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Review Article

Prognostic value of *ERCC1* mRNA expression in non-small cell lung cancer, breast cancer, and gastric cancer in patients from Southern China

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Abstract: Background: Excision repair cross complementation group 1 (*ERCC1*) is a nucleotide excision repair pathway gene which provides protection against platinum-based chemotherapy-induced DNA damage. Methods: *ERCC1* mRNA expression was quantified by quantitative real-time reverse-transcription PCR in paraffin-embedded non-small cell lung cancer (NSCLC; n = 357), gastric cancer (n = 106), and breast cancer (n = 363) tissues. Survival curves were generated by Kaplan-Meier analysis; Cox proportional multivariate regression analysis was applied. Results: *ERCC1* mRNA expression was significantly higher in breast cancer than gastric cancer or NSCLC (both $P < 0.0001$), but not significantly different in NSCLC and gastric cancer ($P = 0.119$). In NSCLC, the low *ERCC1* group had significantly longer disease free survival (DFS) than the high *ERCC1* group (29.1 vs. 21.0 months, $P < 0.0001$); in the surgery alone and postoperative platinum-containing chemotherapy subgroups, DFS was significantly longer for the low *ERCC1* groups than high *ERCC1* groups (30.2 vs. 25.1 months, $P = 0.018$; 27.0 vs. 19.4 months, $P < 0.0001$, respectively). In gastric cancer patients receiving surgery alone, the low *ERCC1* group had significantly longer overall survival than the high *ERCC1* group (47.54 vs. 27.47 months, $P = 0.018$). Conclusions: High *ERCC1* mRNA expression of the NSCLC tumor tissues was associated with poor disease-free survival (DFS), in both the surgery alone and postoperative platinum-containing chemotherapy subgroups. Meanwhile, low *ERCC1*mRNA expression had significantly longer overall survival in gastric cancer patients receiving surgery alone. Therefore, *ERCC1* expression was a prognostic factor and predictive marker in NSCLC, and gastric cancer after surgery alone, but was not a prognostic factor in breast cancer.

Keywords: *ERCC1,* mRNA, expression, prognostic factor, NSCLC, gastric cancer, breast cancer

Introduction

Lung cancer has become the leading cause of cancer-related deaths worldwide [1], and non-small cell lung cancer (NSCLC) accounts for about 80% of lung cancer cases. In Western Europe and North America, breast cancer is the most common malignant tumor type in females. Compared to developed countries, China has lower prevalence of breast cancer; however, the incidence of the disease has increased in recent years [2]. Gastric cancer is the fourth most common malignant tumor type worldwide, and the second leading cause of cancer-related deaths [3]. Radical surgery supplemented with chemotherapy represents an important treatment strategy for early and locally advanced lung cancer, breast cancer, and gastric cancer. However, the postoperative 5-year survival rate for lung cancer is only 50%, and approximately 50% of patients with lung cancer experience local recurrence and/or distal metastasis, and eventual death [4]. The 5-year survival rate for gastric cancer is only 30% [5].

Postoperative adjuvant chemotherapy is an important treatment approach in patients with NSCLC, breast cancer, or gastric cancer. Platinum-based drugs, including cisplatin, carboplatin and oxaliplatin, are mainstays in the first-

Table 1. Clinical characteristics of the patients with NSCLC (n = 357)

Characteristic	No. (%)	Low *ERCC1* (%)	High *ERCC1* (%)	*P* Value
Sex				0.113
Male	218 (61.1%)	102 (57.0%)	116 (65.2%)	
Female	139 (38.9%)	77 (43%)	62 (34.8%)	
Age				0.265
≤ 60 y	184 (51.1%)	87 (48.6%)	97 (54.5%)	
> 60 y	173 (48.9%)	92 (51.4%)	81 (45.5%)	
Pathological TNM stage				< 0.0001
Ia-Ib	186 (52.1%)	164 (91.6%)	22 (12.4%)	
IIb-IIIa	169 (47.3%)	15 (8.4%)	156 (87.6%)	
Histologic type				< 0.0001
Squamous-cell carcinoma	91 (25.5%)	33 (18.4%)	58 (32.6%)	
Adenocarcinoma	348 (69.5%)	133 (74.3%)	115 (64.6%)	
Other	18 (5.0%)	13 (7.3%)	5 (2.8%)	
Differentiation				0.006
Poor	97 (27.2%)	37 (20.7%)	60 (33.7%)	
Good	260 (72.8%)	142 (79.3%)	118 (66.3%)	
Lymph node metastasis				< 0.0001
Yes	151 (42.3%)	13 (7.3%)	138 (77.5%)	
No	206 (57.7%)	166 (92.7%)	40 (22.5%)	
Smoking status				0.014
No	198 (55.5%)	104 (58.1%)	94 (52.8%)	
Yes	116 (32.5%)	47 (26.3%)	69 (38.8%)	
Unknown	43 (12.0%)	28 (15.6%)	15 (8.4%)	

Therefore, we used real-time reverse-transcription polymerase chain reaction (qPCR) to measure the expression levels of *ERCC1* mRNA in paraffin-embedded tissues obtained from patients with NSCLC, gastric cancer, or breast cancer. The association of *ERCC1* mRNA expression with prognosis following platinum-based chemotherapy was analyzed, in order to help predict progosis and treatment efficacy, and guide individualized chemotherapy regimens in patients with NSCLC, gastric cancer, and breast cancer.

line treatment for NSCLC and gastric cancer. Postoperative platinum-based adjuvant chemotherapy improves the survival rate in NSCLC by approximately 5%.

Platinum-based drugs exert anti-tumor activity by entering cells and causing DNA damage. Multiple randomized controlled clinical studies have confirmed that the sensitivity to postoperative adjuvant chemotherapy varies from individual to individual, which may be related to the individuals' ability to repair DNA damage [6-10]. Excision Repair Cross-Complementation group 1 (ERCC1) is a crucial factor in the nucleotide excision repair (NER) process. The gene or protein expression level of ERCC1 is not only a predictive marker for the efficacy of platinum-based chemotherapy in patients with breast cancer, gastric cancer, and non-small cell lung cancer, but also a prognostic factor in NSCLC [11-15]. However, the expression profiles of *ERCC1* mRNA in patients from Southern China with lung, gastric or breast cancer - the three most common tumor types in the region - have not yet been investigated.

Materials and methods

Patients and tumor tissue samples

Tumor tissues were collected from 400 consecutive patients with NSCLC who underwent radical primary lung cancer surgical resection at the First Affiliated Hospital of Guangzhou Medical University, 400 patients with gastric cancer who underwent radical primary gastric cancer surgical resection at Fujian Provincial Hospital; and 400 patients with breast cancer who underwent radical primary breast cancer surgical resection at Xiamen Zhongshan Hospital. Formalin-fixed paraffin-embedded (FFPE) primary three tumor tissues collected during surgery were evaluated by pathologists to determine whether the tumor met the criterion of containing at least 50% tumor cells. Patients with insufficient or poor-quality tissue for molecular analysis were excluded from this study. Excluding the samples which could not be analyzed due to RNA degeneration, *ERCC1* mRNA expression analysis was possible in 357 patients with NSCLC; 106 patients with gastric

cancer; and 363 patients with breast cancer; these patients were enrolled in this retrospective study.

All patients had pathologically-confirmed cancer and were treated between January 2008 and December 2011. NSCLC was pathologically staged according to the Union International Contre le Cancer (UICC-7) staging system for lung cancer [16]; gastric cancer according to the UICC-7 staging system for gastric cancer [17], and breast cancer according to the American Joint Committee on Cancer (AJCC-6) staging system for breast cancer [18].

The patients with NSCLC had early (stage Ia/Ib) or advanced disease (stage IIb/IIIa); their clinicopathological features are shown in **Table 1**. Of the 357 patients with NSCLC, 91 (25.5%) had squamous cell carcinoma, 248 (69.5%) had adenocarcinoma, and 18 (5.0%) had other pathologies (including large cell lung cancer and adenosquamous carcinoma); 218 (61.1%) received platinum-based adjuvant chemotherapy and 139 (38.9%) received surgery alone.

Of the 106 patients with gastric cancer, 91 (85.8%) had adenocarcinoma and 15 (14.2%) had another pathology; 50 (47.2%) patients with gastric cancer received platinum-based adjuvant chemotherapy, 38 (38.9%) received surgery alone, and 18 (16.9%) received non-platinum-based adjuvant chemotherapy (Table S1).

In the 363 patients with breast cancer, 344 had invasive cancer (94.8%) and 19 non-invasive cancer (5.2%); 30 (8.3%) received platinum-based adjuvant chemotherapy, 35 (9.6%) received surgery alone, and 298 (82.1%) received non-platinum-based adjuvant chemotherapy (Table S2).

No patients with NSCLC or gastric cancer had received any anti-cancer therapy before surgery; however, 47 (12.9%) patients with breast cancer received preoperative neoadjuvant chemotherapy. Most patients with locally advanced stage LC, BC and GC received 2-4 cycles of adjuvant platinum-based chemotherapy following surgery.

After tumor resection, the patients were followed up every 3 months in the first 2 years and then every 6 months for the next 3 years. Disease-free survival (DFS) and overall survival (OS) were measured from the day of tumor resection until radiologically/biopsy-confirmed tumor recurrence or death, respectively.

This study was approved by the Institutional Review Boards of the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Fujian Provincial Hospital, Fuzhou, and Xiamen Zhongshan Hospital, Xiamen, China.

Q-PCR analysis of ERCC1 expression

Total RNA was extracted from FFPE tumor tissues using the RNeasy FFPE Kit (Qiagen, Hilden, Germany), and cDNA was reverse-transcribed using a 1:1 mix of random hexamers and oligo-dTs (Amoy Diagnostics Co., Ltd, Xiamen, China). Relative complementary DNA quantitation for ERCC1 and an internal reference gene (β-actin) was done using the commercially available AmoyDx®*ERCC1* Detection Kit (Amoy Diagnostics Co., Ltd.), in a fluorescent temperature cycler (Mx 3000P Real Time PCR System; Stratagene, La Jolla, CA) following the manufacturers' protocols. Briefly, cDNA was PCR-amplified in a final volume of 25 μL containing 3 μL cDNA, 25 mM $MgCl_2$, 25 mM dNTPs, 100 μM of the specific forward and reverse primers, 10× Amoy buffer and 5 U/μL of Amoy HS-Taq. Relative gene expression levels are expressed as ratios (differences between the Ct values) between two absolute measurements (genes of interest/internal reference gene).

Statistical analysis

QPCR data was expressed as the ratio of two absolute measurements (amount of *ERCC1*/ amount of the internal reference gene β-actin). The Maximal v2 method of Halpern was adapted to determine the optimal cut-off values to stratify patients into low ERCC1 expression groups and high ERCC1 expression groups. Fisher's exact test was used to assess the relationship between *ERCC1* expression and clinical characteristics. Kaplan-Meier survival curves were used to compare DFS and OS among patients with different *ERCC1* expression levels. A Cox multivariate proportional hazard model was used for survival analysis, and hazard ratio (HRs) and 95% confidence intervals (CIs) were calculated. All statistical analyses were carried out at a 5% level of significance with a power of 80%, using Statistical Package for the Social Sciences, version 13 (SPSS Inc, Chicago, IL, USA).

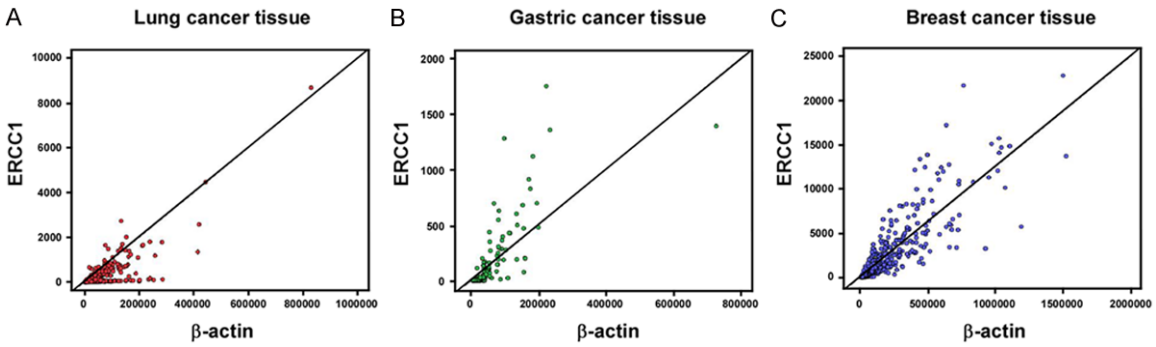

Figure 1. Scatter plots of the ERCC1 and β-actin gene expression profiles for each patient with (A) NSCLC; (B) gastric cancer or (C) breast cancer. The horizontal axis represents the expression of β-actin, and the vertical axis represents the expression of ERCC1, and Slash represents 45 degrees.

Results

Abundance of ERCC1 mRNA expression in NSCLC, gastric cancer, and breast cancer tissues

Analysis of *ERCC1* mRNA expression was possible in 357 patients with NSCLC (**Table 1**), 106 patients with gastric cancer (Table S1), and 363 patients with breast cancer (Table S2), and the RT-PCR system showed no non-specific amplification and had a good reproducibility. In the 357 patients with NSCLC, the median expression level of *ERCC1* relative to the housekeeping gene β-actin was 8.3 × 10E4 (95% CI 7 × 10E7-1.14 × 10E2). Using ≤ 8.3 × 10E4 as a cut-off value, 179/357 (50.14%) patients with NSCLC were assigned to the low *ERCC1* expression group, and 178/357 (49.86%) to the high *ERCC1* expression group. In the 106 patients with gastric cancer, the median expression level of *ERCC1* was 1.45 × 10E3 (95% CI 1.03 × 10E4-6.58 × 10E3). Using ≤ 1.45 × 10E3 as a cut-off value, 53/106 (50%) patients were assigned to the low *ERCC1* expression group, and 53/106 (50%) to the high *ERCC1* expression group. In the 363 patients with breast cancer, the median expression level of *ERCC1* was 1.02 × 10E2 (95% CI 1.89 × 10E6 - 2.79 × 10E2). Using ≤ 1.02 × 10E2 as a cut-off value, 181/363 (49.86%) patients were assigned to low the *ERCC1* expression group, and 182/363 (50.14%) to the high *ERCC1* expression group.

Scatter plots of the *ERCC1* expression profiles were created for each NSCLC, gastric cancer, and breast cancer tissue sample. In NSCLC, most spots were distributed below the 45° diagonal line (200000, 2000, **Figure 1A**); in gastric cancer, most spots were distributed above the 45° diagonal line (200000, 1000, **Figure 1B**), with some spots drifting away from the line; and in breast cancer, most spots were distributed around the 45° diagonal line (1000000, 20000, **Figure 1C**).

ERCC1 mRNA expression was significantly higher in breast cancer (0.118 ± 0.00810) than in NSCLC (0.00335 ± 0.00450) or gastric cancer (0.00228 ± 0.00238; both $P < 0.0001$); however, ERCC1 mRNA expression was not significantly different in NSCLC and gastric cancer ($P = 0.119$).

Association between ERCC1 mRNA expression and the clinicopathological features of NSCLC, gastric cancer, and breast cancer

The clinicopathological features of the patients with NSCLC are shown in **Table 1**. High *ERCC1* mRNA expression in the NSCLC tumor tissues was associated with a smoking history ($P < 0.0001$), squamous carcinoma ($P < 0.0001$), poor differentiation ($P = 0.006$), nodal metastasis ($P < 0.0001$), and relatively advanced resectable disease (IIb and IIIa, $P < 0.0001$). No associations were observed between *ERCC1* expression and any other clinicopathological features in NSCLC.

The clinicopathological features of the patients with gastric cancer are shown in Table S1. No significant associations were observed between *ERCC1* mRNA expression and gender, age, clinical stage, pathology, smoking history, alcohol drinking history, or differentiation ($P > 0.05$) in gastric cancer.

The clinicopathological features of the patients with breast cancer are shown in Table S2. No

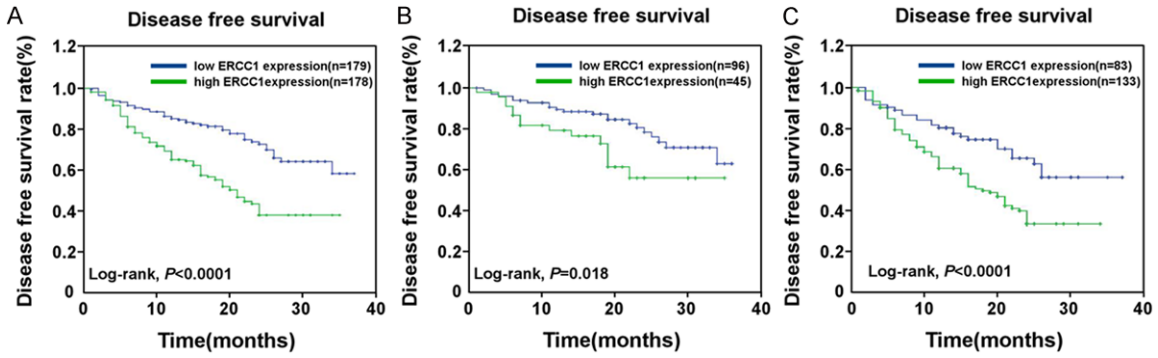

Figure 2. Effect of tumor *ERCC1* mRNA expression on disease-free survival in NSCLC. The patients were stratified into low ($\leq 8.3 \times 10^{-3}$) and high ($> 8.3 \times 10^{-3}$) *ERCC1* mRNA expression groups. Disease-free survival (DFS) for (A) all patients (n = 357); (B) patients who received surgery alone (n = 139); and (C) patients who received surgery and platinum-based chemotherapy (n = 218).

significant associations were observed between *ERCC1* mRNA expression level and gender, pathological stage, pathology, tumor size, or axillary nodal metastasis in breast cancer ($P > 0.05$).

Relationship between ERCC1 mRNA expression and survival in NSCLC

Median DFS for the 357 patients with NSCLC was 27.0 months (1-37 months). Median DFS was significantly longer in the low *ERCC1* mRNA expression group than the high *ERCC1* group (29.1 vs. 21.0 months, $P < 0.0001$; **Figure 2A**). Patients with NSCLC were further stratified into the surgery alone subgroup and postoperative adjuvant platinum-based chemotherapy subgroup. In patients who received surgery alone, median DFS was significantly longer in the low *ERCC1* mRNA expression group than the high *ERCC1* group (30.2 vs. 25.1 months, $P = 0.018$; **Figure 2B**). In patients who received postoperative platinum-based chemotherapy, the low *ERCC1* mRNA expression group had significantly longer median DFS compared to the high *ERCC1* group (27.0 vs. 19.4 months, $P < 0.0001$; **Figure 2C**). Gender, age, clinical stage, pathology, differentiation, nodal metastasis, smoking status, platinum-based chemotherapy and *ERCC1* mRNA expression were introduced into a Cox model for multivariate regression analysis. Only clinical stage ($P = 0.012$, HR = 0.298) and platinum-based chemotherapy (P = 0.035, HR = 0.623) were independent factors for DFS in NSCLC.

Median OS for the 357 patients with NSCLC was 42.3 months (1.2-44.53 months). No significant differences in OS were observed between the low and high *ERCC1* mRNA expression groups in the entire cohort of 357 patients with NSCLC (41.7 vs. 41.6 months, $P = 0.264$), or in the surgery alone subgroup (34.7 vs. 39.8 months, $P = 0.587$) or postoperative adjuvant platinum chemotherapy subgroup (42.9 vs. 42.0 months, $P = 0.910$).

Relationship between ERCC1 mRNA expression and survival in gastric cancer

Median DFS for the 106 patients with gastric cancer was 48.81 months (1.10-60.10 months). Median DFS was not significantly different between the *ERCC1* mRNA low and high expression groups (50.80 vs. 46.39 months, $P = 0.326$; **Figure 3A**). The patients with gastric cancer were stratified into a surgery alone subgroup, a postoperative adjuvant platinum-based chemotherapy subgroup, and a postoperative adjuvant non-platinum-based chemotherapy subgroup. Median DFS was not significantly different between the *ERCC1* low and high groups in the surgery subgroup; however, a tendency towards prolonged median DFS was observed for the *ERCC1* low group (54.69 vs. 46.34 months, $P = 0.094$; **Figure 3B**). Median DFS was not significantly different between the *ERCC1* low and high groups in the platinum-based adjuvant chemotherapy subgroup (43.88 vs. 42.27 months, $P = 0.979$; **Figure 3C**) or non-platinum-based chemotherapy subgroup (54.69 vs. 46.34months, $P = 0.642$). Gender, age, pathological stage, clinical stage, smoking history, alcohol consumption, differentiation, chemotherapy, and *ERCC1* mRNA expression were introduced into the Cox model for

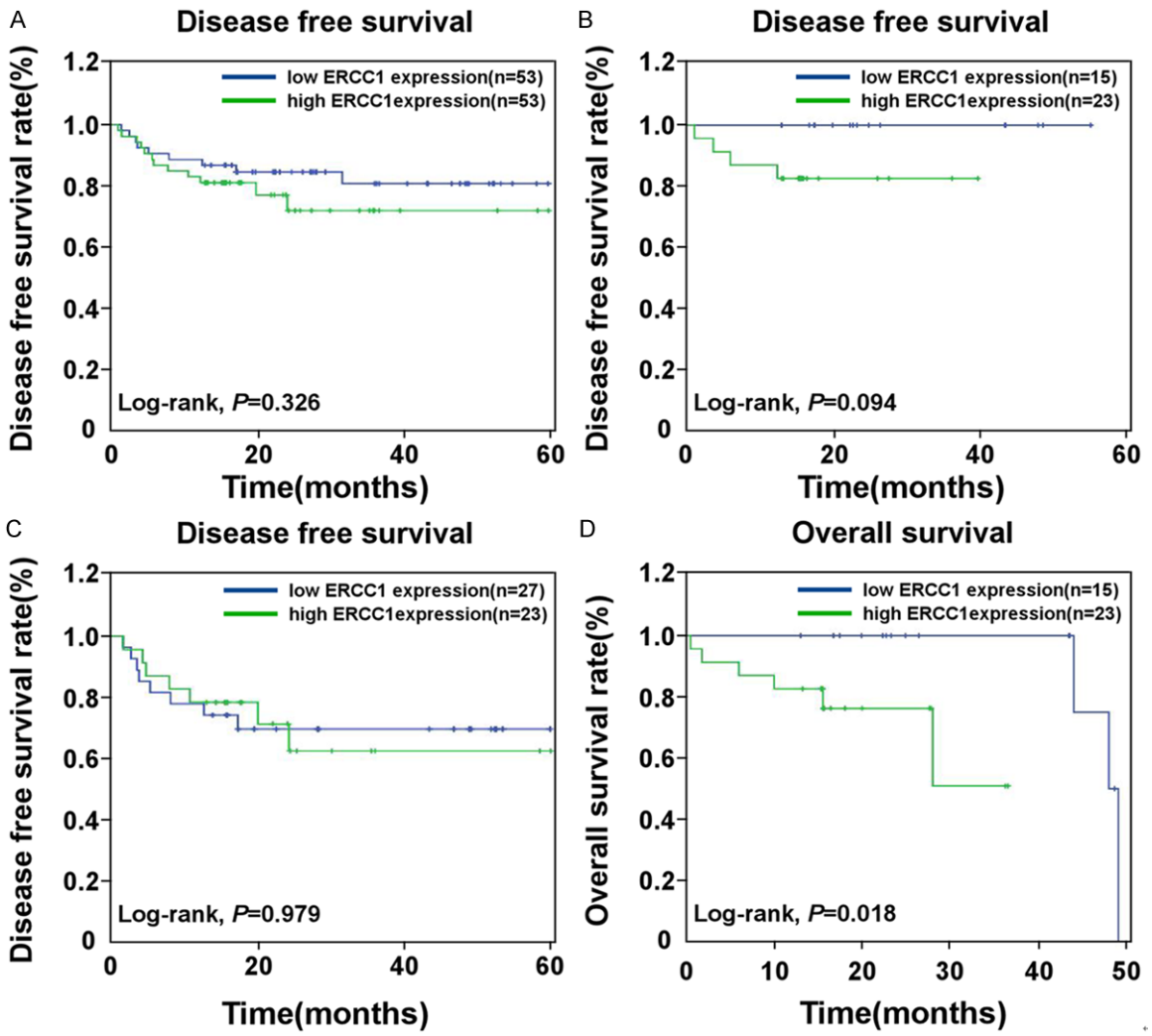

Figure 3. Effect of tumor *ERCC1* mRNA expression on survival in gastric cancer. The patients were stratified into low ($\leq 1.45 \times 10^{-3}$) and high ($> 1.45 \times 10^{-3}$) *ERCC1* mRNA expression groups. Disease-free survival (DFS) for (A) all patients (n = 106); (B) patients who received surgery alone (n = 38); (C) patients who received surgery and platinum-based chemotherapy (n = 50); and (D) overall survival (OS) in patients who received surgery alone (n = 38).

multivariate regression analysis; none of these features were independent factors for DFS in gastric cancer ($P > 0.05$).

Median OS in the 106 patients with gastric cancer was 51.69 months (1.80-60.10 months). No significant difference in OS was noted between the *ERCC1* low and high expression groups (53.97 vs. 49.89 months, $P = 0.193$) for the entire cohort. In the surgery alone subgroup, the low *ERCC1* mRNA expression group had significantly longer median OS compared to the high *ERCC1* group (47.54 vs. 27.47 months, $P = 0.018$; **Figure 3D**). However, median OS was not significantly different in the low and high *ERCC1* expression groups of either the postoperative adjuvant platinum-based chemotherapy subgroup (54.17 vs. 53.16 months, $P = 0.740$) or postoperative adjuvant non-platinum-based chemotherapy subgroup (58.89 vs. 54.12 months, $P = 0.593$).

Relationship between ERCC1 mRNA expression and survival in breast cancer

Median DFS in the 363 patients with breast cancer was 55.32 months (2.03-59.73 months). Median DFS was not significantly different between the low and high ERCC1 mRNA expression groups in the entire cohort (54.99 vs. 45.59 months, $P = 0.433$; **Figure 4A**). No significant differences in DFS were observed between the low and high *ERCC1* mRNA expression groups in the in the surgery alone sub-

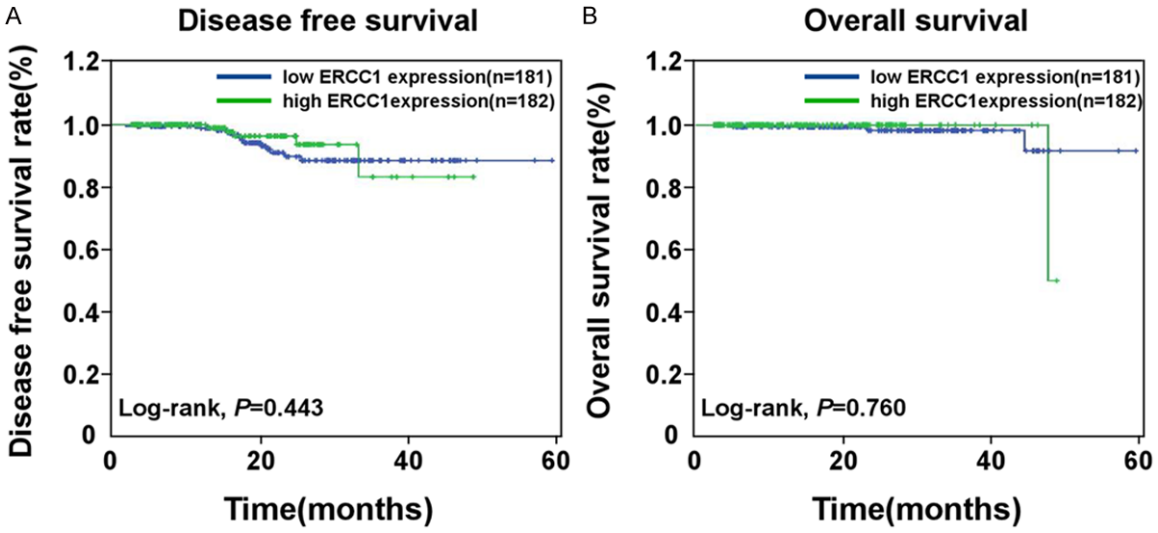

Figure 4. Effect of tumor *ERCC1* mRNA expression on survival in breast cancer. The patients were stratified into low ($\leq 1.02 \times 10^{-2}$) and high ($> 1.02 \times 10^{-2}$) *ERCC1* mRNA expression groups. A. Disease-free survival (DFS) for all patients (n = 363). B. Overall survival (OS) for all patients (n = 363).

group (41.79 vs.43.73 months, $P = 0.949$), or postoperative adjuvant platinum chemotherapy subgroup (29.80 vs.23.01 months, $P = 0.876$) or postoperative adjuvant non-platinum-based subgroup (56.48 vs.45.75 months, $P = 0.666$).

Age, pathology, clinical stage, axillary nodal metastasis, tumor size, neoadjuvant chemotherapy, and *ERCC1* mRNA expression were introduced into the Cox model for multivariate regression analysis. Clinical stage (HR = 0.027, $P < 0.0001$) and nodal metastasis (HR = 7.361, $P = 0.022$) were independent prognostic factors for DFS in breast cancer.

Median OS in the 363 patients with breast cancer was 18.7 months (2.93-59.73 months). No significant difference in OS was observed between the low and high *ERCC1* mRNA expression groups (58.02 vs. 48.52 months, $P = 0.760$; **Figure 4B**) for the entire cohort. No significant differences in OS were observed between the low and high *ERCC1* mRNA expression groups in the in the surgery alone subgroup (44.77 vs.47.93 months, $P = 0.317$), or postoperative adjuvant platinum chemotherapy subgroup (32.33 vs.28.15 months, $P = 0.581$) or postoperative adjuvant non-platinum-based subgroup (58.38 vs.49.44 months, $P = 0.452$).

Discussion

We measured the expression of *ERCC1* mRNA in tumor tissues from patients with lung cancer, gastric cancer, or breast cancer; all of the patients were from Southern China, including Guangdong and Fujian provinces, where these tumor types are the three most common cancers. To date, no study has reported the expression profiles of *ERCC1* mRNA in these three common types of cancer in patients from Southern China. Our study suggests that the abundance of *ERCC1* mRNA expression varies among the three types of cancers; the highest abundance was observed in breast cancer, followed by NSCLC and then gastric cancer. The tendency towards dispersion of the *ERCC1* mRNA expression values was more significant in breast cancer than NSCLC and gastric cancer.*ERCC1* mRNA expression values had a more scattered distribution in patients with breast cancer, while the *ERCC1* mRNA expression values presented a more concentrated distribution in patients with gastric cancer or NSCLC. This suggests that it may be possible to differentiate between breast cancer and NSCLC or gastric cancer on the basis of the *ERCC1* expression profile; however, it would not possible to distinguish NSCLC and gastric cancer based on the *ERCC1* expression profile. These differences may have a number of explanations. Firstly, adenocarcinomas accounted for 94.8% of all breast cancers, 69.5% of all lung cancers, and 85.8% of all gastric cancers in this study. And in this study, high *ERCC1* mRNA expression was observed more frequently in adenocarcinoma than squamous carcinoma in

NSCLC. Both Lu et al. [19] and Simon et al. [20] observed higher *ERCC1* mRNA expression levels in patients with lung adenocarcinoma compared to patients with squamous lung cancer. Therefore, pathological differences may be one factor which accounts for the differential distribution of *ERCC1* mRNA expression among the three tumor types. Secondly, gender may have had an impact, as the sex ratio of the patients was different among the three types of cancer. A recent study revealed an association between ERCC1 protein expression and gender in NSCLC, observed higher *ERCC1* mRNA expression levels in male patients compared to female patients. [21]. Although no significant differences in *ERCC1* expression were noted between male and female patients in the present study, high *ERCC1* expression was observed more frequently in male patients with gastric cancer or NSCLC compared to the corresponding female patients. Thirdly, smoking status may have an effect on *ERCC1* expression. As all of the breast cancer patients were female, they contained a much lower proportion of smokers compared to the patients with NSCLC or gastric cancer. In lung cancer, high *ERCC1* expression was significantly more frequent in non-smokers than patients with a smoking history. Wang et al. [22] also found that smokers had a significantly higher rate of low *ERCC1* expression than non-smokers in NSCLC. and *ERCC1* expression tended to decrease as the smoking exposure increased, indicating that smoking may inhibit *ERCC1* expression.

Not only were there differences in the expression profile of *ERCC1* among the three tumor types, *ERCC1* expression also had a varying prognostic value in patients with different types of cancer. Among the 357 patients with stage I-IIIa NSCLC, the low *ERCC1* mRNA expression group had significantly better DFS than the high *ERCC1* group. Further analysis demonstrated that, in the subgroups of patients receiving platinum-based chemotherapy or surgery alone, DFS was significantly longer in the low *ERCC1* mRNA expression groups than the high expression groups ($P < 0.0001$). Although multivariate analysis did not identify *ERCC1* expression as an independent prognostic factor for survival in NSCLC, low *ERCC1* expression may still represent a potentially favorable prognostic factor and predictor of efficacy in NSCLC. This result is generally consistent with other studies in NSCLC [15, 23]. However, the relationship between *ERCC1* expression and the prognosis of patients with NSCLC receiving surgery alone remains controversial. In studies of patients with NSCLC from America and France who received surgery alone, patients with high *ERCC1* expression had a better prognosis than those with low *ERCC1* expression [20, 21]. However, ERCC1 expression had a worse prognosis than those with low ERCC1 expression in Chinese patients with NSCLC who received surgery alone [14]. These results suggest that ERCC1 has a different effect in patients with NSCLC from different populations; the possibility of a difference in the DNA repair pathways between Chinese and Western populations should be investigated further.

Studies have suggested that overexpression of ERCC1 is associated with insensitivity to oxaliplatin and a poorer prognosis in patients with advanced gastric cancer or operable early-middle disease in GC [24-26]. The present study did not observe an association between *ERCC1* expression and the effects of platinum-based chemotherapy in patients with gastric cancer. This may be related to the fact that all of the patients with gastric cancer enrolled in this study had received surgery, or the relatively small sample size ($n = 50$), of which only 50 patients received adjuvant platinum-based chemotherapy. However, in the subgroup of patients with gastric cancer who received surgery alone, the low *ERCC1* expression group had a better prognosis than the high *ERCC1* group. However, *ERCC1* was not identified as an independent prognostic factor in gastric cancer in multivariate analysis. Therefore, *ERCC1* may represent one of many factors that can influence survival and prognosis in gastric cancer.

We observed that *ERCC1* expression was not a prognostic factor in breast cancer. As platinum-based chemotherapy is not a standard regimen for breast cancer, and most patients received preoperative adjuvant chemotherapy. However, a study have suggested that a possible role for ERCC1 as a predictive and/or prognostic marker in breast cancer in Portugal [27].

In conclusion, the expression levels of *ERCC1* mRNA showed a differential pattern of distribution in tumors from patients from Southern China with NSCLC, gastric cancer, or breast cancer. In addition, *ERCC1* expression had varying prognostic value in these three types of

cancer. *ERCC1* mRNA expression was identified as a prognostic factor for DFS and predictive marker of the efficacy of platinum-based chemotherapy in patients with operable NSCLC, and was a prognostic factor for OS in patients with gastric cancer receiving surgery alone; however, *ERCC1* mRNA expression had no prognostic value in breast cancer.

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Disclosure of conflict of interest

None.

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Table S1. Clinical characteristics of the patients with gastric cancer (n = 106)

Characteristic	No. (%)	Low *ERCC1* (%)	High *ERCC1* (%)	*P* Value
Sex				0.388
Male	76 (71.7%)	40 (75.57%)	36 (67.9%)	
Female	30 (28.3%)	13 (24.5%)	17 (32.1%)	
Age				0.435
≤ 60 y	48 (45.3%)	26 (49.1%)	22 (41.5%)	
> 60 y	58 (54.7%)	27 (50.9%)	31 (58.5%)	
Pathological TNM stage				0.529
I + II	33 (31.1%)	18 (34.0%)	15 (28.3%)	
III + IV	73 (68.9%)	35 (66.0%)	38 (71.7%)	
Histologic type				0.403
Adenocarcinoma	91 (85.8%)	47 (88.7%)	44 (83.0%)	
Other	15 (14.2%)	6 (11.3%)	9 (17.0%)	
Differentiation				0.734
Poor	62 (58.5%)	30 (56.6%)	32 (60.4%)	
Medium	41 (38.7%)	22 (41.5%)	19 (35.8%)	
Good	3 (2.8%)	1 (1.9%)	2 (3.8%)	
Alcohol consumption status				0.363
Yes	23 (21.7%)	13 (24.5%)	9 (17.3%)	
No	83 (78.3%)	40 (75.5%)	43 (82.7%)	
Smoking status				0.328
No	47 (44.3%)	26 (49.1%)	20 (39.6%)	
Yes	59 (55.7%)	27 (50.9%)	32 (60.4%)	

Table S2. Clinical characteristics of the patients with breast cancer (n = 363)

Characteristic	No. (%)	Low *ERCC1* (%)	High *ERCC1* (%)	*P* Value
Age				0.081
≤ 60 y	283 (78.0%)	148 (81.8%)	135 (74.2%)	
> 60 y	80 (22.0%)	33 (18.2%)	47 (25.8%)	
Pathological TNM stage				0.284
I	71 (19.6%)	31 (17.1%)	40 (22.0%)	
II	187 (51.5%)	99 (54.7%)	88 (48.4%)	
III	103 (28.4%)	51 (28.2%)	52 (28.6%)	
IV	2 (0.6%)	0 (0%)	2 (1.1%)	
Histologic type				0.097
invasive cancer	344 (94.8%)	168 (92.8%)	176 (96.7%)	
non-invasive cancer	19 (5.2%)	13 (7.2%)	6 (3.3%)	
Axillary lymph node metastasis				0.371
Yes	188 (51.8)	98 (54.1)	90 (49.5)	
No	175 (48.2)	83 (45.9)	92 (50.5)	
Tumor size				0.888
< 2 cm	78 (21.5)	1 (20.4)	41 (22.5)	
2-5 cm	259 (71.3)	131 (72.4)	128 (70.3)	
> 5 cm	26 (7.3)	13 (7.2)	13 (7.1)	