: first author's name, publication year, country of origin, source of controls, racial descent of the study population (Asian, African, European and mixed), number of different genotypes and Hardy-Weinberg equilibrium (HWE) in controls.

Statistical analysis. Crude ORs with 95% CIs were computed to assess the strength of the association between the XPG Asp1104His polymorphism and breast cancer risk for the allele contrast (His vs. Asp), codominant model (His/His vs. Asp/Asp; Asp/His vs. Asp/Asp), dominant model (His/His+Asp/His vs. Asp/Asp) and recessive model (His/His vs. Asp/Asp+Asp/His). Subgroup statistical analysis was only conducted in Europeans, owing to the small sample of African and Asian subjects. Heterogeneity was assessed with

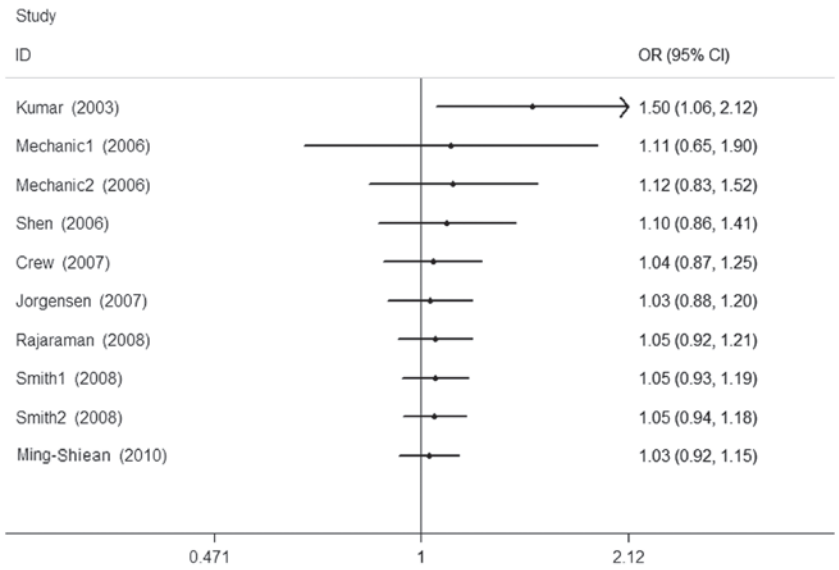

Figure 4. Cumulative meta-analyses according to author name and publication year in the His/His+Asp/His vs. Asp/Asp model. OR, odds ratio; CI, confidence interval.

the Chi-square-based Q test (12) and the pooled OR estimation of each study was calculated with the random-effects model (DerSimonian and Laird method) when P<0.10 (13); otherwise, the fixed-effects model (Mantel-Haenszel method) was used (14). Publication bias was evaluated with the funnel plot and the linear regression asymmetry test by Egger *et al* (15). P<0.05 was considered to reflect significant publication bias. Statistical analysis was performed with STATA software, version 11.0 (StataCorp, College Station, TX, USA), using two-sided P-values.

Results

Study characteristics. A total of 8 eligible articles (10 case-control studies) including 5,235 patients with breast cancer and 5,685 healthy control subjects, were included in this meta-analysis (10,16-22). Of the 10 studies, 6 were conducted in European, 2 in African, 1 in Asian and 1 in mixed populations. The genotyping methods comprised polymerase chain reaction-restriction fragment length polymorphism, TaqMan and sequence detection system. The distribution of genotypes in the controls was in agreement with HWE, as in the study by Smith *et al* (21) in European subjects.

Meta-analysis. The results of this meta-analysis and heterogeneity assessment are presented in Table II. Overall, there were no significant associations between the XPG Asp1104His polymorphism and breast cancer risk (His vs. Asp, OR=1.00, 95% CI: 0.91-1.08, P_h=0.082; His/His vs. Asp/Asp, OR=0.96, 95% CI: 0.83-1.11, P_h=0.265; Asp/His vs. Asp/Asp, OR=1.02, 95% CI: 0.94-1.11, P_h=0.098; His/His+Asp/His vs. Asp/Asp, OR=1.03, 95% CI: 0.92-1.15, P_h=0.089, Fig. 1; and His/His vs. Asp/Asp+Asp/His, OR=0.93, 95% CI: 0.81-1.06, P_h=0.286). In the subgroup analysis by ethnicity, we also did not identify any significant associations between the XPG Asp1104His polymorphism and breast cancer risk in European subjects. Further analysis was performed only with studies that fulfilled HWE and no significant associations were observed.

Publication bias. Funnel plots were drawn and Egger's tests were performed to access publication bias. The shape of the funnel plots revealed symmetricity (Fig. 2, His/His+Asp/His vs. Asp/Asp model). These results were further supported by analysis via Egger's tests, which suggested that all models without significant publication bias (P=0.986 for His vs. Asp; P=0.456 for His/His vs. Asp/Asp; P=0.217 for Asp/His vs. Asp/Asp; P=0.484 for His/His+Asp/His vs. Asp/Asp; and P=0.440 for His/His vs. Asp/Asp+Asp/His).

Cumulative and sensitivity analysis. Studies were sequentially deleted to determine the effect of the individual dataset on the pooled ORs (Fig. 3, His/His+Asp/His vs. Asp/Asp model). The results were consistent in all the genetic models, indicating that our results are statistically robust. In the cumulative meta-analysis, results that became negative from the second study were accumulated (Fig. 4, His/His+Asp/His vs. Asp/Asp model).

Discussion

The XPG gene is located on chromosome 13q33 and encodes a 1,186-amino acid structure-specific endonuclease, which is a member of the flap endonuclease family and plays an important role in the NER system (23). This enzyme may combine actions with XPB helicase and ERCC2/XPD helicase at the DNA damage site (7) and make 3'-incisions in human NER through incising DNA at a junction of single- to double-stranded DNA, such as bubbles and loop structures (24). A dual incision may be performed, with ERCC1-XPF making the 5'-incision. Additionally, XPG may involved in the stabilization of a pre-incision complex on the damaged DNA and stimulate the binding of human endonuclease III to thymine and glycol-containing DNA (25). A previous molecular study reported that the deficiency of XPG may result in certain epithelial diseases, such as XP (26). Furthermore, several studies also indicated that mutations in the XPG gene are associated with the development of diseases such as lung cancer and osteosarcoma (27,28).

Previous reports on the association between the XPG Asp1104His polymorphism and breast cancer were discrepant or even contradictory. Kumar *et al* (10) found that the genotype with the C allele (His) was associated with a ~1.5-fold increased risk for breast cancer in European subjects (OR=1.5, 95% CI: 1.04-2.16) in 2003. By contrast, Ming-Shiean *et al* (22) considered the G allele variant (Asp) to be significantly associated with breast cancer in Asian subjects (OR=1.42, 95% CI: 1.08-1.97). However, other studies reported no association between the XPG Asp1104His polymorphism and breast cancer risk.

This meta-analysis included 10 case-control studies, involving 5,235 patients with breast cancer and 5,685 healthy controls. No significant association was found between the XPG Asp1104His polymorphism and breast cancer risk, not even in the subgroup analysis of European subjects. According to the results, certain limitations of this meta-analysis need to be addressed. First, the sample of breast cancer patients and controls was inadequate to reach a definitive conclusion. Second, we were unable to obtain more original data and the results were based on unadjusted estimates, lacking the evaluation of the covariates of age, menopausal status, smoking and alcohol consumption and other environmental factors, which limited the evaluation of the interaction effect of genes and environmental or other factors. Third, there was some heterogeneity in different models, but it was successfully removed or alleviated in the subgroup analysis. Despite these limitations, the statistical assessment of publication bias, cumulative and sensitivity analyses all indicated that our results are credible.

In conclusion, our meta-analysis indicated that the XPG Asp1104His polymorphism is not associated with breast cancer risk. However, further, large-scale epidemiological studies are required to validate these conclusions.

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