Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

OPEN

Predictive Value of Ercc1 and Xpd Polymorphisms for Clinical Outcomes of Patients Receiving Neoadjuvant Therapy

A Prisma-Compliant Meta-Analysis

Mao Qixing, PhD, MD, Dong Gaochao, MD, Xia Wenjie, MD, Yin Rong, PhD, MD, Jiang Feng, PhD, MD, Xu Lin, PhD, MD, Qiu Mantang, and Chen Qiang

Abstract: Excision repair cross complementing 1 (ERCC1) and xeroderma pigmentosum group D (XPD) play important roles in the nucleotide excision repair (NER) pathway. The correlation between ERCC1 polymorphisms (rs11615 and rs3212986) and XPD polymorphisms (rs13181 and rs1799793) with the response rate and overall survival of cancer patients who accept neoadjuvant therapy has been extensively investigated. However, the results are inconclusive.

In this study, we performed a meta-analysis to determine the strength of this correlation.

A comprehensive literature search was conducted in Medline, PubMed, and Embase up to February 2015.

A review of all titles and abstracts was performed by 2 of the authors to screen the articles based on the eligibility criteria. Clinical trials, observational studies, and epidemiological studies describing ERCC polymorphisms and neoadjuvant treatment were considered for review.

The response rate was analyzed using pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Overall survival was assessed using the hazard ratio (HR) with corresponding 95% confidence intervals.

In the present meta-analysis, we demonstrated that the ERCC1 rs3212986 polymorphism was significantly correlated with the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.49, 95% CI = 0.31–0.76, heterogeneity $P = 0.480$). Furthermore, a considerable correlation was observed between ERCC1 rs11615 and the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.228, 95% CI = 0.125–0.418, heterogeneity $P = 0.291$). No correlation was observed in the meta-analysis of overall survival. The individual studies included in our study differed in their patient selection and therapeutic protocols, which might lead to some bias in the results.

These findings indicate that the ERCC1 rs11615 and ERCC1 rs312986 polymorphisms may be candidate pharmacogenomic factors capable of predicting the response rate of esophageal cancer patients who accept neoadjuvant therapy. Further studies are warranted.

(*Medicine* 94(39):e1593)

Abbreviations: CI = confidence intervals, ERCC1 = excision repair cross complementing 1, HR = hazard ratio, HWE = Hardy–Weinberg equilibrium, NER = nucleotide excision repair, NOS = Newcastle–Ottawa scale, OR = odds ratio, OS = overall survival, RECIST = response evaluation criteria in solid tumor, TNM = tumor node metastasis, TRG = tumor regression, XPD = xeroderma pigmentosum group D.

INTRODUCTION

Neoadjuvant treatment plays a role in a tumor down-staging and has become a promising approach for the treatment of operable advanced stage tumor in the past decades.[1] Neoadjuvant treatment is a component of preoperative chemotherapy and preoperative radiotherapy.[2] A routine neoadjuvant regimen consists of cisplatin-based or 5-fluorouracil (5-FU)-based combinative chemotherapy or the graded radiotherapy schedule.[3] Previous studies demonstrated that partial cancer patients obtained an improved response rate and overall survival after receiving neoadjuvant treatment coupled with standard surgery.[4,5]

However, neoadjuvant therapy is a double-edged sword for advanced cancer patients who are not suitable for this treatment.[6] The decision concerning the best treatment choice for these patients is still based upon the traditional evaluation of the tumor characteristics, and there is a lack of molecular biomarkers to guide therapy. Thus, the identification of these predictive biomarkers remains a promising approach to obtain the best clinical outcome with minimum side effects.[7–9]

The ERCC1 and XPD genes (also named ERCC2) play important roles in the nucleotide excision repair (NER) pathway.[2] Nucleotide excision repair pathways detect and repair DNA damages caused by radiation or chemotherapeutic drugs. ERCC1 and XPD polymorphisms can reduce the DNA repair capacity.[7,10] Recently, a large number of studies suggested that ERCC1 and XPD polymorphisms predicted the therapeutic response to neoadjuvant treatment and the prognosis in human cancer.[11,12] These molecular biomarkers will have vast clinical significance due to the easily clinical applications.

Editor: Sayed Daoud.
Received: July 8, 2015; revised: August 21, 2015; accepted: August 24, 2015.
From the Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, Jiangsu Province, P. R. China.
Correspondence: Lin Xu, Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital, No. 42 Baiziting Road, Nanjing 210009, China (e-mail: xulin83cn@gmail.com).
Jiang Feng, Department of Thoracic Surgery, Nanjing Medical University Affiliated Cancer Hospital, No. 42 Baiziting Road, Nanjing 210009, China (e-mail: zengnljf@hotmail.com).
This work was supported by the Jiangsu key laboratory of molecular and translation cancer research grant from the National Natural Science Foundation of China (grant number 81472702), Natural Science Foundation of Jiangsu Province (grant number BK2012482), and Jiangsu Provincial Special Program of Medical Science (grant number BL2012030).
Mao Qixing, Dong Gaochao and Xia wenjie contribute equally to the article.
The authors have no conflicts of interest to disclose.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001593

Using previous studies, we analyzed ERCC1 and XPD polymorphisms and the clinical outcome of neoadjuvant therapy in cancer patients by a meta-analysis.

METHODS

Information Sources and Search Strategy

To identify relevant studies, a comprehensive literature search was conducted in Medline, PubMed, and Embase up to February 2015. The following terms were used to search for relevant investigations in the above-mentioned databases: ''ERCC'' or ''excision repair cross-complementing,'' ''polymorphism,'' ''variation,'' or ''nucleotide excision repair (NER) pathway genes'' in combination with ''neoadjuvant,'' ''neoadjuvant chemoradiotherapy,'' or ''cancer treatment.'' To prevent the loss of any important and useful data, we also identified additional investigations by screening the reference lists of key studies and reviews. Only articles written in English were included. This meta-analysis was conducted and reported in accordance with the PRISMA guidelines for systematic reviews and meta-analyzes (Table S1, http://links.lww.com/MD/A437. PRISMA-checklist).[13] The literature retrieval was completed in duplicate by 2 authors (QM and WX).

Inclusion and Exclusion Criteria

Clinical trials, observational studies, and epidemiological studies describing ERCC polymorphisms and neoadjuvant treatment were considered for review. Eligibility criteria were as follows: human-based studies; pathologically confirmed cancer receiving neoadjuvant regimens; full text written in English; evaluation of the association between ERCC polymorphisms and clinical outcomes (ie, therapeutic response rate, overall survival (OS) or progression-free survival (PFS)); and the largest study from all studies with overlapping data published by the same investigators was chosen. Studies that did not include the data necessary to extract the therapeutic response rate, OS, or PFS were excluded. Studies that addressed the association of ERCC expression and neoadjuvant treatment were also removed from this review.

Study Selection

Based on the eligibility criteria, a preliminary review of all titles and abstracts was necessary to screen the articles. Full text publications of all studies that were not eliminated during the previous screening were retrieved for comprehensive review. Two individuals (GD and WX) independently screened all of the search results. Differences were resolved by discussion with another author (JF).

Outcome Definition and Data Extraction

In this meta-analysis, we focused on the 2 major clinical outcomes: response to neoadjuvant therapy and overall survival. Response to the regimen was evaluated using the RECIST[14] or TRG criteria.[15] Data concerning overall survival (HR and 95% CIs) were directly gained from the studies which displayed in text. Data extraction was performed independently by the 2 reviewers (QM and WX) in terms of tumor type, tumor node metastasis (TNM) stage, author, publishing year, ethnicity, treatments, numbers of cases and controls, and 2 major clinical outcomes.

Methodological Quality Assessment

The quality of the methodology of the included studies was assessed with the Newcastle–Ottawa scale (NOS).[16] Studies scored 5 or more stars were defined as high-quality studies. Quality assessment was performed by 2 authors (QM and GD).

Statistical Analysis

The correlation strength of ERCC polymorphisms and response of cancer patients to neoadjuvant treatment was assessed by pooled odds ratios with corresponding 95% CIs. The hazard ratio (HR) was utilized to estimate the relationship between ERCC variations and the prognosis of cancer patients. A χ^2 -based Q test was used to measure heterogeneity; $P < 0.10$ indicated the existence of significant heterogeneity.[17] Both fixed-effects and random-effects models were utilized to test the effect of ERCC polymorphisms in influencing the response to neoadjuvant therapy. The random-effects model was applied in the existence of significant heterogeneity, while the fixed-effects model was used in the absence of heterogeneity. Hardy–Weinberg equilibrium (HWE) was calculated to evaluate the quality of the data in the control population. Publication bias was assessed by Begg's funnel plot and Egger's linear regression test; $P < 0.05$ was considered significant.[18] STATA version 12 was used in all statistical analyzes (Stata-Corp, College Station, Texas).

RESULTS

Eligible Studies

A total of 120 studies were identified by a comprehensive search using the aforementioned key words. After screening the titles and abstracts, we found 23 studies that reported ERCC polymorphisms and neoadjuvant treatment. The full text of the remainder of the studies was reviewed based on the inclusion criteria. Four studies were excluded: 1 publication was a literature review, 2 articles did not present sufficient genotype or allelic data, and 1 article did not include HR (hazard ratios) and 95% CI. Finally, 19 studies were included in this meta-analysis. Figure 1 portrays the screening process.[1,2,11,19–34]

Clinical Characteristics of Studies

The main clinical characteristics of the 19 studies included in the meta-analysis are summarized in Table 1. Fourteen studies were conducted in Caucasian populations, while the remainders were performed in Asian and African populations. All studies enrolled patients treated with neoadjuvant regimens. Neoadjuvant regimens consisting of chemotherapy and radiotherapy were reported in all studies. ERCC1 polymorphisms were investigated in 15 studies, while XPD polymorphisms were explored in 11 studies. The results of quality assessment are presented in Table 2S, http://links.lww.com/MD/A437.

ERCC Polymorphisms and Response Rates

ERCC1 rs11615 polymorphism Nine studies were performed to assess the correlation of the ERCC1 rs11615 polymorphism and neoadjuvant therapy. The genotype data for ERCC1 rs11615 were separated for CC, CT, and TT. Subjects carrying the CC genotype maintained a weak trend toward a better response rate to neoadjuvant therapy compared with subjects with the CT-TT genotype (OR = 1.11, 95% CI = 0.83–1.48, heterogeneity $P = 0.836$) (Fig. 2). In contrast, no significant associations were observed in the comparisons of CC-CT versus TT and CC-TT versus CT. However, subgroup analysis based on the tumor type identified a significant correlation in esophageal cancer patients receiving neoadjuvant therapy. There was a significantly increased chance of treatment

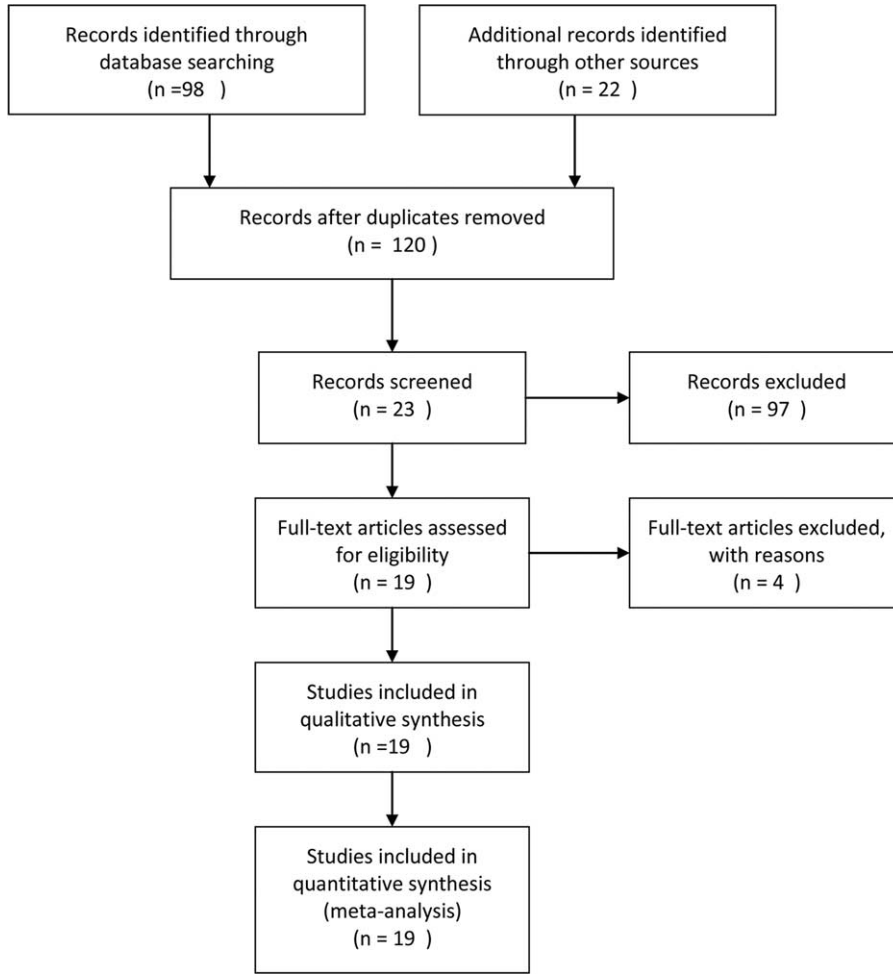

FIGURE 1. Flow chart of the literature search performed in this meta-analysis.

response in the subjects carrying the CC-CT genotype compared with subjects carrying the TT genotype (OR = 4.002, 95% CI = 2.078–7.707, heterogeneity $P = 0.253$) (Fig. 3). Furthermore, we demonstrated that patients carrying the homozygous CC-TT genotype presented a worse response rate compared with subjects with the heterogeneous CT genotype (OR = 0.228, 95% CI = 0.125–0.418, heterogeneity $P = 0.291$). By testing the impact of the CT and TT genotypes, we found that the probability of response was also decreased in subjects with the TT genotype compared with subjects carrying the CT genotype (OR = 0.199, 95% CI = 0.098–0.403, heterogeneity $P = 0.247$). No evidence of publication bias was detected. All of the results are listed in Table 2.

ERCC1 rs3212986 polymorphism In this group of genes, subjects with the mutation genotype presented a higher rate of response to neoadjuvant chemotherapy in 4 studies (OR = 1.93, 95% CI = 0.82–4.56, heterogeneity $P = 0.847$) compared with subjects with the wild-type genotype. However, no significant association was found in patients with the CC genotype compared with subjects with the CA-AA genotype in 6 studies. Additionally, none of the patients carrying the homozygous genotypes CC and AA showed a better response rate to neoadjuvant therapy than the subjects with the heterozygous genotype CA. The results of subgroup analysis by tumor type indicated that a significant correlation was observed between the ERCC1 rs3212986 polymorphism and the response rate of esophageal cancer patients to neoadjuvant therapy (OR = 0.49, 95% CI = 0.31–0.76, heterogeneity $P = 0.480$) (Fig. 4). The finding demonstrated that subjects carrying ERCC1 rs3212986 with at least one A allele (CA-AA genotype) presented a better response rate than subjects with the CC genotype. In the rectal subgroup, patients carrying the CC-AA genotype had a higher probability of obtaining a better response rate than subjects with the CA genotype (OR = 2.55, 95% CI = 1.551–4.192, heterogeneity $P = 0.666$). No evidence of publication bias was detected. These results are presented in Table 2.

XPD rs1799793 polymorphism A total of 5 studies with 547 subjects were included in this analysis. No correlation with the XPD polymorphism (GG vs. GA-AA) was confirmed for the response rate to neoadjuvant therapy (OR = 0.86, 95% CI = 0.56–1.31, heterogeneity $P = 0.516$) (Table 3S, http://links.lww.com/MD/A437). Owing to the scarcity of literature regarding the other 2 comparison models (GG-AA vs. GA and GG-GA vs. AA), we did not find any significant differences. Subgroup analysis was not performed due to the insufficient number of studies in each subgroup.

XPD rs13181 polymorphism (Lys751Gln) The correlation of the XPD polymorphism and response rate of neoadjuvant

TABLE 1. Baseline of Eligible Studies

Author	Year	Country	Ethnicity	Treatment	Cases	Age	Tumor type
Rumiato	2013	Italy	Italian	Neoadjuvant cisplatin/5-FU-based chemotherapy	63	62/68	esophageal cancer
Metzger	2012	Germany	German	Cisplatin/5-fluorouracil (5-FU)	153	63	esophageal cancer
Biason	2011	Italy	Caucasion	IOR OS-N4/IOR OS-N5	130	16	osteosarcoma
Cecchin	2010	Italy	Caucasion	Fluoropyrimidine-based chemotherapy/ Raltitrexed	238	61	rectal cancer
Chung	2006	Korea	Asian	5-FU-based combination/etoposide chemotherapy	36	–	bulky cervical cancer
Lamas	2012	Spain	Caucasion	Radiotherapy 50.4 Gy and with 5-FU 225 mg/m2/d.	93	67	rectal cancer
Okuda	2011	Japan	Asian	Platinum-based chemotherapy	90	66	NSCLC
Ryu	2004	Korea	Asian	Cisplatin combination chemotherapy	109	60	NSCLC
Stocker	2009	Germany	Caucasion	Platinum/5FU-based chemotherapy	178	56	gastric carcinoma
Wang	2011	China	Asian	5-fluorouracil and cisplatin chemotherapy	241	58	esophageal cancer
Warnecke-Eberz	2009	Germany	Caucasion	Cisplatin, 5-fluorouracil, radiation 36 Gy	52	59	esophageal cancer
Yoon	2011	USA	Mixed	Radiotherapy 45 Gy, cisplatin	81	–	esophageal cancer
Sebio	2015	Spain	Spainish	Radiotherapy 45 Gy, capecitabine/ FOLFOX	84	67.6	rectal cancer
Ott	2011	Germany	German	Cisplatin (50 mg/m^2)+fluorouracil (2000 mg/m^2 over 24 h)	258	58	Esophagus or Stomach cancer
Wu	2006	USA	American	Platinum analogs, 5-FU+radiotherapy	210	65	Esophagus cancer
Li-Min Yang	2012	China	Chinese	Methotrexate, cisplatin	187	61	Bone tumor
TENGSTR Ö M	2014	Finland	Caucasion	Adjuvant tamoxifen/TAM and radiation	65	–	Breast cancer
Castro	2014	Spain	Spanish	Anthracyclines/Tamoxifen	84	62.5	Breast cancer
Pedro Sánchez-Rovira	2012	Spain	Spanish	Paclitaxel/gemcitabine	46	49.5	Breast cancer

NSCLC = non-small-cell lung cancer.

therapy was explored in 7 studies containing 1687 patients. We detected no significant difference in the response rate between patients carrying the variant 751Lys allele and patients with the 751Gln allele after pooling all eligible studies (LysGln+GlnGln vs. LysLys, OR = 0.98, 95% CI = 0.66–1.46, heterogeneity $P = 0.406$). Similarly, the XPD polymorphism had no effect on the response rate to neoadjuvant therapy in the other 2 genotype model comparisons. No correlation was identified in the subgroup analysis.

ERCC Polymorphisms and Overall Survival (OS)

ERCC1 rs11615 polymorphism The ERCC1 rs11615 polymorphism and OS were reported in 5 studies. A greater than 1.5-fold higher risk of poor prognosis was observed for genotype CC compared with genotype CT-TT. The analysis indicated that genotype CC was potentially relevant to the poor prognosis compared with genotype CT-TT (HR = 1.57, 95% CI = 0.95–2.61, heterogeneity $P = 0.005$). Out of the 5 studies, 2 studies were conducted in NSCLC patients and 2 investigations were performed in osteosarcoma patients. Subgroup analysis on the basis of tumor type suggested no significant correlation between the ERCC1 rs11615 polymorphism and NSCLC or osteosarcoma prognosis (Table 3).

ERCC1 rs3212986 polymorphism The genotype data were classified into 3 genotypes (CC, CA, and AA). No significant associations were observed between the ERCC1 rs3212986 polymorphism and OS in the comparison model (CC vs. CA-AA). No correlation was observed between the rs3212986 polymorphism and neoadjuvant regimens in the subgroup analysis of tumor types.

XPD rs1799793 polymorphism Only 3 investigations were available to assess the XPD rs1799793 polymorphism. The HR of the comparison (GG vs. GA-AA) was 0.87, with a 95% CI ranging from 0.6 to 1.26 (heterogeneity $P = 0.574$). Subjects carrying genotype GG did not gain any advantage from neoadjuvant treatment compared with subjects carrying genotype GA-AA. The XPD rs1799793 polymorphism was not of prognostic relevance for neoadjuvant regimens.

XPD rs13181 polymorphism Six studies with 689 patients investigating the XPD rs13181 polymorphism and OS were included in this meta-analysis. The pooled HR from the 6 studies was 0.90, with a 95% CI ranging from 0.68 to 1.19 (heterogeneity $P = 0.331$). No association was observed between the XPD rs13181 polymorphism and OS. Analysis of the esophageal cancer subgroup revealed that the XPD rs13181 polymorphism was not significantly associated with OS (HR = 1.01, 95% CI = 0.74–1.38, heterogeneity $P = 0.512$). No publication bias was found.

Publication Bias

The funnel plot and Begg's test were performed to estimate publication bias. No significant bias was indicated by the Begg's and Egger's test.

DISCUSSION

Neoadjuvant chemotherapy and radiotherapy have been adopted as a routine therapy for operable advanced stage cancer.[7] However, severe toxicity and side effects from the

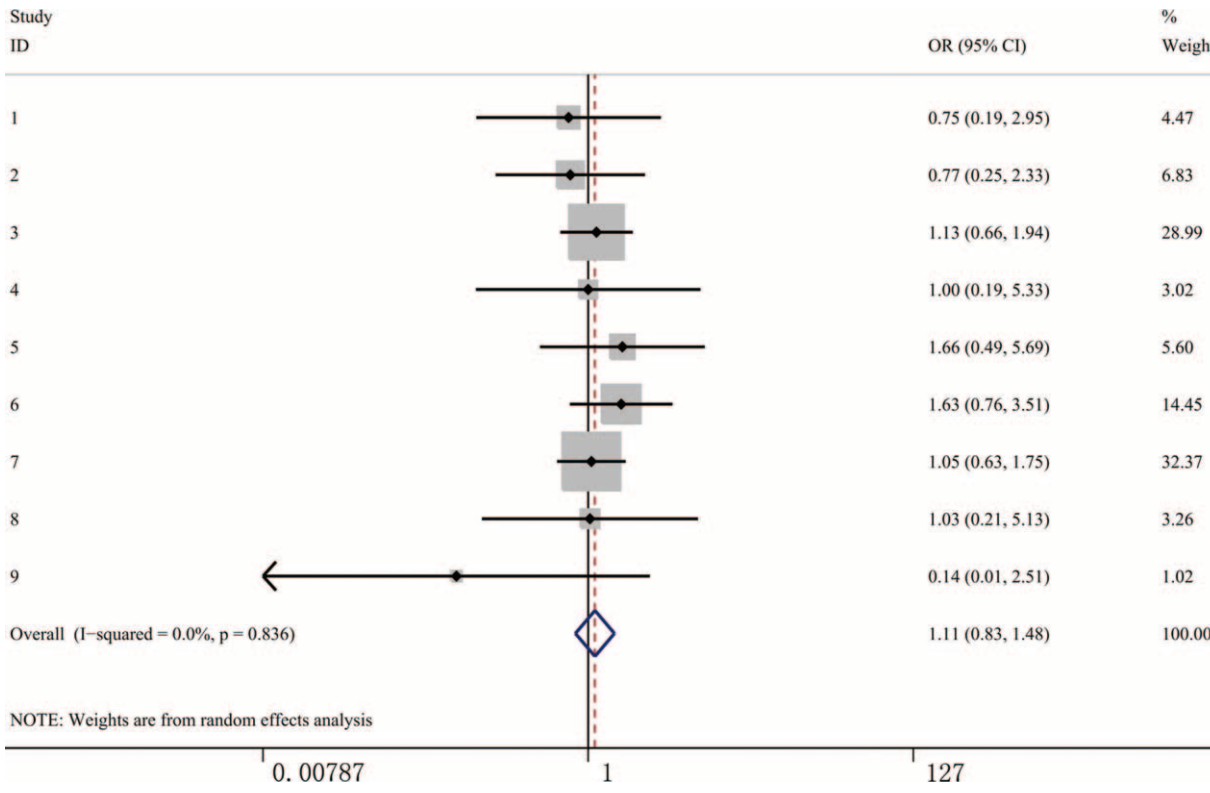

FIGURE 2. Forest plot for the ERCC1 rs11615 polymorphism and response rate in cancer patients receiving neoadjuvant therapy.

neoadjuvant therapy contribute to patient morbidity and may limit the promotion and efficacy of treatment.[1] Moreover, a significant proportion of patients receive only minor benefits from therapy, and delaying surgery may negatively influence their clinical outcome.[4,8,35,36] No appropriate predictive methods have been applied to evaluate the clinical outcome of the neoadjuvant approach in locally advanced cancer to date. Established predicted methods are insufficient to predict and guide individualized treatment.[6,12,37,38] Therefore, mature predictive methods are urgently needed in order to select more efficient treatment strategies with minimal toxicity and side effects.

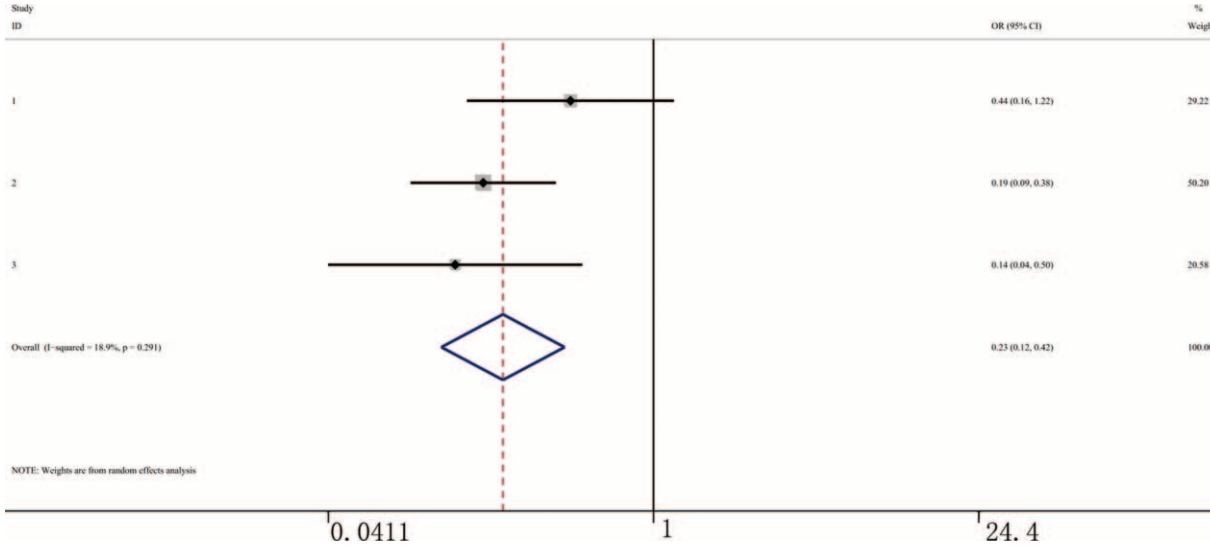

FIGURE 3. Forest plot for the ERCC1 rs11615 polymorphism and response rate in esophageal cancer patients receiving neoadjuvant therapy.

TABLE 2. ERCC1 Polymorphisms and Response Rate of Neoadjuvant

		Dominant Model			Recessive Model			Heterozygote Comparison		
SNP	Tumor Type	Studies	OR	*P*	Studies	OR	*P*	Studies	OR	*P*
ERCC rs11615	Overall	9	1.11.(0.83–1.48)	0.836	8	1.46.(0.69–3.08)	0.000	8	0.70.(0.36–1.40)	0.000
	Esophageal	4	0.969.(0.634–1.48)	0.939	3	4.002.(2.078–7.707)	0.253	3	0.228.(0.125–0.418)	0.291
	Rectal	3	1.114.(0.566–2.192)	0.290	3	0.73.(0.352–1.51)	0.147	3	1.221.(0.814–1.833)	0.776
ERCC rs3212986	Overall	6	0.98.(0.47–2.08)	0.003	4	1.93.(0.82–4.56)	0.847	5	0.86.(0.42–1.76)	0.062
	Esophageal	4	0.487.(0.311–0.762)	0.480	3	0.337.(0.034–3.357)	0.003	3	0.509.(0.234–1.108)	0.883
	Rectal	2	2.142.(0.717–6.39)	0.111	2	0.659.(0.123–3.527)	0.184	2	2.55.(1.551–4.192)	0.666

OR = odds ratios; SNP = single-nucleotide polymorphism.

Nucleotide excision repair plays an important role in DNA repair pathways. ERCC1 is part of the nucleotide excision repair (NER) complex and can repair chemical drug-induced DNA injuries.[10] The XPD gene encodes an ATP-dependent 5′–3′ helicase. The helicase is a subunit of the basal transcription factor IIH (TFIIH) complex that functions to separate the double helix structure of DNA during NER.[36] Studies have indicated that XPD polymorphisms are also involved in chemical drug resistance.

A number of studies have investigated the detection and validation of predictive and prognostic markers of neoadjuvant therapy. Both ERCC1 and XPD have been extensively studied among all of the molecular markers. However, the findings of previous studies concerning the predictive impact of ERCC1 and XPD polymorphisms toward neoadjuvant therapy are discordant with one another. Rumiato, Metzger, Biason, and Cecchin reported in 4 independent studies that ERCC1 and XPD played a vital role in the response rate and predicted the outcome of patients who receiving the neoadjuvant regimens.[1,19,20] However, no association between the ERCC gene and the response to neoadjuvant therapy was reported by Ott, Castro, and Pedro Sánchez-Rovira et al, which brought new impetus to the debate concerning neoadjuvant efficiency.[29,34,39]

In the present meta-analysis, we demonstrated that the ERCC1 rs11615 and rs3212986 polymorphisms were significantly correlated with the response rate to neoadjuvant therapy in esophageal cancer patients. However, no significant correlation was identified between XPD polymorphisms and the response rate of neoadjuvant regimens. Meta-analysis of overall survival revealed that subjects carrying the ERCC1 rs11615 genotype CC had a significant tendency toward shorter OS than subjects with genotype CT-TT. However, there was no correlation between other ERCC1 and XPD polymorphisms and OS.

In this study, a total of 4 SNPs in ERCC1 and XPD were studied in an attempt to predict the clinical outcome of cancer patients who received neoadjuvant treatments. We found that ERCC1 rs3212986 was significantly correlated with the response rate of esophageal cancer patients who received the neoadjuvant regimens. Esophageal cancer patients carrying the CC genotype presented a poorer response rate to neoadjuvant

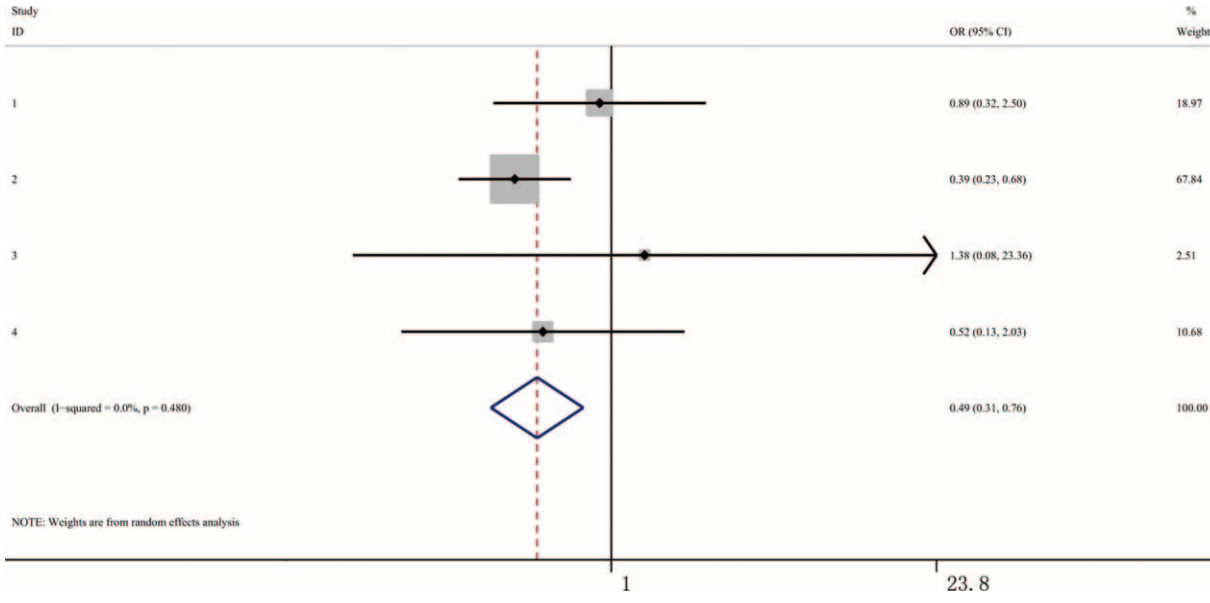

FIGURE 4. Forest plot for the ERCC1 rs3212986 polymorphism and response rate in esophageal cancer patients receiving neoadjuvant therapy.

TABLE 3. Polymorphisms and OS of Neoadjuvant

	ERCC1 rs11615			ERCC1 rs3212986			XPD rs13181			XPD rs1799793		
SNP	Studies	HR* (95% CI)†	*P*	Studies	HR (95% CI)	*P*	Studies	HR (95% CI)	*P*	Studies	HR (95%CI)	P
Overall	5	1.57 (0.95–2.61)	0.005	5	0.88 (0.57–1.35)	0.009	6	0.90 (0.68–1.19)	0.331	3	0.87 (0.60–1.26)	0.574
NSCLC	2	0.97 (0.49–1.44)	0.285	–	–	–	–	–	–	–	–	–
Esophageal	–	–	–	2	0.604 (0.25–1.46)	0.043	3	1.01 (0.74–1.38)	0.512	–	–	–
Osteosarcoma	2	1.30 (0.53–3.19)	0.027	–	–	–	–	–	–	–	–	–

* Hazard ratio.
† Confidence intervals.

therapy compared with subjects carrying the CA-AA genotype. These results were in accordance with Rumiato and Wang's conclusions. The ERCC1 rs3212986 polymorphism is located in the 3′ UTR of the gene, which contributes to ERCC1 mRNA stability.[1] Consequently, the rs3212986 polymorphism results in a limited DNA repair capacity, thereby impacting the response to treatment and overall survival. This finding indicated that ERCC1 rs3212986 might predict the response of esophageal cancer patients to neoadjuvant therapy and offered a minimally invasive and practicable approach to detect the outcome of neoadjuvant regimens. Additionally, we observed a correlation between ERCC1 rs3212986 and the response rate to neoadjuvant therapy in rectal cancer patients. However, the weight of the study by Cecchin was 86.2%; therefore, this study may exert a dominating effect on the result of the rectal subgroup analysis. The ERCC1 rs11615 polymorphism is located at codon 118 and may reduce ERCC1 mRNA and protein expression levels, thereby reducing the DNA repair capacity.[11] Therefore, we investigated whether ERCC1 rs11615 was correlated with the response rate to neoadjuvant therapy in esophageal cancer patients. Subjects with the CC-CT genotype showed a better response rate compared with subjects with the TT genotype, and patients carrying the CT genotype showed a better response rate than patients carrying the CC-TT genotype. These results indicated that the CT genotype might be correlated with a better response rate to neoadjuvant therapy in esophageal cancer patients. To evaluate the impact of the CT and TT genotypes, we compared CT and TT and found that subjects carrying the CT genotype presented a better response rate than subjects with the TT genotype. These results were in agreement with Metzger's studies and suggested that ERCC1 rs11615 might predict the response rate to neoadjuvant therapy in esophageal cancer. On the other hand, our analysis indicated that XPD rs13181 and rs1799793 did not present any correlation with the response rate to neoadjuvant therapy. The subgroup analysis was similar to those described above. As a result, 2 SNPs of XPD failed to predict the therapeutic response rate to neoadjuvant therapy. These results are in agreement with Chung and Castro's studies. Furthermore, we investigated the impact of the ERCC and XPD polymorphisms on the overall survival of cancer patients in the neoadjuvant setting. We demonstrated that ERCC1 rs11615 exhibited a marginal correlation with the OS of patients receiving neoadjuvant therapy (HR = 1.57, 95% CI = 0.95–2.61, heterogeneity $P = 0.005$), which was similar to the findings of Metzger and Ryu's studies. To the best of our knowledge, low expression of the ERCC1 protein will result in a longer OS after neoadjuvant therapy.[10,40] However, with detecting other ERCC1 and XPD polymorphisms, we were unable to discriminate between shorter OS and longer OS. Similarly, no differences were detected in the subgroup analyzes. Therefore, more investigations are needed in the future to confirm the correlation between ERCC1 and XPD with OS following neoadjuvant therapy.

We assessed the heterogeneity of each comparison model. No significant heterogeneity was found in any of analyzes or subgroup analyzes. For the purpose of identifying publication bias, we used the funnel plot and Begg's test. No publication bias was presented. However, several limitations should be addressed when interpreting the results of our meta-analysis. First, the data of this meta-analysis were extracted directly from the literature. Insufficient data were available to perform further stratified analyses. Second, the numbers of studies included in the some subgroup analyzes were too small. Finally, the individual studies included in our study differed in their patient selection and therapeutic protocols, which might lead to some bias in the results.

CONCLUSION

In summary, in the present meta-analysis, we tested whether the ERCC1 rs3212986 and rs11615 polymorphisms had the potential capable of predicting the response rate in esophageal cancer patients who received neoadjuvant therapy. This approach may offer a minimally invasive and practicable method to predict the outcome of neoadjuvant therapy. More studies regarding ERCC1 and XPD polymorphisms are needed in the future to explore and identify the response rate and OS associated with neoadjuvant therapy.

REFERENCES

1. Biason P, Hattinger CM, Innocenti F, et al. Nucleotide excision repair gene variants and association with survival in osteosarcoma patients treated with neoadjuvant chemotherapy. *Pharmacogenomics J.* 2012;12:476–483.
2. Metzger R, Warnecke-Eberz U, Alakus H, et al. Neoadjuvant radiochemotherapy in adenocarcinoma of the esophagus: ERCC1 gene polymorphisms for prediction of response and prognosis. *J Gastrointest Surg.* 2012;16:26–34.
3. Okumura H, Uchikado Y, Setoyama T, et al. Biomarkers for predicting the response of esophageal squamous cell carcinoma to neoadjuvant chemoradiation therapy. *Surg Today.* 2014;44:421–428.
4. Choi IJ, Kim DW, Kim DY, et al. Predictive markers for neoadjuvant chemotherapy in advanced squamous cell carcinoma of maxillary sinus: preliminary report. *Acta Otolaryngol.* 2013;133:291–296.
5. Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol.* 2014;32:1889–1894.

6. Zhao X, Zhang Z, Yuan Y, et al. Polymorphisms in ERCC1 gene could predict clinical outcome of platinum-based chemotherapy for non-small cell lung cancer patients. *Tumour Biol.* 2014;35:8335–8341.
7. Bergot E, Levallet G, Campbell K, et al. Predictive biomarkers in patients with resected non-small cell lung cancer treated with perioperative chemotherapy. *Eur Respir Rev.* 2013;22:565–576.
8. Kawashima A, Takayama H, Kawamura N, et al. Co-expression of ERCC1 and Snail is a prognostic but not predictive factor of cisplatin-based neoadjuvant chemotherapy for bladder cancer. *Oncol Lett.* 2012;4:15–21.
9. Bonneau C, Rouzier R, Geyl C, et al. Predictive markers of chemoresistance in advanced stages epithelial ovarian carcinoma. *Gynecol Oncol.* 2015;136:112–120.
10. Ozcan MF, Dizdar O, Dincer N, et al. Low ERCC1 expression is associated with prolonged survival in patients with bladder cancer receiving platinum-based neoadjuvant chemotherapy. *Urol Oncol.* 2013;31:1709–1715.
11. Warnecke-Eberz U, Vallbohmer D, Alakus H, et al. ERCC1 and XRCC1 gene polymorphisms predict response to neoadjuvant radiochemotherapy in esophageal cancer. *J Gastrointest Surg.* 2009;13:1411–1421.
12. Ge H, Lu Y, Chen Y, et al. ERCC1 expression and tumor regression predict survival in esophageal squamous cell carcinoma patients receiving combined trimodality therapy. *Pathol Res Pract.* 2014;210:656–661.
13. Panic N, Leoncini E, de Belvis G, et al. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One.* 2013;8:e83138.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
15. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer.* 1994;73:2680–2686.
16. Cota GF, de Sousa MR, Fereguetti TO, et al. Efficacy of anti-leishmania therapy in visceral leishmaniasis among HIV infected patients: a systematic review with indirect comparison. *PLoS Neglected Tropical Diseases.* 2013;7:e2195.
17. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med.* 1997;127:820–826.
18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629–634.
19. Rumiato E, Cavallin F, Boldrin E, et al. ERCC1 C8092A (rs3212986) polymorphism as a predictive marker in esophageal cancer patients treated with cisplatin/5-FU-based neoadjuvant therapy. *Pharmacogenet Genomics.* 2013;23:597–604.
20. Cecchin E, Agostini M, Pucciarelli S, et al. Tumor response is predicted by patient genetic profile in rectal cancer patients treated with neo-adjuvant chemo-radiotherapy. *Pharmacogenomics J.* 2011;11:214–226.
21. Chung HH, Kim MK, Kim JW, et al. XRCC1 R399Q polymorphism is associated with response to platinum-based neoadjuvant chemotherapy in bulky cervical cancer. *Gynecol Oncol.* 2006;103:1031–1037.
22. Lamas MJ, Duran G, Gomez A, et al. X-ray cross-complementing group 1 and thymidylate synthase polymorphisms might predict response to chemoradiotherapy in rectal cancer patients. *Int J Radiat Oncol Biol Phys.* 2012;82:138–144.
23. Okuda K, Sasaki H, Hikosaka Y, et al. Excision repair cross complementation group 1 polymorphisms predict overall survival after platinum-based chemotherapy for completely resected non-small-cell lung cancer. *J Surg Res.* 2011;168:206–212.
24. Ryu JS, Hong YC, Han HS, et al. Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. *Lung Cancer.* 2004;44:311–316.
25. Stocker G, Ott K, Henningsen N, et al. CyclinD1 and interleukin-1 receptor antagonist polymorphisms are associated with prognosis in neoadjuvant-treated gastric carcinoma. *Eur J Cancer.* 2009;45:3326–3335.
26. Wang Y, Chen J, Li X, et al. Genetic polymorphisms of ERCC1 and their effects on the efficacy of cisplatin-based chemotherapy in advanced esophageal carcinoma. *Oncol Rep.* 2011;25:1047–1052.
27. Yoon HH, Catalano PJ, Murphy KM, et al. Genetic variation in DNA-repair pathways and response to radiochemotherapy in esophageal adenocarcinoma: a retrospective cohort study of the Eastern Cooperative Oncology Group. *BMC Cancer.* 2011;11:176.
28. Sebio A, Salazar J, Paez D, et al. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. *Pharmacogenomics J.* 2015;15:77–83.
29. Ott K, Rachakonda PS, Panzram B, et al. DNA repair gene and MTHFR gene polymorphisms as prognostic markers in locally advanced adenocarcinoma of the esophagus or stomach treated with cisplatin and 5-fluorouracil-based neoadjuvant chemotherapy. *Ann Surg Oncol.* 2011;18:2688–2698.
30. Wu X, Gu J, Wu TT, et al. Genetic variations in radiation and chemotherapy drug action pathways predict clinical outcomes in esophageal cancer. *J Clin Oncol.* 2006;24:3789–3798.
31. De Castro G Jr, Pasini FS, Siqueira SA, et al. ERCC1 protein, mRNA expression and T19007C polymorphism as prognostic markers in head and neck squamous cell carcinoma patients treated with surgery and adjuvant cisplatin-based chemoradiation. *Oncol Rep.* 2011;25:693–699.
32. Yang L-M, Li X-H, Bao C-F. Glutathione S-transferase P1 and DNA polymorphisms with the response to chemotherapy and the prognosis of bone tumors. *Asian Pac J Cancer Prev.* 2012;13:5883–5886.
33. Tengstrom M, Mannermaa A, Kosma VM, et al. MnSOD rs4880 and XPD rs13181 polymorphisms predict the survival of breast cancer patients treated with adjuvant tamoxifen. *Acta Oncol.* 2014;53:769–775.
34. Sanchez-Rovira P, Anton A, Barnadas A, et al. Classical markers like ER and ki-67, but also survivin and pERK, could be involved in the pathological response to gemcitabine, adriamycin and paclitaxel (GAT) in locally advanced breast cancer patients: results from the GEICAM/2002-01 phase II study. *Clin Transl Oncol.* 2012;14:430–436.
35. Duldulao MP, Lee W, Nelson RA, et al. Gene polymorphisms predict toxicity to neoadjuvant therapy in patients with rectal cancer. *Cancer.* 2013;119:1106–1112.
36. Metzger R, Bollschweiler E, Holscher AH, et al. ERCC1: impact in multimodality treatment of upper gastrointestinal cancer. *Future Oncol.* 2010;6:1735–1749.
37. Geva R, Shamai S, Brazowsky E, et al. The Predictive Role of ERCC1 Status in Oxaliplatin Based Neoadjuvant Therapy for Metastatic Colorectal Cancer (mCRC) to the Liver. *Cancer Invest.* 2015;33:89–97.
38. Kolacinska A, Fendler W, Szemraj J, et al. Gene expression and pathologic response to neoadjuvant chemotherapy in breast cancer. *Mol Biol Rep.* 2012;39:7435–7441.
39. Castro E, Olmos D, Garcia A, et al. Role of XRCC3, XRCC1 and XPD single-nucleotide polymorphisms in survival outcomes following adjuvant chemotherapy in early stage breast cancer patients. *Clin Transl Oncol.* 2014;16:158–165.
40. Shilkrut M, Wu A, Thomas DG, et al. Expression of ribonucleoside reductase subunit M1, but not excision repair cross-complementation group 1, is predictive in muscle-invasive bladder cancer treated with chemotherapy and radiation. *Mol Clin Oncol.* 2014;2:479–487.