RESEARCH ARTICLE

The ERCC1 C118T Polymorphism Predicts Clinical Outcomes of Colorectal Cancer Patients Receiving Oxaliplatin-Based Chemotherapy: a Meta-analysis Based on 22 Studies

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Abstract

Background: Although the predictive value of the excision repair cross-complementing group 1 (ERCC1) C118T polymorphism in clinical outcomes of patients with colorectal cancer (CRC) receiving oxaliplatin-based chemotherapy has been evaluated in numerous published studies, the conclusions are conflicting. Therefore, we performed the present meta-analysis to determine the precise role of the ERCC1 C118T polymorphism in this clinical situation and help optimize individual chemotherapy. Materials and Methods: A multiple search strategy was used to identify eligible studies. Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were used to estimate objective response and oxaliplatin-induced toxicity, with hazard ratios (HRs) with 95%CIs for progression-free survival (PFS) and overall survival (OS). Results: A total of 22 studies including 2,846 CRC patients were eligible in the analysis. Overall, no significant correlation was found between the ERCC1 C118T polymorphism and objective response to oxaliplatin-based chemotherapy, in all patients or in the Asian and Caucasian subgroups. However, the pooled analysis showed that the PFS and OS were significantly shorter in patients who carried T/T or T/C genotypes of ERCC1 C118T as compared to the C/C genotype. On stratified analysis by ethnicity, the ERCC1 118T allele was associated with a favorable prognosis in Caucasians (PFS, HR=0.58, 95%CI: 0.24-1.44; OS, HR=0.38, 95%CI: 0.22-0.64) but an unfavorable prognosis in Asians (PFS, HR=2.49, 95%CI: 1.87-3.33; OS, HR=2.63, 95%CI: 1.87-3.69) based on a dominant model. In addition, we failed to find a statistically significant impact of ERCC1 C118T polymorphism on oxaliplatin-induced toxicity. Conclusions: The ERCC1 C118T polymorphism may have prognostic value in patients with CRC undergoing oxaliplatin-based chemotherapy.

Keywords: ERCC1 - oxaliplatin - prognosis - chemotherapy - meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and is the fourth main cause of cancer-related mortality worldwide, with 1.2 million new cases and over 600, 000 deaths estimated in 2008 (Jemal et al., 2011). Of these cases, a significant proportion is diagnosed at an advanced, inoperation stage. Even after resection, sixty percent to 80% patients develop distant or local regional recurrence (Siegel et al., 2012). Therefore, the majority of patients need chemotherapy either in the adjuvant or palliative setting.

Oxaliplatin, a relatively new cytotoxic platinum compound, is the first platinum-based chemotherapeutic agent that has shown antitumor efficacy in the treatment of CRC (Raymond et al., 1998). In combined with fluoropyrimidines, oxaliplatin has been approved as first-line therapy for metastatic CRC (mCRC), with an object response rate >50% and a median survival time approaching 2 years (Alberts et al., 2005; Cassidy et al., 2008). Despite this demonstrated efficacy, virtually a large part of patients developed varying levels of resistance to oxaliplatin. In addition, oxaliplatin has led to severe toxicity without any clinical benefits in some patients' therapies, indicating that the therapeutic efficacy has a wide interpatient variability. Recently studies have suggested that functional genomic polymorphisms may have an important role in inter-individual effectiveness of treatment (Boige et al., 2010; Yang et al., 2013). Therefore, determination the relationship between genomic markers and the clinical outcomes may improve the prediction of treatment effect while limiting the adverse effects.

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Oxaliplatin mainly makes a contribution to inhibit the DNA replication and transcription by forming DNA-platinum macromolecular adducts in cancer cells (Faivre et al., 2003). These adducts are predominantly repaired by the nucleotide excision repair (NER) pathway, which is thought to remove bulky, helix-distorting DNA adducts produced by platinum agents (Martin et al., 2008). Recently, several single nucleotide polymorphisms (SNPs) in NER pathway have been found to induce inter-individual variation in drug response to platinum by influencing DNA repair capacity of NER pathway in various tumors (Li et al., 2012; Zhang et al., 2012; Sun et al., 2013). The excision repair cross-complementing group 1 (ERCC1) is a key protein in NER pathway acting as the rate-limiting enzyme. One common nucleotide polymorphism at codon 118 of ERCC1 (Asn118Asn, C118T, T19007C, dbSNP No. rs11615) has been frequently studied and identified to be related to the levels of ERCC1 mRNA and protein expression those have been shown to affect NER capacity (Reed, 2005; Woelfelschneider et al., 2008; Chang et al., 2009). Therefore, ERCC1 C118T polymorphism may be an efficient prognostic factor for clinical end points in patients with CRC undergoing oxaliplatin-based chemotherapy.

Recently, numerous studies have evaluated the effects of ERCC1 C118T polymorphism on clinical outcomes of oxaliplatin-based chemotherapy in CRC patients, but the results are not consistent. Therefore, we performed a meta-analysis of published studies to systematically address the relationship between ERCC1 C118T SNP and the efficacy of oxaliplatin-based chemotherapy in CRC patients.

Materials and Methods

Search strategy and study selection

A extensive search for relevant articles was conducted before June 1, 2014 using two electronic databases (MEDLINE and ISI Web of Science) with the following terms "ERCC1 or excision repair cross-complementation group 1", "colon cancer or colorectal cancer" and "polymorphism or variant". References of all relevant studies were further screened at the same time.

Articles involving the relationship between the ERCC1 variants and clinical outcomes of oxaliplatin-based chemotherapy in CRC were included. The following elaborate inclusion criteria were used: (1) patients with CRC received oxaliplatin-based chemotherapy; (2) the ERCC1 C118T polymorphism was genotyped; (3) primary outcomes of interest including objective response, progression-free survival (PFS), overall survival (OS) or toxicity were available. The following exclusion criteria were used: (a) patients received other adjuvant treatment, such as radiotherapy or immunotherapy; (b) critical information was inaccessible 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 researchers (Yingying Qian and Xinyou Liu) independently retrieved the published articles and extracted the data from included studies. Disagreement was resolved by discussion. The following data were extracted: the name of the first author, publication date, country of origin, ethnicity of patients, the number of enrolled patients, clinical stage, treatments, biomarkers, genotype distribution data among responders and non-responders, the number of patients with mild to moderate or severe toxicity in different genotypes, hazard ratios (HRs) for OS and PFS, and their 95% confidence intervals (CIs). Ethnicity of the population was categorized simply as Asian or Caucasian. If HR and 95%CI were not directly extracted from a report (Liang et al., 2008; Pare et al., 2008; Chang et al., 2009; Farina Sarasqueta et al., 2011), 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 conducted in the calculation spreadsheet appended to Tierney's paper. The methodological quality of the included studies was assessed by using the Newcastle Ottawa Scale (NOS) for cohort studies. Three major components (Selection, Comparability and Outcome) of a cohort study were evaluated. 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. Also, quality assessment was independently carried out by two authors (Qian and Liu).

Statistical analysis

To represent the objective response rate and incidence of adverse events, the pooled odds ratio (OR) and 95%CI were evaluated using five genetic comparison models (allele comparison, heterozygote comparison, homozygote comparison, dominant model and recessive model). Response to chemotherapy was evaluated according to WHO criteria or the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse et al., 2000), divided into the following categories: "objective response" defined as ''complete response+partial response'' and ''no response'' which was ''stable disease+progressive disease''. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), divided into the following categories: "mild to moderate toxicity" defined as ''grade 0-2" and "severe toxicity" which was "grade 3-4". 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 estimated for PFS and OS. We executed initial analyses by a fixed effects model with HRs and CIs derived from each study assuming homogeneity of individuals. The presence of heterogeneity among studies was assessed using the I^2 statistic and the Chi-square test based on Cochran's Q statistic. P-value < 0.05 for the Q-test or I^2>50% indicated the existence of heterogeneity among the studies, and the random effects model was used for meta-analysis. Subgroup analyses were performed according to ethnicities. The differences in the effect estimates between subgroups were compared as described

previously (Altman and Bland, 2003). Sensitivity analysis was conducted to assess the influence of a single study on the pooled estimate by omitting individual study in this meta-analysis once at a time. Publication bias and the differential magnitude of effect between small and large studies were evaluated using Egger's linear regression test and Harbord's test. 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).

Results

Search results and study selection

We identified related 1378 records through a primary search of databases and reference lists according to the searching criteria. By browsing the titles and abstracts, 25 full-text studies were seemed to meet the inclusion criteria and retrieved for further evaluation. After reviewing the full text, 3 literatures were excluded, of which the data of two studies were inestimable and the authors were unreachable (Braun et al., 2008; Lamas et al., 2011), and patients in another additional study were treated with radiotherapy (Fakih et al., 2008). As a result, a total of 2846 CRC patients were enrolled in the 22 studies (Stoehlmacher et al., 2004; Viguier et al., 2005; Ruzzo et al., 2007; Liang et al., 2008; Martinez-Balibrea et al., 2008; Pare et al., 2008; Chang et al., 2009; Chua et al., 2009; Boige et al., 2010; Chen et al., 2010; Inada et al., 2010; Liang et al., 2010; Spindler et al., 2010; Farina Sarasqueta et al., 2011; Huang et al., 2011; Chai et al., 2012; Li et al., 2012; Cortejoso et al., 2013; Kumamoto et al., 2013; Lee et al., 2013; Nishina et al., 2013; Oguri et al., 2013) included in the pool-analysis. The selection procedure is shown in Figure 1 and the key patient characteristics are listed by study in Table1. The overall quality of included studies assessed by using NOS was good, ranging from 6 to 9.

The ERCC1 C118T polymorphism and objective response

Ten studies including 1231 patients were eligible to estimate the association between ERCC1 C118T polymorphism and the objective response to oxaliplatin-based chemotherapy in CRC patients. In overall analysis, there was no association between ERCC1 C118T polymorphism and response rate in any of the 5 comparison models (Table 2, Figure 2). Likewise, stratified analysis by ethnicity showed no association in the estimates of the ERCC1 C118T polymorphism effect on response to oxaliplatin between Asians and Caucasians under either kinds of genetic model (Table 2, Figure 2).

The ERCC1 C118T polymorphism and PFS

A total of 8 studies with 924 patients were available for the final analysis of ERCC1 C118T polymorphism and PFS. The pooled results shown in Table 3 indicated that the T/T genotype was associated with a markedly increase of hazard for PFS in homozygous comparison in all patients (T/T *vs* C/C, HR=1.91, 95%CI: 1.36-2.68, $P_{heterogeneity}$=0.18; Table 3). Stratified analyses in the

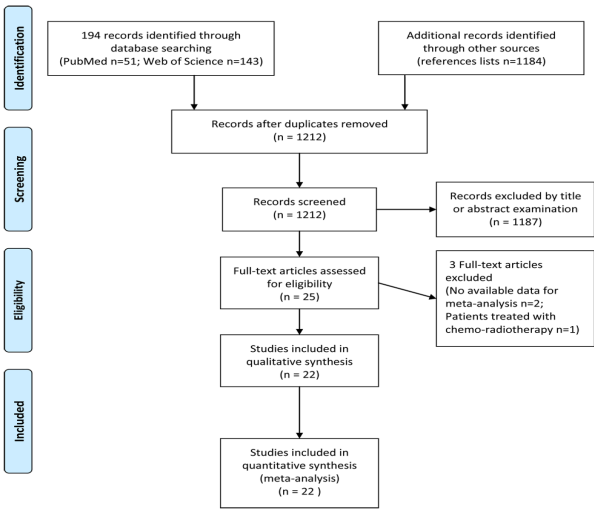

Figure 1. Flow Chart of Search Strategy and Study Selection

Table 1. Baseline Characteristics of Included Studies

First author	Year	Country	Ethnicity	Cases	Age	Clinical stage	Treatment	Outcomes
Stoehlmacher	2004	USA	Caucasian	106	60 (24-84)	Advanced CRC	FUOX	OS, PFS
Viguier	2005	France	Caucasian	61	55.1 (48.3-62.3)	Metastatic CRC	FUOX	TR
Ruzzo	2007	Italy	Caucasian	166	66 (38-79)	Advanced CRC	FOLFOX4	PFS
Liang	2008	China	Asian	99	NR	Stage IV CRC	FOLFOX or XELOX	PFS
Pare	2008	Spain	Caucasian	126	66 (34–83)	Metastatic CRC	FUOX	TR, PFS,OS
Martinez-Balibrea	2008	Spain	Caucasian	96	63 (35.9–81.6)	Metastatic CRC	XELOX or FUOX	PFS
Chang	2009	China	Asian	168	NR	Metastatic CRC	FOLFOX4	TR, PFS, OS, AE
Liang	2010	China	Asian	113	57 (33–75)	Metastatic CRC	mFOLFOX4 or XELOX	OS
Spindler	2010	Denmark	Caucasian	66	60 (42-79)	Advanced CRC	XELOX	TR
Chua	2009	Australia	Caucasian	115	61 (31– 75)	Metastatic CRC	FOLFOX	TR, PFS, OS, AE
Chen	2010	China	Asian	166	NR	Metastatic CRC	FOLFOX4	TR, OS
Inada	2010	Japan	Asian	51	65 (37 – 81)	CRC	mFOLFOX6	AE
Huang	2011	China	Asian	157	62.5 (36-82)	Metastatic CRC	FOLFOX4	TR, PFS, OS
Boige	2010	France	Caucasian	291	NR	Metastatic CRC	FOLFOX	TR, AE
Farina Sarasqueta	2011	Netherlands	Caucasian	48	64 (30–85)	Stage III colon cancer	FOLFOX or XELOX	PFS
Li	2012	China	Asian	335	61.5±6.9	Advanced CRC	FOLFOX6	OS
Kumamoto	2013	Japan	Asian	63	65 (32-84)	Metastatic CRC	FOLFOX6	AE
Lee	2013	Korea	Asian	288	59 (30-76)	Stage III or II colon cancer	FOLFOX	AE
Cortejoso	2013	Spain	Caucasian	106	64 (38-85)	CRC	FOLFOX or XELOX	AE
Nishina	2013	Japan	Asian	68	63 (28-81)	Advanced/recurrent CRC	mFOLFOX6+Bevacizum	TR
Chai	2012	China	Asian	73	59 (24-87)	CRC	FOLFOX4	TR
Oguri	2013	Japan	Asian	70	65 (37-81)	CRC	mFOLFOX6	AE

*NR not report; CRC colorectal cancer; TR tumor response; PFS progression-free survival; OS overall survival; AE adverse effect; FUOX 5-fluorouracil plus oxaliplatin; FOLFOX oxaliplatin plus 5-FU and leucovorin; XELOX capecitabine plus oxaliplatin; mFOLFOX modified FOLFOX

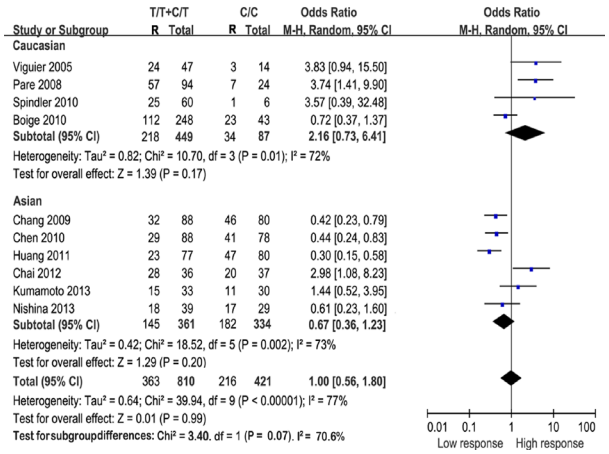

Figure 2. Association of the ERCC1 C118T Polymorphism with Objective Response to Oxaliplatin-Based Chemotherapy for Colorectal Cancer. Forest Plot of the Dominant Model (T/T+T/C *vs* C/C)

homozygous comparison and heterozygous comparison indicated more clinically substantial effects on PFS in Asians (T/T *vs* C/C, HR=2.53, 95%CI: 1.07-6.00; T/C *vs* C/C, HR=2.69, 95%CI: 1.16-6.25), compared with the Caucasians (T/T *vs* C/C, HR=1.81, 95%CI: 1.25-2.62; T/C *vs* C/C, HR=1.21, 95%CI: 0.86-1.86; Table 3). Nevertheless, in the dominant model, subgroup analysis by ethnicity showed that carriers of the T allele were correlated with poor PFS in Asian patients (HR=2.49, 95%CI: 1.87-3.33) but with favorable PFS in Caucasian patients (HR=0.58, 95%CI: 0.24-1.44; Figure 3A, Table 3). Further comparison displayed a markedly significant difference in the estimates of effect between Asian and Caucasian populations (p=0.003).

The ERCC1 C118T polymorphism and OS

Six studies including 794 patients qualified for the analysis of the association between the ERCC1

Table 2. Meta-Analysis of the Association between the ERCC1 C118T Polymorphism and Objective Response to Oxaliplatin-based Chemotherapy

Contrast	Ethnicity	N of studies	OR	95%CI	P value of Egger's test	*P* value of Harbord's test	Heterogeneity *P*	Heterogeneity I^2(%)
T *vs* C	Overall	7	1.37	0.85-2.18	0.473	0.288	0.0002	77
(allele comparison)	Caucasian	4	1.11	0.62-1.96	0.791	0.396	0.005	76
	Asian	3	1.85	0.87-3.96	0.91	0.268	0.03	71
T/T+T/C *vs* C/C	Overall	10	1.00	0.56-1.80	0.011	0.009	<0.00001	77
(dominant model)	Caucasian	4	2.16	0.73-6.41	0.26	0.291	0.01	72
	Asian	6	0.67	0.36-1.23	0.037	0.04	0.002	73
T/T *vs* C/C	Overall	7	1.85	0.74-4.66	0.638	0.554	0.02	62
(homozygote comparison)	Caucasian	4	2.25	0.69-7.30	0.298	0.344	0.01	71
	Asian	3	1.37	0.18-10.60	/	0.479	0.07	62
T/C *vs* C/C	Overall	7	1.40	0.63-3.11	0.036	0.025	0.004	76
(heterozygote comparison)	Caucasian	4	2.02	0.71-5.71	0.212	0.227	0.03	66
	Asian	3	0.94	0.25-3.49	0.116	0.138	0.003	83
C/C+T/C *vs* T/T	Overall	7	1.16	0.84-1.61	0.987	0.587	0.16	41
(recessive model)	Caucasian	4	1.20	0.66-2.16	0.622	0.62	0.09	48
	Asian	3	1.56	0.62-3.92	/	0.691	0.15	54

OR odds ratio; CI confidence interval

Table 3. Meta-Analysis of the Association between the ERCC1 C118T Polymorphism and Progression-Free Survival and Overall Survival

	Contrast	Ethnicity	N of studies	HR	95%CI	*P* value of Egger's test	Heterogeneity *P*	Heterogeneity I^2(%)
PFS	T/T+T/C vs. C/C	Overall	5	1.40	0.60-3.28	0.603	<0.00001	93
	(dominant model)	Caucasian	2	0.58	0.24-1.44	/	0.01	85
		Asian	3	2.49	1.87-3.33	0.563	0.99	0
	T/T vs. C/C	Overall	4	1.91	1.36-2.68	0.491	0.18	38
	(homozygote comparison)	Caucasian	3	1.81	1.25-2.62	0.478	0.11	54
		Asian	1	2.53	1.07-6.00	/	/	/
	T/C vs. C/C	Overall	4	1.35	0.99-1.83	0.871	0.33	12
	(heterozygote comparison)	Caucasian	3	1.21	0.86-1.68	0.138	0.81	0
		Asian	1	2.69	1.16-6.25	/	/	/
OS	T/T+T/C vs. C/C	Overall	4	1.50	0.53-4.26	0.99	<0.00001	92
	(dominant model)	Caucasian	1	0.38	0.22-0.64	/	/	/
		Asian	3	2.63	1.87-3.69	0.327	0.51	0
	T/T vs. C/C	Overall	3	1.70	1.12-2.57	0.835	0.95	0
	(homozygote comparison)	Caucasian	1	1.86	0.90-3.84	/	/	/
		Asian	2	1.62	0.97-2.70	/	0.92	0
	T/C vs. C/C	Overall	3	1.72	1.22-2.42	0.538	0.52	0
	(heterozygote comparison)	Caucasian	1	2.29	1.20-4.38	/	/	/
		Asian	2	1.53	1.02-2.30	/	0.63	0

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

C118T polymorphism and OS. As shown in Table 3, the homozygous comparison (T/T *vs* C/C, HR=1.70, 95%CI: 1.12-2.57, $P_{heterogeneity}$=0.95) and the heterozygous comparison (T/C *vs* C/C, HR=1.72, 95%CI: 1.22-2.42, $P_{heterogeneity}$=0.52) identified a significantly negative impact on prognosis in all patients. We did not find any significant association in the dominant model. However, stratified analysis by ethnicity in the dominant model indicated T/T and T/C genotypes were associated with poor survival in the Asian patients (T/T+T/C *vs* C/C, HR=2.63, 95%CI: 1.87-3.69, $P_{heterogeneity}$=0.51), while in the subgroup of Caucasians, the T allele showed an inverse effect on survival (T/T+T/C *vs* C/C, HR=0.38, 95%CI: 0.22-0.64; Figure 3B, Table 3); however, only one study was included in this subgroup. Moreover, a significant difference has existed in the estimates of effect between Asian and Caucasian populations (p<0.00001).

The ERCC1 C118T polymorphism and oxaliplatin-induced toxicities

Data from 1166 subjects participating in eight studies were applicable for analyzing the association between the ERCC1 C118T polymorphism and oxaliplatin-induced toxicities; of these, 6 studies (772 patients) reported ERCC1 C118T polymorphism and neurological toxicity, 4 studies (813 patients) reported ERCC1 C118T polymorphism and hematological toxicity, and 2 studies (419 patients) reported ERCC1 C118T polymorphism and gastrointestinal toxicity. Therefore, we pooled the data of eligible studies which showed the correlation between ERCC1 C118T polymorphism and neuropathy or hematological toxicity respectively. The pooled results from all patients showed no significant correlation between ERCC1 C118T polymorphism and severe hematological toxicity under either genetic model (Figure 4A). However, subgroup analysis by ethnicity, using the recessive model, found that patients with T/C or C/C genotype were at significantly higher risk for experiencing grade 3/4 hematological toxicity compared with patients with T /T genotype in Asians (T/C+C/C *vs* T/T, HR=1.97, 95%CI: 1.04-3.75, $P_{heterogeneity}$=0.14). In the dominant model, the T allele was associated with a non-significantly increased risk for developing severe neurological toxicity (T/T+T/C *vs* C/C, HR=1.24, 95%CI: 0.84-1.81, $P_{heterogeneity}$=0.90; Figure 4B). Likewise, we did not obverse any association between ERCC1 C118T polymorphism and severe gastrointestinal toxicity.

Sensitivity analysis and publication bias

We performed the sensitivity analysis to evaluate the effect of an individual study on the pooled estimates. The single study by Pare et al (Pare et al., 2008) showed substantial influence over the pooled HR for PFS and OS in dominant model, the exclusion of which elevated the HR significantly (PFS, HR=1.98, 95%CI: 1.26-3.13; OS, HR=2.62, 95%CI: 1.87-3.69). The publication bias and differential magnitude of effect between small and large studies were assessed by the Egger's test and Harbord's test. No statistical evidence of a publication bias among studies was identified either from the results of Egger's test or Harbord's test (Table 2, 3).

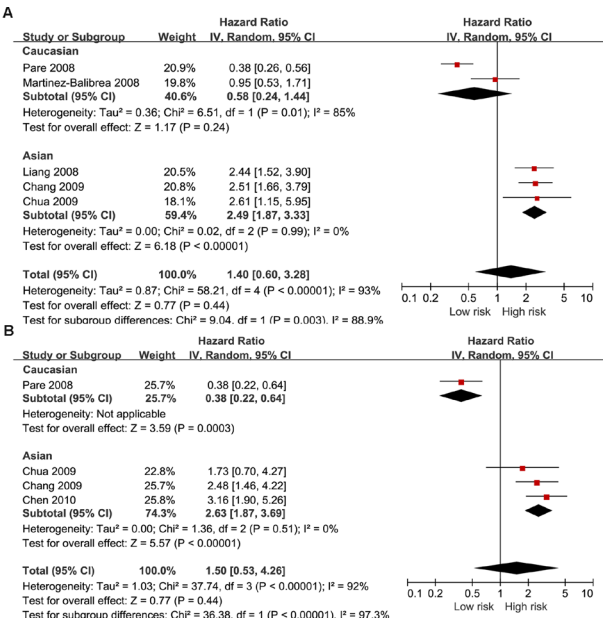

Figure 3. Association of the ERCC1 C118T Polymorphism with Survival Following Oxaliplatin-Based Chemotherapy for Colorectal Cancer. Forest plot of the dominant model (T/T+T/C *vs* C/C). (A) progression-free survival and (B) overall survival

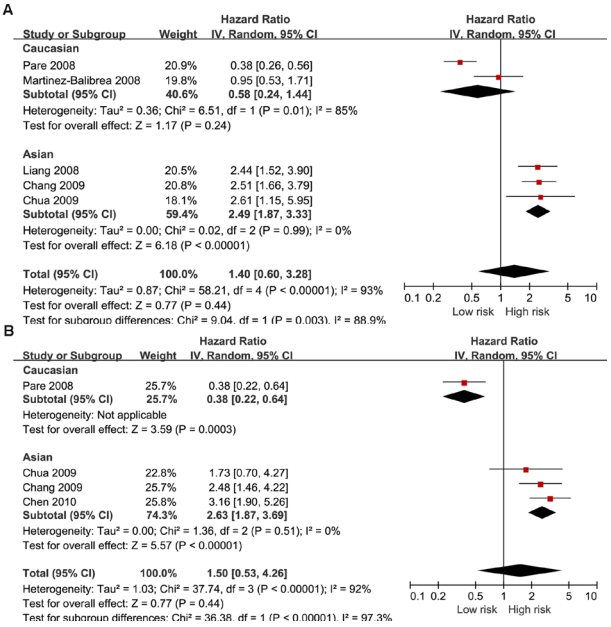

Figure 4. Association of the ERCC1 C118T Polymorphism with Oxaliplatin-Induced Toxicities. Forest plot of the dominant model (T/T+T/C *vs* C/C). (A) hematological toxicity and (B) neuropathy

Discussion

In this meta-analysis, we included 22 studies containing 2846 CRC patients treated with oxaliplatin-based regiments. Our analysis provided evidences that patients with T/T or T/C genotype of ERCC1 C118T polymorphism tended to have a short PFS and OS, while no significant association between ERCC1 C118T polymorphism and objective response to oxaliplatin-based chemotherapy was observed in the population as a whole or in the Asian and Caucasian subgroups. In addition,

we identified T/T genotype was associated with lower frequency of hematological toxicity in Asians.

To date, oxaliplatin-based chemotherapy is widely used as first-line therapy in the treatment for advanced or metastatic CRC, but its objective response has been found to change between 10% and 50% (Moreno et al., 2006). Despite that the clinical factors such as patient age, performance status and disease stages are the major prognostic predictors, the variability in individual response to oxaliplatin-based chemotherapy could not be fully explained. Recently, SNPs are expected to have critical influence on drug efficacy by modifying functions of important genes, indicating that SNPs of functional genes may have critical prognostic value (Huang et al., 2011; Lamas et al., 2011; Yue et al., 2013).

The mechanism of action of oxaliplatin is known to induce intra-stand crosslinking in DNA, leading to inhibition of DNA synthesis and then apoptosis of cancer cells (Faivre et al., 2003). Resistance to oxaliplatin has been attributed to multiple factors, among which enhanced DNA repair capability is a key factor that modulates sensitivity to oxaliplatin (Ahmad, 2010). NER is the predominant DNA repair pathway in the regulation of resistance to platinum-based chemotherapy in a variety of malignant diseases through recognizing and removing platinum-produced DNA damage (Cheng et al., 2012; Li et al., 2012; Kang et al., 2013). An essential member of the NER pathway is ERCC1, which is responsible for recognition and removal of DNA damage. Previous studies have indicated that the increased levels of ERCC1 mRNA and protein expression are correlated with the clinical resistance to platimun-based chemotherapy in gastric cancer (Kwon et al., 2007), non-small cell lung cancer (Vilmar and Sorensen, 2009) and colorectal cancer (Noda et al., 2012). The ERCC1 C118T polymorphism has been extensively investigated and identified to be involved in the regulation of mRNA and protein expression of ERCC1 (Reed, 2005). Therefore, the functional ERCC1 C118T polymorphism may reveal the mechanism to resistance to oxaliplatin and serve as a useful predictive biomarker.

In our meta-analysis, we 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. We also conduct an analysis of the association between the ERCC1 C118T polymorphism and oxaliplatin-induced toxicities because toxicity is an important issue of oxaliplatin-based chemotherapy. Pooling the data in our analysis demonstrated that the T/T or T/C genotype of ERCC1 C118T polymorphism showed a remarkably shorter PFS and OS compared with C/C genotype in all patients. Stratification of data by ethnicity indicated that patients with T allele were likely to have a poor prognosis in Asians, but a favorable prognosis in Caucasians. The apparent ethnic discrepancy in the prognostic values for the ERCC1 C118T polymorphism between Asians and Caucasians might be due to the influence of gene-gene interaction from different genetic background and gene-environment interaction from different lifestyle. However, considering the small sample size in Caucasian subgroup, it is likely that further studies are needed to validate the relationship. On the other hand, we failed to demonstrate that the influence of ERCC1 C118T polymorphism on objective response was significant, which was consistent with the findings of the previous meta-analysis (Yin et al., 2011). In addition, we also did not find any statistical evidence to assume a correlation between ERCC1 C118T polymorphism and oxaliplatin-induced severe adverse effects, which can be explained by the fact that the limited eligible studies and different oxaliplatin dosages were involved in this evaluation. Compared with the previous meta-analysis (Yin et al., 2011), we performed a more accurate and comprehensive comparison. Since oxaliplatin has been especially used for the treatment of mCRC which is known to be insensitive to platinum, our meta-analysis focused on the predictive value of the ERCC1 C118T polymorphism in CRC patients treated with oxaliplatin-based chemotherapy solely, while the previous meta-analysis evaluated prognostic effects of ERCC1 C118T polymorphism on the clinical outcomes of gastric cancer as well as CRC. Additionally, the present meta-analysis is based on 22 articles including many new and important studies, which significantly increased statistical power of the analysis. Also, we combined five different genetic models for the response and toxicity, and three models for PFS and OS, while the previous meta-analysis applied only the dominant model.

Despite our efforts to conduct an accurate and comprehensive analysis, a few limitations of our meta-analysis should be addressed. Firstly, a lack of uniformity in the reporting of study design including patient selection, chemotherapy protocol, and follow-up time possibly contributes to presence of heterogeneity between included studies. However, stratified analysis on the basis of these important factors 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, the relatively small sample size in the subgroup analysis by ethnicity may have caused some bias and reduced the statistic power of our estimates. Thus, the significantly pooled estimates of subgroups analyses should be interpreted cautiously. 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 ERCC1 C118T polymorphism may be a useful predictive factor for poor prognosis in CRC patients treated with oxaliplatin-based chemotherapy. To validate our findings, prospective studies with large sample sizes and standardized study designs are warranted.

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