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ORIGINAL RESEARCH

Association between the ERCC1 rs11615 polymorphism and clinical outcomes of oxaliplatin-based chemotherapies in gastrointestinal cancer: a meta-analysis

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Purpose: The relationship between the excision repair cross-complementing 1 (*ERCC1*) rs11615 polymorphism (C/T) and responses to oxaliplatin-based chemotherapy for gastric cancer (GC) and colorectal cancer (CRC) patients is controversial. Therefore, we performed a meta-analysis to assess this relationship.

Method: Relevant studies were retrieved by searching the PubMed database. A systematic review and meta-analysis was performed to evaluate the predictive value of the *ERCC1* rs11615 polymorphism for the clinical outcomes of GC and CRC patients receiving oxaliplatin-based chemotherapy. Therapeutic response to chemotherapy, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: A total of 22 studies were included in this meta-analysis, including 1,242 cases of GC and 1,772 cases of CRC. For the *ERCC1* rs11615 polymorphism, the T allele was associated with a reduced response to chemotherapy in Asians and GC patients ($P<0.05$). On the other hand, the T allele was associated with a significant increase in the risk for shorter PFS and OS in all patients (PFS: hazard ratio [HR] =1.22, $P<0.001$, 95% confidence interval [CI] =0.93–1.51 and OS: HR =1.12, $P<0.001$, 95% CI =0.85–1.40).

Conclusion: The *ERCC1* rs11615 polymorphism was closely associated with the clinical outcomes of GC and CRC patients treated with oxaliplatin-based chemotherapy.

Keywords: *ERCC1* rs11615, polymorphism, oxaliplatin-based chemotherapy, gastric cancer, colorectal cancer, meta-analysis

Introduction

Gastrointestinal cancer, including gastric cancer (GC) and colorectal cancer (CRC), is a major health problem that accounts for a large proportion of all human malignancies;[1] approximately 3.25 million people are diagnosed with the disease each year worldwide.[2] Despite recent advances in the diagnosis and therapy of this disease, most gastrointestinal cancer patients present with advanced disease with poor prognoses and low survival rates. Chemotherapy for advanced gastrointestinal cancer has some advantages over best supportive care, including improved quality of life; however, survival does not increase dramatically, with the overall survival (OS) ranging from 6.0 to 12.0 months with chemotherapy.[3] Combination treatment with 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX) is now considered the standard treatment for GC and CRC, with a response rate of over 40% for first-line treatment.[4] Oxaliplatin is a frequently used agent that is part of many chemotherapy regimens used to treat several gastrointestinal cancers. It is an organoplatinum complex that can produce both

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inter- and intra-strand platinum-DNA cross-links that, in turn, lead to the inhibition of DNA replication and transcription.[5] However, oxaliplatin-based therapies have a critical drawback: tumor cell drug resistance. Although resistance to chemotherapy is multifactorial, DNA repair plays a key role in the resistance of tumors to oxaliplatin.

Excision repair cross-complementing 1 (*ERCC1*) is a gene encoding a protein of the nucleotide excision repair (NER) complex, which is a group of proteins that are able to repair the DNA damage induced by substances forming adducts, such as platinum.[6] In the past years, the role of single-nucleotide polymorphisms (SNPs) in *ERCC1* as predictive factors for treatment outcomes in oxaliplatin-based chemotherapy-treated gastrointestinal cancer patients has been extensively investigated; rs11615 is a common SNP in the coding region of the *ERCC1* gene, and its polymorphisms might predict patients' response to oxaliplatin and the survival of patients with gastrointestinal cancer. However, other studies have suggested that there is no association of the *ERCC1* rs11615 polymorphism with the clinical outcomes of gastrointestinal cancer patients receiving oxaliplatin-based chemotherapy.[7,8] Thus, we performed this meta-analysis to evaluate the effects of the *ERCC1* rs11615 (C/T) polymorphisms on the efficacy of oxaliplatin-based chemotherapy in gastrointestinal cancer patients by assessing therapeutic response, progression-free survival (PFS), and OS.

Materials and methods

Publication search

This meta-analysis adheres to the relevant criteria of the preferred reporting items for systemic reviews and meta-analyses statement.[9] The PubMed database was searched for material published in English; the latest search was updated on December 20, 2014. The searching strategy consisted of combinations of medical subheadings and key words, such as "gastrointestinal cancer" or "gastric cancer" or "colorectal cancer" and "excision repair cross-complementing 1" or "ERCC1" or "ERCC1 rs11615" and "polymorphisms, single-nucleotide polymorphisms" or "polymorphism" and "oxaliplatin." All references cited in the original studies or review articles concerning the relevant topic were retrieved to broaden the search for relevant publications.

Inclusion and exclusion criteria

In this meta-analysis, publications of studies that met the following criteria were included: 1) inclusion of gastrointestinal cancer patients (GC and CRC); 2) investigation of the relationship between the *ERCC1* rs11615 polymorphism and response to chemotherapy or survival; 3) restriction of the regimen to oxaliplatin-based chemotherapy for investigation of the response to chemotherapy; 4) primary outcomes of interest of objective response, PFS, or OS; and 5) available data for quantitative synthesis, namely, genotype distribution data for response or hazard ratios (HRs) and 95% confidence intervals (CIs) for survival. The following exclusion criteria were used: 1) oxaliplatin-based chemotherapy was used as neoadjuvant treatment; 2) abstracts and reviews; 3) studies without available or exact data; 4) written in a non-English language; and 5) repeated or overlapping publications.

Data extraction

Two authors independently extracted the following items from all of the included studies: name of the first author, publication year of the article, country or area, tumor types (GC or CRC), number of patients, chemotherapy regimens, and genotyping method and outcomes. In addition, the response to chemotherapy according to genotype, HRs for OS and PFS, and their 95% CIs were collected for statistical analysis. We resolved any discrepancies through discussion or by consultation with a third person.

Statistical analysis

Pooled odds ratio (OR) and corresponding 95% CIs were calculated to estimate the association strength of the *ERCC1* rs11615 polymorphism (mutant gene vs wild-type gene, TT + CT vs CC) with the response to oxaliplatin-based chemotherapy. PFS and OS were evaluated by using pooled Cox proportional HRs and 95% CIs. A chi-square-based *Q*-test was used to test the assumption of heterogeneity. $P>0.1$ for the *Q*-test suggested a lack of heterogeneity among studies and required the use of the fixed-effects model (the Mantel–Haenszel method) to estimate the pooled OR of all studies. Otherwise, the random effects model was used. Statistical analyses were performed using STATA statistical software (Version 10.0, StataCorp LP, College Station, TX, USA). $P<0.05$ was considered statistically significant, and all *P*-values were two sided.

Results

Characteristics of studies

In this meta-analysis, 22 studies were identified to evaluate the relationship between the *ERCC1* rs11615 polymorphism and the clinical outcomes of oxaliplatin-based chemotherapy in GC and CRC patients.[10–31] A total of 3,014 patients with gastrointestinal cancer were enrolled in this study, including 1,242 with GC and 1,772 with CRC. There

were 12 studies from Asian populations[11,12,16–19,21–24,26,28] and 10 from Caucasian populations.[10,13–15,20,25,27,29–31] Oxaliplatin-based chemotherapy was investigated in all studies, and FOLFOX was the most popular regimen. The most common genotyping methods were polymerase chain reaction and restriction fragment length polymorphism analysis. Characteristics of the eligible studies are summarized in Table 1.

Association between the *ERCC1* rs11615 polymorphism and therapeutic response

Fourteen studies including 1,879 patients qualified for analysis of the association between the *ERCC1* rs11615 polymorphism and therapeutic response in GC and CRC patients. In the dominant model, the mutant gene was not associated with the objective response for all patients (TT + CT vs CC: OR =1.09, *P*=0.337, 95% CI =0.92–1.28) (Figure 1). However, stratified analysis by ethnicity showed a significant difference in the estimates of the effect between Asians and Caucasians, with the T allele being associated with a significantly lower objective response rate in Asians (TT + CT vs CC: OR =1.25, *P*<0.001, 95% CI =1.14–1.38). In addition, in a stratified analysis according to tumor site, the mutant gene was associated with the objective response in GC patients (TT + CT vs CC: OR =1.18, *P*=0.004, 95% CI =1.05–1.38) (Table 2).

Association between the *ERCC1* rs11615 polymorphism and PFS

Data from 13 included studies (including 1,464 patients) were applicable for the analysis. As shown in Figure 2, the T allele was associated with a significant increase in the risk of shorter PFS in all patients (TT + CT vs CC: HR =1.22, *P*<0.001, 95% CI =0.93–1.51). Similarly, we also performed stratified analysis by ethnicity and the tumor site, as shown in Table 2.

Table 1 Study characteristics

Study	Area	N	Tumor types	Genotyping method	Chemotherapy regimen	Outcome
Martinez-Balibrea et al[10]	Spain	95	mCRC	PCR-RFLP	FOLFOX or XELOX	PFS
Chang et al[11]	Taiwan	168	CRC	PCR-RFLP	FOLFOX	TR, PFS, OS
Chen et al[12]	Taiwan	166	mCRC	PCR-RFLP	FOLFOX	TR, OS
Chua et al[13]	Australia	118	mCRC	PCR-RFLP	FOLFOX	PFS, OS
Goekkurt et al[14]	Germany	134	GC	PCR-RFLP	FOLFOX	TR
Etienne-Grimaldi et al[15]	France	117	CRC	PCR-RFLP	FOLFOX	TR, PFS, OS
Huang et al[16]	People's Republic of China	89	GC	PCR-LDR	FOLFOX	PFS, OS
Huang et al[17]	People's Republic of China	102	GC	PCR-LDR	FOLFOX	PFS, OS
Keam et al[18]	Korea	73	GC	PCR-RFLP	FOLFOX	TR, PFS, OS
Kumamoto et al[19]	Japan	63	mCRC	PCR-RFLP	FOLFOX	TR
Lamas et al[20]	Spain	72	mCRC	PCR-RFLP	FOLFOX	TR
Li et al[21]	People's Republic of China	335	CRC	PCR-RFLP	FOLFOX	OS
Liang et al[22]	People's Republic of China	113	CRC	TaqMan-PCR	FOLFOX or XELOX	TR, PFS, OS
Liu et al[23]	People's Republic of China	116	GC	TaqMan-PCR	FOLFOX	PFS, OS
Lu et al[24]	People's Republic of China	447	GC	TaqMan-PCR	FOLFOX	TR, OS
Paré et al[25]	Spain	126	CRC	TaqMan-PCR	FOLFOX	TR, PFS, OS
Qi et al[26]	People's Republic of China	206	GC	RT-PCR	FOLFOX	TR
Ruzzo et al[27]	Italy	166	CRC	PCR-RFLP	FOLFOX	PFS
Seo et al[28]	Korea	75	GC	PCR-RFLP	FOLFOX	TR, PFS, OS
Spindler et al[29]	Denmark	66	CRC	PCR	XELOX	TR
Stoehlmacher et al[30]	USA	106	CRC	PCR-RFLP	FOLFOX	PFS, OS
Viguier et al[31]	France	61	CRC	PCR	FOLFOX	TR

Abbreviations: N, number of patients; mCRC, metastatic colorectal cancer; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; FOLFOX, 5-fluorouracil plus oxaliplatin; XELOX, capecitabine plus oxaliplatin; PFS, progression-free survival; CRC, colorectal cancer; TR, therapeutic response; OS, overall survival; GC, gastric cancer; PCR-LDR, polymerase chain reaction-ligation detection reaction; PCR, polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction.

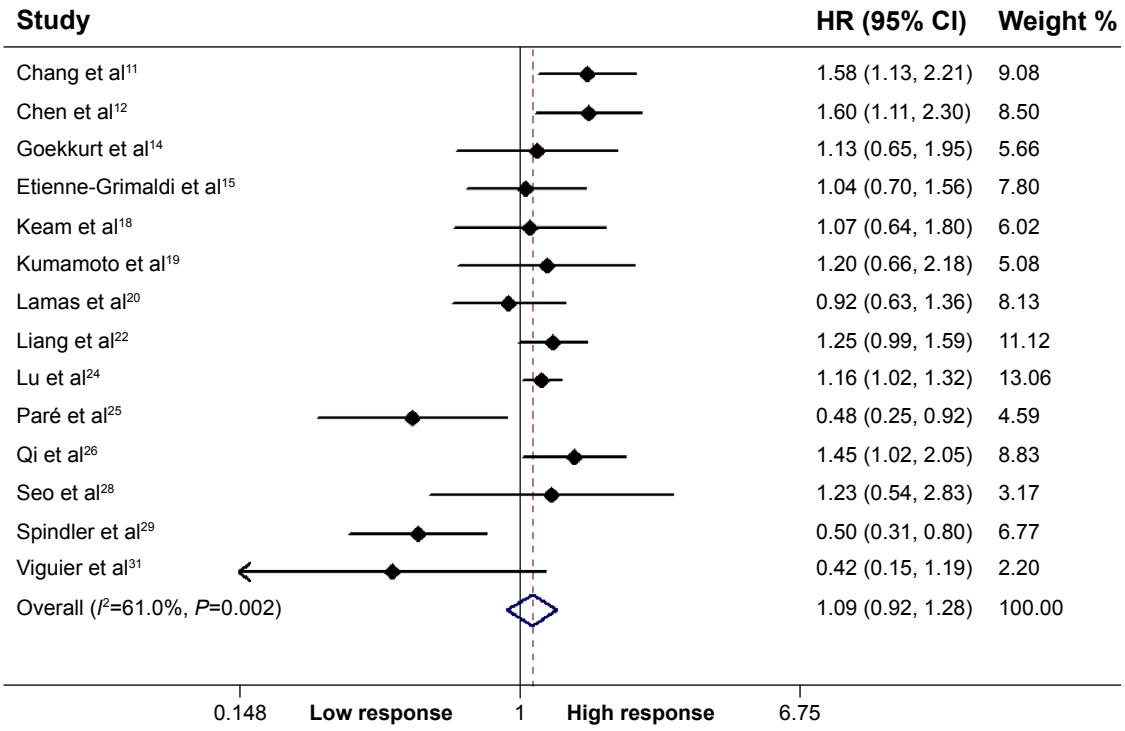

Figure 1 Association of the *ERCC1* rs11615 polymorphism with response to oxaliplatin-based chemotherapy.
Note: Weights are from random-effects analysis.
Abbreviations: ERCC1, excision repair cross-complementing 1; HR, hazard ratio; CI, confidence interval.

Association between the *ERCC1* rs11615 polymorphism and OS

Fourteen studies including 2,078 subjects were included in the final analysis. There was a significant effect of the *ERCC1* rs11615 polymorphism on OS in all patients (TT + CT vs CC: HR =1.12, $P<0.001$, 95% CI =0.85–1.40) (Figure 3). In subgroup analysis stratified by ethnicity and tumor site, the significant differences were retained, as shown in Table 2.

Discussion

Oxaliplatin-based chemotherapy is the primary therapeutic option for gastrointestinal cancer, especially for advanced or

Table 2 Association between the *ERCC1* rs11615 polymorphism and therapeutic response, PFS, and OS

	Studies	OR/HR (95% CI)	*Z*-value	*P*-value	I^2 (%)
Therapeutic response					
Asian	8	1.25 (1.14, 1.38)	4.58	<0.001	0.0
Caucasian	6	0.75 (0.54, 1.04)	1.73	0.083	56.8
GC	5	1.18 (1.05, 1.38)	2.85	0.004	0.0
CRC	9	0.98 (0.74, 1.30)	0.14	0.889	74.4
PFS					
Asian	8	1.49 (1.05, 1.92)	6.72	<0.001	58.9
Caucasian	5	0.91 (0.59, 1.24)	6.74	<0.001	59.2
GC	5	1.25 (0.82, 1.67)	5.73	<0.001	48.8
CRC	8	1.21 (0.80, 1.62)	5.83	<0.001	74.2
OS					
Asian	10	1.21 (0.86, 1.55)	6.87	<0.001	61.5
Caucasian	4	1.02 (0.44, 1.60)	3.44	0.001	61.1
GC	6	1.15 (0.71, 1.60)	5.05	<0.001	59.2
CRC	8	1.17 (0.76, 1.58)	5.58	<0.001	65.4

Abbreviations: *ERCC1*, excision repair cross-complementing 1; PFS, progression-free survival; OS, overall survival; OR/HR, odds ratio/hazard ratio; CI, confidence interval; GC, gastric cancer; CRC, colorectal cancer; PFS, progression-free survival; OS, overall survival.

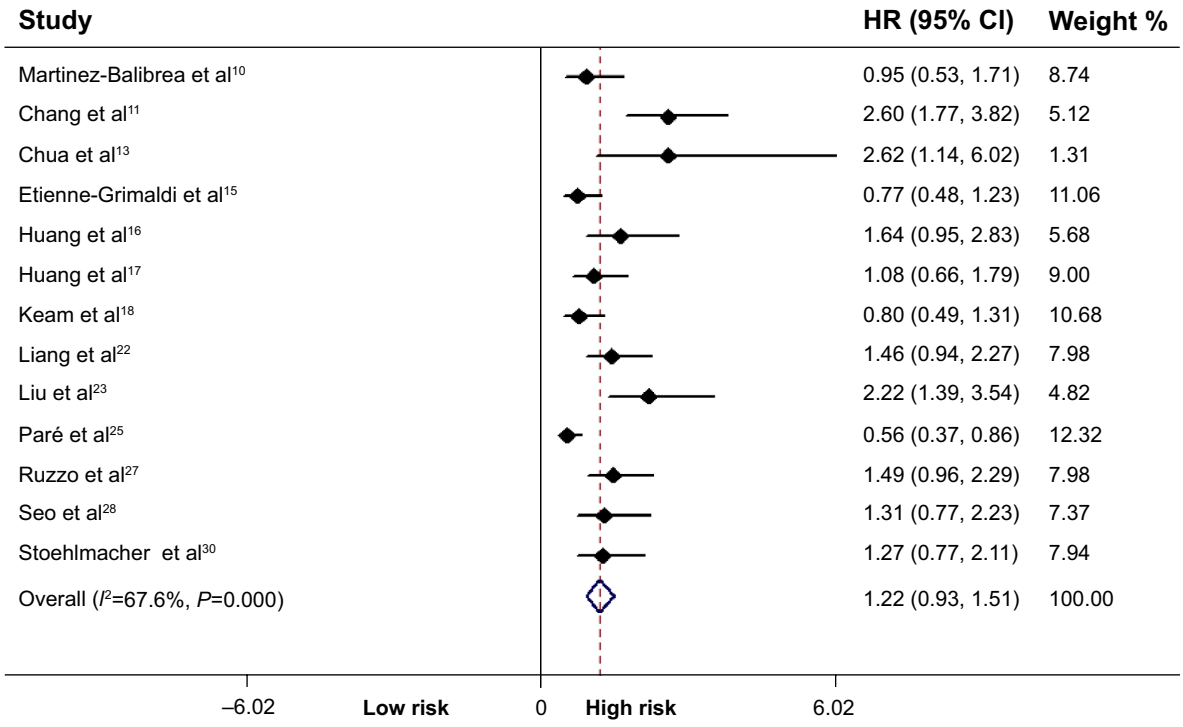

Figure 2 Correlation between the *ERCC1* rs11615 polymorphism and progression-free survival.
Note: Weights are from random-effects analysis.
Abbreviations: ERCC1, excision repair cross-complementing 1; HR, hazard ratio; CI, confidence interval.

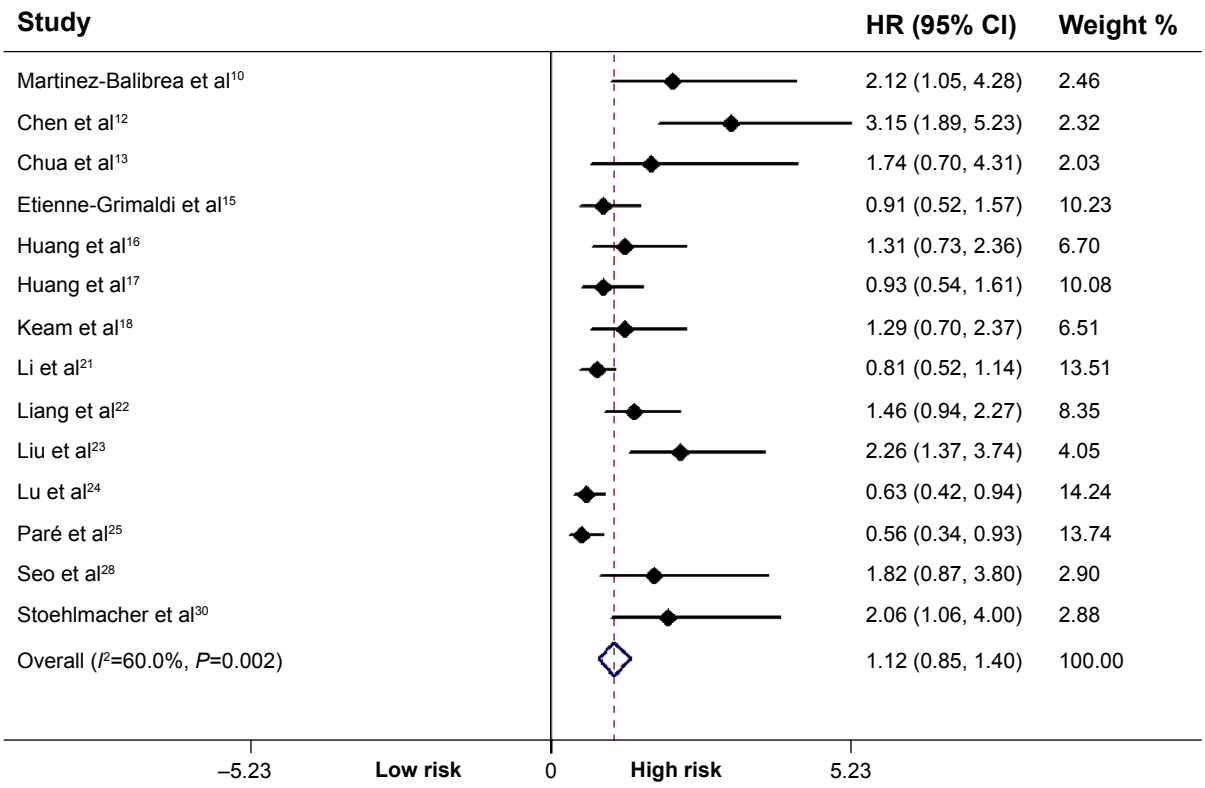

Figure 3 Correlation between the *ERCC1* rs11615 polymorphism and overall survival.
Note: Weights are from random-effects analysis.
Abbreviations: ERCC1, excision repair cross-complementing 1; HR, hazard ratio; CI, confidence interval.

relapsed cancer. The mechanism of action of platinum agents is based on the formation of DNA adducts that result in the alteration of the DNA structure and, eventually, the inhibition of DNA replication and transcription.[32] Hence, the expression of genes involved in the mechanisms of DNA repair has been studied as a possible predictive factor in patients treated with platinum-based chemotherapy.[33] ERCC1, which has a variety of gene forms, is the lead enzyme in the NER DNA repair pathway.[34] The DNA repair system plays a vital role in maintaining the stability of cellular functions and genomic integrity through the reversal of the DNA damage induced by various endogenous and/or exogenous factors, including therapeutic agents; therefore, host DNA repair capacity may contribute to cancer patient outcomes.[35] One possible theory postulates that in the absence of platinum therapy, poor DNA repair may result in more biologically aggressive tumors through their susceptibility to greater genetic aberrations over time, resulting in worse outcomes.[36]

The different polymorphisms of *ERCC1* may be related to the effect of chemotherapy in cancer patients. *ERCC1* rs11615 (C to T), belonging to the NER pathway, is associated with its diminished expression levels (mRNA and protein), with downstream functional consequences in the repair of cisplatin-induced DNA lesions. Recently, the *ERCC1* rs11615 gene polymorphism was shown to provide better prognostic information for cancer patients treated with platinum-based chemotherapy, including those with non-small cell lung cancer, ovarian cancer, testicular germ cell tumors, and gastrointestinal cancer.[37–40] Previous studies have revealed that *ERCC1* rs11615 genotypes are associated with the clinical outcome of GC or CRC patients who receive oxaliplatin-based chemotherapy, but the end results of these studies are not consistent, and current evidence is insufficient to confirm a statistically significant correlation. Some references describing association of rs11615 with ERCC1 diminished expression.[7,8,25,29,31] This meta-analysis examined the association between the *ERCC1* rs11615 polymorphism and the clinical outcomes of gastric and CRCs that were treated by oxaliplatin-based chemotherapy. Therapeutic response, PFS, and OS were used as the main parameters. We found no statistical evidence for an association between two *ERCC1* rs11615 SNPs and the objective response for all patients. However, stratified analysis indicated the *ERCC1* rs11615 T allele was a biomarker of low therapeutic response in Asian patients and GC patients. At the same time, our meta-analysis provided evidence that the *ERCC1* rs11615 polymorphism was associated with PFS or OS. Notably, there was an apparent ethnic discrepancy in the prognostic value between Asians and Caucasians, and statistical tests also confirmed the existence of ethnic differences in the estimates of the effect of the *ERCC1* allele. This discrepancy could be explained by the fact that the treatment outcome of platinum agents may be influenced by gene–gene interactions in different genetic backgrounds and gene–environment interactions in different lifestyles. As the previous studies gave controversial results, there may be some other reasons, such as the following: 1) different pathological types (GC and CRC) may produce different results; 2) there was different incidences of GC or CRC in different regions of worldwide, for example, higher incidence of GC in East Asia; 3) the positive result of some studies might be attributed to small sample size; 4) the other factors of population included cannot be analyzed in detail, such as age, sex, smoking, and drinking status, which could make the result masked; and 5) some studies are hospital-based design, which would not represent the people who live in a certain region.

Attention should be paid to the limitations of the meta-analysis, although some effort was made to perform a precise and comprehensive analysis. First, there are very few studies comparing Asians and Caucasians, with even fewer involving the black population. Further, with original data lacking for every study, we could only present an extensive subgroup analysis. In addition, the differences in national characteristics in different regions are influencing factors in the study results. Oxaliplatin is used with 5-fluorouracil in the regimen, and not as a single compound, and owing to the limited available publications on the subject, the latent gene–gene associations between NER variants and folate-metabolizing gene variants still cannot be investigated. Finally, some confounding factors such as sex, age, TNM stage, and chemotherapy regimens can never change the results based on the initial data.

To summarize, polymorphisms of *ERCC1* rs11615 are closely associated with the clinical outcomes of GC and CRC patients treated with oxaliplatin-based chemotherapy. Future studies with larger sample sizes using multivariant analyses may provide more persuasive data on this putative association.

Disclosure

The authors report no conflicts of interest in this work.

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