RESEARCH ARTICLE

The XPD Lys751Gln Polymorphism has Predictive Value in Colorectal Cancer Patients Receiving Oxaliplatin-Based Chemotherapy: a Systemic Review and Meta-analysis

Ying-Ying Qian[1&], Xin-You Liu[2&], Dong Pei[1], Jia-Li Xu[1], Hua Shen[1], Xiao-Feng Chen[1], Yi-Qian Liu[1], Li-Zong Shen[2], Yong-Qian Shu[1*]

Abstract

Background: The predictive value of the xeroderma pigmentosum group D (XPD) Lys751Gln polymorphism regarding clinical outcomes of patients with colorectal cancer (CRC) receiving oxaliplatin-based chemotherapy has been evaluated in numerous published studies, but the results remain inconclusive. Therefore, we performed a meta-analysis to determine the precise role of the XPD Lys751Gln polymorphism in this clinical situation and optimize individual chemotherapy. Materials and Methods: A multiple search strategy was used to identify eligible studies. Pooled odds ratios (ORs), generalized odds ratio (ORG) and their 95% confidence intervals (CIs) were used to estimate the objective response, while hazard ratios (HRs) with 95%CIs were used for progression-free survival (PFS) and overall survival (OS). Results: A total of 17 studies including 2,286 patients met the inclusion criteria. Overall, the XPD 751Gln allele was associated with a non-significant reduced objective response to oxaliplatin-based chemotherapy in all patients or in the Asian and Caucasian subgroups. However, poor PFS and OS of CRC patients treated with oxaliplatin-based regimens were significantly related to the XPD 751Gln allele in the dominant model (PFS: HR=2.10, 95%CI: 1.65-2.67; OS: HR=3.18, 95%CI: 1.57-6.47). On stratified analysis by ethnicity, these relationships were more pronounced in Asians (PFS: HR=2.49, 95%CI: 1.79-3.47; OS: HR=5.25, 95%CI: 3.46-7.94) than in Caucasians (PFS: HR=1.73, 95%CI: 1.22-2.46; OS: HR=1.78, 95%CI: 1.06-2.99). Conclusions: The XPD Lys751Gln polymorphism may have prognostic value in patients with CRC undergoing oxaliplatin-based chemotherapy.

Keywords: XPD - oxaliplatin - prognosis - chemotherapy - meta-analysis

Asian Pac J Cancer Prev, **15 (22)**, 9699-9706

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and is the fourth main cause of cancer-related mortality worldwide. Upon diagnosis, a significant proportion of cases are in the advanced stage, whose prognosis is dismal, as less than 10% of patients survive beyond 5 years (Jemal et al., 2011). Chemotherapy either in the adjuvant or palliative setting has been the mainstay for advanced CRC. Oxaliplatin, a relatively new cytotoxic platinum compound, is considered the standard first-line treatment for advanced or metastatic CRC in combination with fluoropyrimidines; together they have been proven to reduce the relative risk of recurrence by 20-23% and to increase overall survival by 4.2% (Kuebler et al., 2007; Haller et al., 2011). However, previous studies have shown that a large proportion of patients developed varying levels of resistance to oxaliplatin. Oxaliplatin has shown to exert its antitumor action through the generation of platinum-DNA adducts that result in blockage of DNA replication, inhibition of transcription and ultimately apoptosis of tumor cells (Faivre et al., 2003). Therefore, it is conceivable that DNA repair capacity (DRC) plays a key role in the oxaliplatin sensitivity of colorectal tumors and influences clinical outcomes of treated cancer patients.

The nucleotide excision repair (NER) pathway, one of the major DNA repair systems, is thought to remove bulky, helix-distorting DNA adducts produced by platinum agents such as oxaliplatin in various tumor cells (Martin et al., 2008; Zhang et al., 2012; Sun et al., 2013). The xeroderma pigmentosum group D (XPD), also known as the excision repair cross-complementing group 2 (ERCC2), encodes a helicase that is a component of transcription factor TFIIH, which participates in the opening of the damaged DNA during NER (Fuss and Tainer, 2011). One common nucleotide polymorphism at codon 751 of the XPD [Lys751Gln (rs13181, G>A)], which has been frequently studied and identified to contribute to inter-individual diversity in DRC (Spitz et al., 2001; Wang et al., 2013), may be an efficient prognostic

*[1]Department of Oncology, [2]Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China [&]Equal contributors *For correspondence: shuyongqian2014@gmail.com*

factor for both CRC overall survival and oxaliplatin-based chemotherapy response.

Recently a large number of studies have evaluated the effects of XPD Lys751Gln on clinical outcomes of oxaliplatin-based chemotherapy in CRC patients, but the results are inconsistent. Therefore, we performed a meta-analysis of published studies to systematically address the relationship between the XPD Lys751Gln SNP and the efficacy of oxaliplatin-based chemotherapy in CRC patients.

Materials and Methods

CliSearch strategy and Study selection

We carried out a comprehensive search for relevant publications before August 1, 2014 in English or Chinese literature using electronic MEDLINE and EMBASE databases with the following terms "ERCC2 or XPD", "colon or colorectal cancer", and "polymorphism or variant".

Studies related to the relationship between the XPD polymorphism and clinical outcomes of oxaliplatin-based chemotherapy in CRC were included. The following detailed inclusion criteria were used: (1) patients with CRC received oxaliplatin-based chemotherapy; (2) patients received no other adjuvant treatment, such as radiotherapy or immunotherapy; (3) the XPD Lys751Gln (rs13181) polymorphism was genotyped; (4) primary outcomes of interest including objective response, progression-free survival (PFS) or overall survival (OS) were available. The following exclusion criteria were used: (a) oxaliplatin-based chemotherapy was used as the neoadjuvant treatment; (b) critical information was unavailable or could not be obtained by our repeated requests; (c) the report was unpublished or only an abstract was available; (d) studies by the same authors had similar or overlapping data.

Data extraction and quality assessment

Two investigators (Yingying Qian and Xinyou Liu) independently screened the published articles and extracted the data from included studies with a pre-designed data collection form. The two authors reached consensus on every item. The name of the first author, publication date, country of origin, ethnicity of patients, the number of enrolled patients, clinical stage, treatments, outcomes, and allele frequency were included as publication characteristics. Genotype distribution data among responders and non-responders, hazard ratios (HRs) for OS and PFS, and their 95% confidence intervals (CIs) were collected as result data. Ethnicity was categorized simply as Asian or Caucasian. If HR and 95%CI were not directly available from a report (Park et al., 2001; Le Morvan et al., 2007; Pare et al., 2008; Lai et al., 2009; Lamas et al., 2011; Chen et al., 2012), estimated value was obtained indirectly from Kaplan-Meier curves using the methods described by Tierney et al. (Tierney et al., 2007). Survival rates on Kaplan-Meier curves were identified by OriginPro 8 version 8.0725, and then the data read from Kaplan-Meier curves were entered in the calculation spreadsheet appended to Tierney's paper. In addition, the methodological quality of the included studies was assessed with the Newcastle-Ottawa scale (NOS) for cohort studies. The quality of the studies was evaluated based on the following three major components: Selection (4 items), Comparability (1 item), and Outcome (3 items). A study can be awarded a maximum of 4 stars, 2 stars and 3 stars for Selection, Comparability and Outcome, respectively. Studies with higher scores represent studies of higher quality.

Statistical analysis

To demonstrate the objective response rate, the pooled odds ratios (ORs) and 95%CI were estimated using five genetic comparison models (allele comparison, heterozygote comparison, homozygote comparison, dominant model and recessive model). We also performed the generalized odds ratio (ORG) which is a single statistic that utilizes the complete genotype distribution and provides an estimate of the overall risk effect to overcome the shortcomings of multiple model testing or erroneous model specification (Zintzaras, 2010). Response to chemotherapy was evaluated according to WHO criteria or the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse et al., 2000), which were divided into the following categories: "objective response" defined as ''complete response+partial response'' and ''no response'' which was ''stable disease+progressive disease''. The statistical significance of the pooled OR was determined by the Z-test. Pooled HRs for the homozygote comparison, heterozygote comparison and dominant model were calculated for PFS and OS. The presence of heterogeneity among studies was assessed using the I^2 statistic and the Chi-square test based on Cochran's Q statistic. A significant Q-test ($p<0.05$) or $I^2 > 50\%$ demonstrated the existence of heterogeneity, and the random effects model was used for meta-analysis; while $I^2<25\%$ and Q-test ($p\geq0.05$) were considered to display no significant heterogeneity, and a fixed effects model was used. Subgroup analyses were conducted according to ethnicities. WHO and RECIST criteria may overlap to a certain extent but are not the same. Thus, we also evaluated the effects of the XPD Lys751Gln polymorphism on the response to treatment separately for studies on RECIST and studies on WHO classification of response. The differences in the effect estimates between subgroups were compared as described previously (Altman and Bland, 2003). We performed the sensitivity analyses by removing each individual study once at a time to assess the influence of a single study on the pooled estimate. Egger's linear regression tests and Harbord's test were performed to evaluate the publication bias and differential magnitude of effect between small and large studies. Values of $p<0.05$ were indicative of statistically significant publication bias. All statistical tests were two-sided, and all analyses were performed using Stata software (version 10.0; Stata Corporation, College Station, Texas, USA) and Review Manager (Version 5.2; Oxford, England). The generalized odds ratio (ORG) was conducted using"ORGGASMA" software (University of Thessaly School of Medicine, Larissa, Greece).

Results

Search results and study selection

We identified 358 related records through a primary search of databases according to the search criteria. A total of 45 duplicate studies were eliminated. Following an initial screening of the title and abstract, 21 full-text articles met the preliminary inclusion criteria and were retrieved for further evaluation. We excluded three studies in which the data could not be estimated and whose authors were unreachable (Monzo et al., 2007; McLeod et al., 2010; Lee et al., 2013). Another additional study was excluded because patients were treated without oxaliplatin-based chemotherapy (Moreno et al., 2006) and patients in one study were treated with chemo-radiotherapy (Balboa et al., 2010). By contrast, one article consisted of two independent studies, and studies included in this article were treated as separate studies (Martinez-Balibrea et al., 2008). As a result, a total of 2286 CRC patients were enrolled in the 17 studies included in the pool analysis (Park et al., 2001; Stoehlmacher et al., 2004; Le Morvan et al., 2007; Ruzzo et al., 2007; Martinez-Balibrea et al., 2008; Pare et al., 2008; Lai et al., 2009; Boige et al., 2010; Chen et al., 2010; Etienne-Grimaldi et al., 2010; Farina Sarasqueta et al., 2011; Lamas et al., 2011; Chen et al., 2012; Gan et al., 2012; Li et al., 2012; Kumamoto et al., 2013). The selection procedure is shown in Figure 1, and the key patient characteristics are listed by study in Table 1. The quality of included studies was assessed by using NOS quality scale and the overall quality of studies was good, ranging from 6 to 9.

The XPD Lys751Gln polymorphism and objective response

Ten studies including 1195 patients were eligible to estimate the association between the XPD Lys751Gln polymorphism and the objective response to oxaliplatin-based chemotherapy in CRC patients. In the dominant model, carriers of the 751Gln allele were marginally correlated with reduced objective response in all patients (LysGln+GlnGln *vs* LysLys, OR=0.65, 95%CI: 0.43-1.00, Pheterogeneity=0.006; Figure 2, Table 2). However, there was no association between the XPD Lys751Gln polymorphism and the response rate in the allele, homozygous, heterozygous and recessive models (Table 2). The results of these different models were not consistent with each other and comprised a set of different estimates which were difficult to interpret. Thus, we introduced the ORG which utilized the complete genotype distribution and provided a global test for an association. We did not find significant results for ORG in all patients (ORG=0.65, 95%CI: 0.41-1.03), indicating that the XPD Lys751Gln polymorphism was not associated with objective response to oxaliplatin-based treatment in CRC patients (Table 2). Neither stratified analysis by ethnicity (Caucasians *vs* Asians) nor stratified analysis by response criteria (WHO *vs* RESICT) showed an association in the estimates of the effect of the XPD Lys751Gln polymorphism on response rate in any of the five comparison models (Figure 2, Table 2).

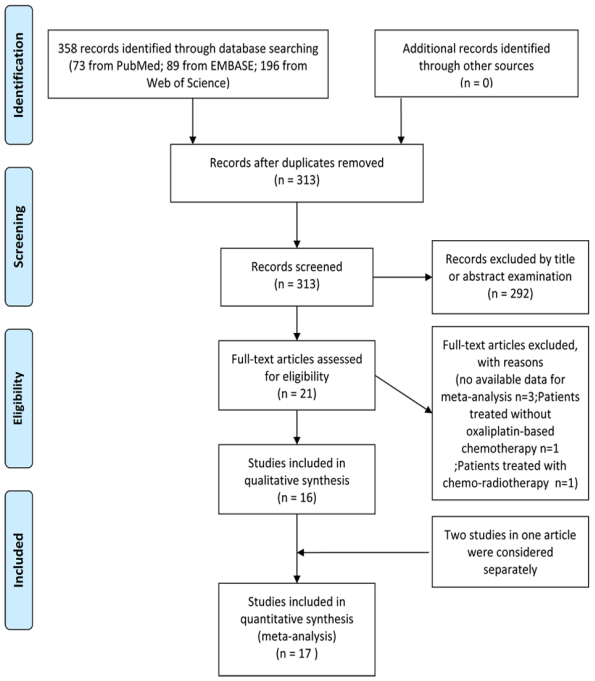

Figure 1. Flow Chart of Search Strategy and Study Selection

Table 1. Baseline Characteristics of Included Studies

First author	Year	Country	Ethnicity	Cases	Clinical stage	Treatment	Outcomes	Allele Freq
Park et al.	2001	U.S	Caucasian	70	Advanced CRC	FUOX	TR,OS	G:0.37
Stoehlmacher et al.	2004	U.S	Caucasian	106	Advanced CRC	FUOX	OS,PFS	G:0.41
Ruzzo et al.	2007	Italy	Caucasian	166	Advanced CRC	FOLFOX4	PFS	G:0.44
Le Morvan et al.	2007	France	Caucasian	59	Metastatic CRC	FOLFOX or XELOX	TR,PFS,OS	G:0.38
Martinez-Balibrea et al.	2008	Spain	Caucasian	47	Advanced CRC	XELOX	PFS	G:0.35
Martinez-Balibrea et al.	2008	Spain	Caucasian	49	Advanced CRC	FUOX	PFS	G:0.36
Pare´ et al.	2008	Spain	Caucasian	126	Metastatic CRC	FUOX	TR,PFS,OS	G:0.38
Chen et al.	2009	Taiwan	Asian	166	Metastatic CRC	FOLFOX4	TR,OS	G:0.08
Lai et al.	2009	Taiwan	Asian	188	Metastatic CRC	FOLFOX4	TR,PFS,OS	G:0.07
Etienne-Grimaldi et al.	2009	France	Caucasian	117	Advanced CRC	FOLFOX7	TR,PFS	G:0.39
Boige et al.	2010	France	Caucasian	292	Metastatic CRC	FOLFOX	TR	G:0.37
Farina Sarasqueta et al.	2011	Netherlands	Caucasian	43	Stage III colon cancer	FOLFOX or XELOX	PFS	G:0.38
Lamas et al.	2011	Spain	Caucasian	72	Metastatic CRC	FUOX	PFS	G:0.38
Gan et al.	2012	China	Asian	289	Advanced CRC	FUOX	TR,OS	G:0.30
Li et al.	2012	China	Asian	335	Advanced CRC	FOLFOX6	OS	G:0.31
Chen et al.	2012	China	Asian	98	Advanced CRC	FOLFOX	TR,PFS	G:0.14
Kumamoto et al.	2013	Japan	Asian	63	Metastatic CRC	FOLFOX6	TR	G:0.04

*OS, overall survival; PFS, progression-free survival; TR, therapeutic response; CRC colorectal cancer;; FUOX 5-fluorouracil plus oxaliplatin; FOLFOX oxaliplatin plus 5-FU and leucovorin; XELOX capecitabine plus oxaliplatin

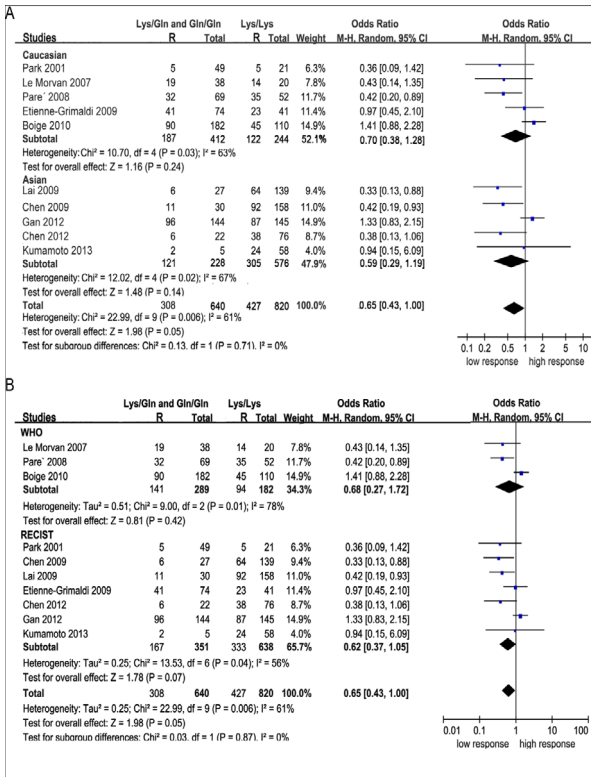

Figure 2. Association of the XPD Lys751Gln Polymorphism with Objective Response to Oxaliplatin-Based Chemotherapy for Colorectal Cancer. Forest plot of the dominant model (LysGlnZGlnGln *vs* LysLys). (A) stratified analysis according to ethnicity and (B) stratified analysis according to response criteria

The XPD Lys751Gln polymorphism and PFS

A total of 11 studies with 1648 patients were available for the final analysis of the XPD Lys751Gln polymorphism and PFS. The pooled results shown in Table 3 indicated that the minor variant 751Gln allele was associated with a markedly increased hazard for PFS in the homozygous comparison (GlnGln *vs* LysLys, HR=1.43, 95%CI: 1.06-1.93, Pheterogeneity=0.47) as well as in the dominant model (LysGln+GlnGln *vs* LysLys, HR=2.10, 95%CI: 1.65-2.67, Pheterogeneity=0.53; Figure 3A, Table 3). Likewise, we also observed significant correlation in the subgroups of Asian patients (dominant model, HR=2.49, 95%CI: 1.79-3.47, Pheterogeneity=0.88; Figure 3A, Table 3) and Caucasian patients (dominant model, HR=1.73, 95%CI: 1.22-2.46, Pheterogeneity=0.94; Figure 3A, Table 3).

The XPD Lys751Gln polymorphism and OS

Eight studies including 952 patients qualified for the analyses of the association between the XPD Lys751Gln polymorphism and OS. As shown in Figure 3B, pooled data from all patients demonstrated that the GlnGln and LysGln genotypes of XPD were remarkably correlated with poorer survival compared with the wild Lys751Gln genotype (LysGln+GlnGln *vs* LysLys, HR=3.18, 95%CI: 1.57-6.47, Pheterogeneity=0.0004). We did not find any significant association in the other two genetic models. Stratified analysis by ethnicity in the dominant model indicated more clinically substantial effects on OS in Asians (HR=5.25, 95%CI=3.46-7.94; Figure 3B, Table

Table 2. Meta-analysis of the Association between the XPD Lys751Gln Polymorphism and Objective response to Oxaliplatin-based Chemotherapy Treatment

Contrast	Subgroup	N of studies	OR	95%CI	P value of Egger's test	P value of Harbord's test	Heterogeneity P	Heterogeneity I^2(%)
Gln *vs* Lys	Overall	8	0.78	0.54-1.13	0.042	0.050	0.2	29
(allele comparison)	Caucasian	3	0.77	0.42-1.42	0.473	0.470	0.16	46
	Asian	5	0.71	0.40-1.30	0.122	0.158	0.19	35
	WHO	2	0.80	0.37-1.75	/	/	0.07	69
	RECIST	6	0.72	0.43-1.20	0.063	0.089	0.33	13
Lys/Gln+Gln/Gln *vs* Lys/Lys	Overall	10	0.65	0.43-1.00	0.018	0.030	0.006	61
(dominant model)	Caucasian	5	0.70	0.38-1.28	0.091	0.105	0.03	63
	Asian	5	0.59	0.29-1.19	0.239	0.304	0.02	67
	WHO	3	0.68	0.27-1.72	0.347	0.354	0.01	78
	RECIST	7	0.62	0.37-1.05	0.101	0.148	0.04	56
Gln/Gln *vs* Lys/Lys	Overall	5	0.76	0.34-1.69	0.441	0.354	0.07	53
(homozygote comparison)	Caucasian	3	0.70	0.40-1.22	0.577	0.579	0.16	45
	Asian	2	0.95	0.11-7.88	/	/	0.08	67
	WHO	2	0.65	0.21-1.97	/	/	0.07	70
	RECIST	3	0.78	0.17-3.66	0.085	0.105	0.11	54
Lys/Gln *vs* Lys/Lys	Overall	8	0.66	0.39-1.11	0.054	0.095	0.004	67
(heterozygote comparison)	Caucasian	3	0.72	0.27-1.93	0.322	0.331	0.02	75
	Asian	5	0.59	0.29-1.22	0.303	0.424	0.02	67
	WHO	2	0.88	0.28-2.83	/	/	0.02	83
	RECIST	6	0.56	0.30-1.07	0.189	0.289	0.03	61
Lys/Lys+Lys/Gln *vs* Gln/Gln	Overall	5	0.85	0.55-1.31	0.687	0.598	0.27	22
(recessive model)	Caucasian	3	0.70	0.42-1.18	0.718	0.734	0.65	0
	Asian	2	1.00	0.16- 6.45	/	/	0.12	59
	WHO	2	0.71	0.42-1.21	/	/	0.35	0
	RECIST	3	1.03	0.31-3.38	0.168	0.216	0.23	32
Generalized Odds Ratio	Overall	8	0.65	0.41-1.03	0.357	/	0.004	66

*OR, odds ratio; CI, confidence intervals

Table 3. Meta-analysis of the Association Between the XPD Lys751Gln Polymorphism and Progression-free Survival and Overall Survival

	Contrast	Subgroup	N of studies	HR	95%CI	P value of Egger's test	Heterogeneity *P*	Heterogeneity I^2(%)
PFS	Lys/Gln+Gln/Gln *vs* Lys/Lys (dominant model)	Overall	4	2.10	1.65-2.67	0.974	0.53	0
		Caucasian	2	1.73	1.22-2.46	/	0.94	0
		Asian	2	2.49	1.79-3.47	/	0.88	0
	Gln/Gln *vs* Lys/Lys (homozygote comparison)	Overall	7	1.43	1.06-1.93	0.056	0.47	0
		Caucasian	7	1.43	1.06-1.93	0.056	0.47	0
		Asian	/	/	/	/	/	/
	Lys/Gln *vs* Lys/Lys (heterozygote comparison)	Overall	8	1.13	0.78- 1.61	0.129	0.005	65
		Caucasian	7	1.03	0.82-1.30	0.235	0.16	35
		Asian	1	2.44	1.55-3.35	/	/	/
OS	Lys/Gln+Gln/Gln *vs* Lys/Lys (dominant model)	Overall	4	3.18	1.57-6.47	0.392	0.0004	83
		Caucasian	2	1.78	1.06-2.99	/	0.21	0
		Asian	2	5.25	3.46-7.94	/	0.37	36
	Gln/Gln *vs* Lys/Lys (homozygote comparison)	Overall	4	1.26	0.45- 3.51	0.183	0.002	85
		Caucasian	2	3.09	1.57-6.08	/	0.28	14
		Asian	2	0.51	0.33- 0.80	/	0.97	0
	Lys/Gln *vs* Lys/Lys (heterozygote comparison)	Overall	5	1.44	0.77-2.68	0.589	<0.0001	85
		Caucasian	2	1.51	0.94-2.43	/	0.17	46
		Asian	3	1.5	0.57-3.92	0.51	<0.0001	92

*CI, confidence interval; HR, Hazard ratio; OS, overall survival; PFS, progression-free survival

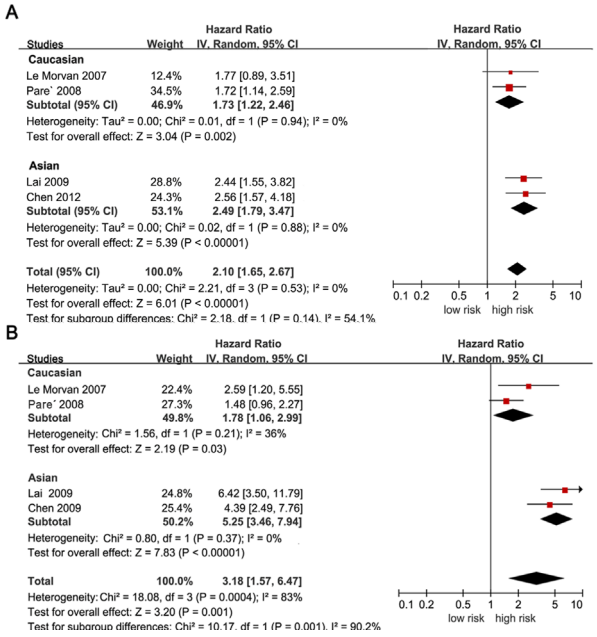

Figure 3. Association of the XPD Lys751Gln Polymorphism with Survival Following Oxaliplatin-Based Chemotherapy for Colorectal Cancer. Forest plot of the dominant model (LysGln+GlnGln *vs* LysLys). (A) progression-free survival and (B) overall survival

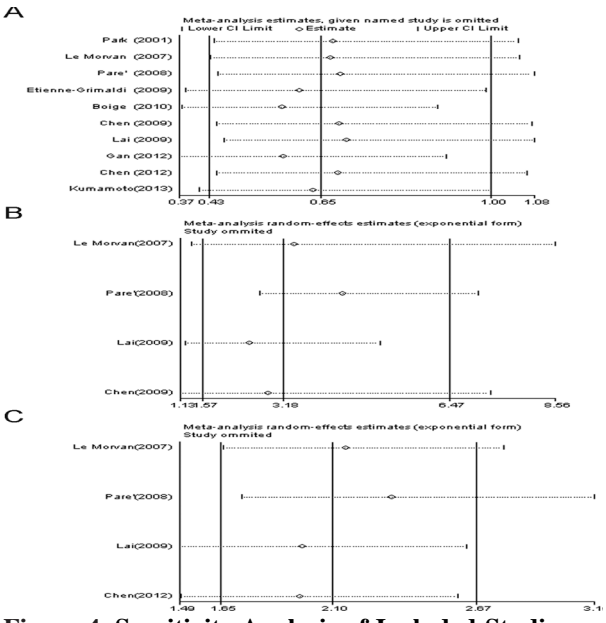

Figure 4. Sensitivity Analysis of Included Studies on Assessment of Association between the XPD Lys751Gln Polymorphism and (A) Objective response, (B) Progression-free Survival and (C) Overall Survival. The dominant model for the XPD Lys751Gln polymorphism (GlnGln+GlnLys *vs* LysLys)

3) than in Caucasians (HR=1.78, 95%CI=1.06-2.99; Figure 3B, Table 3). Further comparison displayed a markedly significant difference in the estimates of effect between Asian and Caucasian populations (p<0.0001). Nevertheless, according to the homozygous comparison, GlnGln genotype was associated with poor survival in Caucasian patients (HR=3.09, 95%CI: 1.57-6.08) but with favorable survival in Asian patients (HR=0.51, 95%CI: 0.33-0.80; Table 3).

Heterogeneity and publication bias

The results of heterogeneity are presented in Table 2, 3. Significant heterogeneity existed among studies for OS in all comparison and for PFS in heterozygote comparison. When we conducted the stratified analysis by ethnicity, we found that the results in each subgroup turned to be homogenous (Table 3). Thus, we considered that race was a significant source of heterogeneity. The effect of an individual study on the overall results was examined by the sensitivity analysis. The single study by Ruzzo et al. (Ruzzo et al., 2007) showed substantial influence over the pooled HR for PFS in homozygous model, the exclusion of which led to loss of significance of the pooled result (HR=1.28, 95%CI: 0.89-1.84). Sensitivity analysis also

demonstrated the substantial influence from the studies by Boige et al. (Boige et al., 2010) and Gan et al. (Gan et al., 2012) on the pooled OR in the allele and dominant model. When the two studies were excluded respectively, a statistically significant association was identified (Figure 4). The publication bias and differential magnitude of effect between small and large studies were assessed by the Egger's test and Harbord's test. There was no statistical evidence of a publication bias among studies either from the results of Egger's test or Harbord's test (Table 2, 3).

Discussion

Although oxaliplatin-based chemotherapy is widely used as first-line therapy in the treatment for advanced or metastatic CRC, its objective response has been found to change between 10% and 50% indicating that the therapeutic efficacy has a remarkable inter-individual variability (Moreno et al., 2006). To optimize individual chemotherapy, an effective prognostic biomarker of CRC patients treated with oxaliplatin-based regimens is urgently needed. Recently a number of studies have explored the correlation of the XPD Lys751Gln polymorphism and sensitivity to oxaliplatin-based chemotherapy. However, the results from individual records are inconsistent. In our meta-analysis, we included 17 studies containing 2286 CRC patients and comprehensively assessed clinical outcomes using objective response, PFS and OS as primary parameters. These factors are related but are not necessarily consistent with each other. Our analysis provided evidence that XPD Lys751Gln polymorphism did not display significant association with the objective response in CRC patients receiving oxaliplatin-based chemotherapy based on the results of ORG. However, the data indicated that the patients with 751Gln allele tended to have a short PFS and OS in the population as a whole or in the Asian and Caucasian subgroups.

Resistance to platinum has been attributed to multiple factors: enhanced tolerance to DNA-platinum adducts, decreased drug accumulation , or enhanced DNA repair (Ahmad, 2010). Oxaliplatin is a cytotoxic platinum compound, and the mechanism of action of oxaliplatin is known to induce intra-stand crosslinking in DNA, leading to inhibition of DNA synthesis and apoptosis of cancer cells (Faivre et al., 2003; Yu et al., 2012). Thus, DNA repair capability is a key factor that modulates sensitivity to oxaliplatin. In the regulation of resistance to platinum-based chemotherapy in a variety of malignant diseases, NER is the predominant pathway, through recognizing and removing platinum-produced DNA damage (Leichman et al., 2011; Li et al., 2012; Kang et al., 2013). An essential member of the NER pathway is XPD, which is a key rate-limiting enzyme in NER and works as an ATP-e. Previous studies have indicated that the XPD Lys751Gln polymorphism is associated with suboptimal DRC and determined the effects on clinical outcomes of oxaliplatin-based regimens in CRC (Park et al., 2001; Stoehlmacher et al., 2004), esophageal cancer (Leichman et al., 2011) and gastric cancer (Keam et al., 2008). Therefore, the functional XPD Lys751Gln polymorphism may reveal the mechanism to resistance to oxaliplatin and serve as a useful predictive biomarker.

Several studies have indicated that patients carrying the 751Gln allele tend to have a worse clinical outcome to oxaliplatin-based chemotherapy than those carrying the wild type 751Lys allele (Park et al., 2001; Le Morvan et al., 2007; Pare et al., 2008; Lai et al., 2009; Chen et al., 2010; Leichman et al., 2011). However, the opposite association was identified by two separate studies (Gan et al., 2012; Li et al., 2012), and three studies failed to provide evidence of any correlation (Martinez-Balibrea et al., 2008; Lamas et al., 2011; Kumamoto et al., 2013). Pooling the data in our analysis demonstrated that the XPD 751Gln allele showed a non-significant relationship with low objective response, and a marked association with short PFS and OS in patients overall, in Caucasians and especially in Asians in dominant model, which is consistent with the findings of the previous meta-analysis by Ming Yin et al. (2011) However, subgroup analysis by ethnicity in homozygous comparison found that the Gln/Gln genotype was significantly associated with favorable OS in Asians but with unfavorable OS in Caucasian. Subgroup analysis also indicated that ethnicity was a significant source of heterogeneity. Thus, the discrepant results might be due to the influence of gene-gene interaction from different genetic background and gene-environment interaction from different lifestyle on the treatment outcomes of oxaliplatin-based chemotherapy in CRC patients. Although sensitivity analysis showed that some single studies may have effects on the significance of the pooled results, the association tendency was obvious with or without these studies.

The mechanism by which the XPD Lys751Gln polymorphism alters the efficacy of chemotherapy containing oxaliplatin remains elusive. It has been identified that the XPD Lys751Gln polymorphism may potentially reduce XPD mRNA levels by affecting mRNA stability as well as influencing XPD function by evoking alterations in protein-folding properties (Wolfe et al., 2007). However, no significant association between the XPD Lys751Gln polymorphism and XPD protein expression levels has been observed (Lai et al., 2009). In addition, the 751Lys variant has been posited to be found in the proximity of the substituted polar amino acid to the poly (A) signal and thus affect XPD protein function (Dybdahl et al., 1999). Further studies have found that the 751Lys variant is associated with a decreased DNA repair proficiency (Dybdahl et al., 1999; Lunn et al., 2000). Therefore, we suggest that patients with the Lys/Lys genotype may have a lower DRC because of less efficient XPD protein function rather than because of protein expression levels, making these patients more sensitive to oxaliplatin-based chemotherapy than those with the Gln/Gln genotype.

Compared with the previous meta-analysis of the XPD Lys751Gln polymorphism and clinical outcomes of gastric cancer as well as CRC treated with oxaliplatin-based regimens (Yin et al., 2011), our meta-analysis emphasized the predictive value of the XPD Lys751Gln polymorphism in CRC solely since oxaliplatin has been especially used for the treatment of metastatic CRC, a disease known to be insensitive to platinum. Additionally, the present

meta-analysis is based on 17 studies including many new and important studies. Also, we combined five different genetic models and employed the ORG calculation for the response and three models for PFS and OS, while the previous meta-analysis applied only the dominant model. Besides, the quality of all included studies was assessed by using NOS, and all of them had acceptable quality (scored at least 6).

Despite our efforts to conduct an accurate and comprehensive analysis, limitations of our meta-analysis must be addressed. Firstly, significant differences in study design including patient selection, chemotherapy protocol, and follow-up time as well as in frequencies of the XPD 751Gln allele among patients of different ethnicities may result in wide heterogeneity between included studies. Although stratified analysis by ethnicity was used to reduce the heterogeneity, further analyses stratifying for other important factors such as gender, chemotherapy regimens, pathological classification of tumors and follow-up cannot be performed since few of these available studies provided detailed information about these factors. Secondly, our analysis relied on unadjusted estimates because not all eligible studies gave adjusted estimates, and even they did, the estimates were not adjusted by the same potential confounders, making evaluation of confounding factors impossible. Thirdly, because of the limited studies (only 2 or 3 studies) included in some subgroups, the significantly pooled estimates of such subgroups should be interpreted cautiously. Fourthly, toxicity is an important issue of oxaliplatin-based chemotherapy, and analysis of the association between the XPD Lys751Gln polymorphism and oxaliplatin toxicities would make our estimates more clinically useful and provide additional helpful information. However, few studies provided related data, or when they did, the included studies used different toxicity profiles, thus making such analysis difficult. Finally, oxaliplatin was used in combination with other agents such as 5-Fu and capecitabine, but we were unable to compare different oxaliplatin-based chemotherapies because of the limited publications available on this topic.

In conclusion, our meta-analysis indicated that the XPD Lys751Gln polymorphism may have a negative influence on the clinical outcomes of oxaliplatin-based chemotherapy in CRC. To validate our findings, prospective studies with large sample sizes and standardized study designs are warranted.

References

Ahmad S (2010). Platinum-DNA interactions and subsequent cellular processes controlling sensitivity to anticancer platinum complexes. *Chem Biodivers*, **7**, 543-66.

Altman DG, Bland JM (2003). Interaction revisited: the difference between two estimates. *BMJ*, **326**, 219.

Balboa E, Duran G, Lamas MJ, et al (2010). Pharmacogenetic analysis in neoadjuvant chemoradiation for rectal cancer: high incidence of somatic mutations and their relation with response. *Pharmacogenomics*, **11**, 747-61.

Boige V, Mendiboure J, Pignon JP, et al (2010). Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. *J Clin Oncol*, **28**, 2556-64.

Chen YC, Tzeng CH, Chen PM, et al (2010). Influence of GSTP1 I105V polymorphism on cumulative neuropathy and outcome of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. *Cancer Sci*, **101**, 530-5.

Chen YM, Wu XL, Zhang LW, et al (2012). Relationship between single nucleotide polymorphism in repair gene XPD751 and prognosis in colorectal carcinoma patients. *Zhonghua Zhong Liu Za Zhi*, **34**, 501-5 (in Chinese).

Dybdahl M, Vogel U, Frentz G, et al (1999). Polymorphisms in the DNA repair gene XPD: correlations with risk and age at onset of basal cell carcinoma. *Cancer Epidemiol Biomarkers Prev*, **8**, 77-81.

Etienne-Grimaldi MC, Milano G, Maindrault-Goebel F, et al (2010). Methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and FOLFOX response in colorectal cancer patients. *Br J Clin Pharmacol*, **69**, 58-66.

Faivre S, Chan D, Salinas R, et al (2003). DNA strand breaks and apoptosis induced by oxaliplatin in cancer cells. *Biochem Pharmacol*, **66**, 225-37.

Farina Sarasqueta A, van Lijnschoten G, Lemmens VE, et al (2011). Pharmacogenetics of oxaliplatin as adjuvant treatment in colon carcinoma: are single nucleotide polymorphisms in GSTP1, ERCC1, and ERCC2 good predictive markers? *Mol Diagn Ther*, **15**, 277-83.

Fuss JO, Tainer JA (2011). XPB and XPD helicases in TFIIH orchestrate DNA duplex opening and damage verification to coordinate repair with transcription and cell cycle via CAK kinase. *DNA Repair (Amst)*, **10**, 697-713.

Gan Y, Li X-R, Chen D-J, et al (2012). Association between polymorphisms of XRCC1 Arg399Gln and XPD Lys751Gln genes and prognosis of colorectal cancer in a chinese population. *Asian Pac J Cancer Prev*, **13**, 5721-4.

Haller DG, Tabernero J, Maroun J, et al (2011). Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*, **29**, 1465-71.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Kang S, Sun HY, Zhou RM, et al (2013). DNA repair gene associated with clinical outcome of epithelial ovarian cancer treated with platinum-based chemotherapy. *Asian Pac J Cancer Prev*, **14**, 941-6.

Keam B, Im SA, Han SW, et al (2008). Modified FOLFOX-6 chemotherapy in advanced gastric cancer: Results of phase II study and comprehensive analysis of polymorphisms as a predictive and prognostic marker. *BMC Cancer*, **8**, 148.

Kuebler JP, Wieand HS, O'Connell MJ, et al (2007). Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*, **25**, 2198-204.

Kumamoto K, Ishibashi K, Okada N, et al (2013). Polymorphisms of , and -3'UTR are associated with the clinical outcome of mFOLFOX6 in colorectal cancer patients. *Oncol Lett*, **6**, 648-54.

Lai JI, Tzeng CH, Chen PM, et al (2009). Very low prevalence of XPD K751Q polymorphism and its association with XPD expression and outcomes of FOLFOX-4 treatment in Asian patients with colorectal carcinoma. *Cancer Sci*, **100**, 1261-6.

Lamas MJ, Duran G, Balboa E, et al (2011). Use of a comprehensive panel of biomarkers to predict response to a fluorouracil-oxaliplatin regimen in patients with metastatic colorectal cancer. *Pharmacogenomics*, **12**, 433-42.

Le Morvan V, Smith D, Laurand A, et al (2007). Determination of ERCC2 Lys751Gln and GSTP1 Ile105Val gene

polymorphisms in colorectal cancer patients: relationships with treatment outcome. *Pharmacogenomics*, **8**, 1693-703.

Lee KH, Chang HJ, Han SW, et al (2013). Pharmacogenetic analysis of adjuvant FOLFOX for Korean patients with colon cancer. *Cancer Chemother Pharmacol*, **71**, 843-51.

Leichman LP, Goldman BH, Bohanes PO, et al (2011). S0356: a phase II clinical and prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. *J Clin Oncol*, **29**, 4555-60.

Li H-Y, Ge X, Huang G-M, et al (2012). GSTP1, ERCC1 and ERCC2 Polymorphisms, Expression and Clinical Outcome of Oxaliplatin-based Adjuvant Chemotherapy in Colorectal Cancer in Chinese Population. *Asian Pac J Cancer Prev*, **13**, 3465-9.

Lunn RM, Helzlsouer KJ, Parshad R, et al (2000). XPD polymorphisms: effects on DNA repair proficiency. *Carcinogenesis*, **21**, 551-5.

Martin LP, Hamilton TC, Schilder RJ (2008). Platinum resistance: the role of DNA repair pathways. *Clin Cancer Res*, **14**, 1291-5.

Martinez-Balibrea E, Abad A, Aranda E, et al (2008). Pharmacogenetic approach for capecitabine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. *Eur J Cancer*, **44**, 1229-37.

McLeod HL, Sargent DJ, Marsh S, et al (2010). Pharmacogenetic predictors of adverse events and response to chemotherapy in metastatic colorectal cancer: results from North American Gastrointestinal Intergroup Trial N9741. *J Clin Oncol*, **28**, 3227-33.

Monzo M, Moreno I, Navarro A, et al (2007). Single nucleotide polymorphisms in nucleotide excision repair genes XPA, XPD, XPG and ERCC1 in advanced colorectal cancer patients treated with first-line oxaliplatin/fluoropyrimidine. *Oncology*, **72**, 364-70.

Moreno V, Gemignani F, Landi S, et al (2006). Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. *Clin Cancer Res*, **12**, 2101-8.

Pare L, Marcuello E, Altes A, et al (2008). Pharmacogenetic prediction of clinical outcome in advanced colorectal cancer patients receiving oxaliplatin/5-fluorouracil as first-line chemotherapy. *Br J Cancer*, **99**, 1050-5.

Park DJ, Stoehlmacher J, Zhang W, et al (2001). A Xeroderma pigmentosum group D gene polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. *Cancer Res*, **61**, 8654-8.

Ruzzo A, Graziano F, Loupakis F, et al (2007). Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. *J Clin Oncol*, **25**, 1247-54.

Spitz MR, Wu X, Wang Y, et al (2001). Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. *Cancer Res*, **61**, 1354-7.

Stoehlmacher J, Park DJ, Zhang W, et al (2004). A multivariate analysis of genomic polymorphisms: prediction of clinical outcome to 5-FU/oxaliplatin combination chemotherapy in refractory colorectal cancer. *Br J Cancer*, **91**, 344-54.

Sun XH, Hou WG, Zhao HX, et al (2013). Single nucleotide polymorphisms in the NER pathway and clinical outcome of patients with bone malignant tumors. *Asian Pac J Cancer Prev*, **14**, 2049-52.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000). New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, national cancer institute of Canada. *J Natl Cancer Inst*, **92**, 205-16.

Tierney JF, Stewart LA, Ghersi D, et al (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**, 16.

Wang LE, Gorlova OY, Ying J, et al (2013). Genome-wide association study reveals novel genetic determinants of DNA repair capacity in lung cancer. *Cancer Res*, **73**, 256-64.

Wolfe KJ, Wickliffe JK, Hill CE, et al (2007). Single nucleotide polymorphisms of the DNA repair gene XPD/ERCC2 alter mRNA expression. *Pharmacogenet Genomics*, **17**, 897-905.

Yin M, Yan J, Martinez-Balibrea E, et al (2011). ERCC1 and ERCC2 polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: a systemic review and meta-analysis. *Clin Cancer Res*, **17**, 1632-40.

Yu YJ, Li YM, Hou XD, et al (2012). Effect of tissue factor on invasion inhibition and apoptosis inducing effect of oxaliplatin in human gastric cancer cell. *Asian Pac J Cancer Prev*, **13**, 1845-9.

Zhang ZY, Tian X, Wu R, et al (2012). Predictive role of ERCC1 and XPD genetic polymorphisms in survival of Chinese non-small cell lung cancer patients receiving chemotherapy. *Asian Pac J Cancer Prev*, **13**, 2583-6.

Zintzaras E (2010). The generalized odds ratio as a measure of genetic risk effect in the analysis and meta-analysis of association studies. *Stat Appl Genet Mol Biol*, **9**, 21.