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Excision Repair Cross Complementing Group 1 (Ercc1): An Independent Prognostic Marker for Endometrial and Ovarian Cancer

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Abstract

Most ovarian cancers are epithelial in nature (EOC), and the US annual deaths from the disease exceed all other gynecological cancer deaths combined. In endometrial carcinoma (EC), the International Federation of Gynecology and Obstetrics (FIGO) staging and grading provides the basis for treatment selection and outcomes prediction. Excision repair cross complementing group 1 (ERCC1) is involved in DNA synthesis and repair and has been reported as a prognostic and a predictive marker of platinum efficacy in lung cancer patients among others. We investigated the clinical significance of this marker in EC and EOC.

Archived cases of EC (421) and EOC (198) were reviewed, and analyzed for ERCC1 protein levels with immunofluorescence staining (Automated Quantitative Analysis, AQUA). The average levels from replicate cores were used to determine cutoff points using log-rank testing on overall survival (OS). Kaplan-Meier survival curve with log rank test and multivariable Cox regression analysis were performed to evaluate the prognostic role of ERCC1.

Patients with high ERCC1 levels had significantly longer OS than those with low ERCC1 for both EC (P=0.013) and ovarian cancer (P=0.007). Multivariable COX regression analysis also revealed that high ERCC1 expression was associated with better OS rates in EC (P=0.031) and ovarian cancer (P=0.267). While type-II tumors and FIGO stage III-IV tumors could not be subdivided into good and poor survival groups based on ERCC1 levels, patients with high ERCC1 levels had better OS compared to those with low levels for both type-I tumors (P=0.014) and FIGO stage I-II tumors (P=0.037). Exclusion of patients treated with neoadjuvant chemoradiotherapy yielded similar results. In conclusion, ERCC1 is an independent prognostic factor of OS in endometrial and ovarian cancers. These studies require independent validation and may provide a basis for future molecular classification and treatment decision making.

Abbreviations: ERCC1: Excision Repair Cross Complementing Group 1; EC: Endometrial Carcinoma; MMMT: Malignant Mixed Mullerian Tumor; BLT: Borderline Tumor; EOC: Ovarian Cancers of Epithelial Nature

Introduction

Endometrial and ovarian cancers are the most common invasive gynecologic malignancies among women in developed countries [1,2]. Although it has been demonstrated that different subtypes of ovarian and endometrial cancers are associated with different molecular alternations, current treatments for these diseases are not subtype specific. FIGO staging and grading in these cancers provides the basis for treatment selection and outcomes prognosis.

Endometrial cancer is generally classified as type I or II based on etiology and clinical manifestation. Most cancers are of type-

1, associated with unopposed exposure to estrogen and more frequent in pre- and peri-menopausal women. Type-II cancers account for 10 to 20% of cases, are estrogen-independent, arise in the background of atrophic endometrium, and clinically follow a more aggressive course [3]. Genetic alterations segregate with the cancer type and differences in molecular pathway activation underlie their manifestation. In type-I, mutations in both alleles of PTEN lead to complete loss of function [4]. An uncontrolled PI3K-AKT signaling pathway and microsatellite instability (MSI) resulting from erroneous DNA mismatch repair (MMR) are also common features of type-I endometrial cancer [5-7]. The most common genetic alterations associated with type-II endometrial cancers are in p53 and epidermal growth factor signaling.

Ninety percent of ovarian cancers are epithelial in nature (EOC), and the US annual deaths from the disease exceed all other gynecological cancer deaths combined. The 5-year overall survival of 45% is largely due to advanced presentation of the disease at the time of diagnosis. The standard approach for treatment is surgery followed by platinum and taxane based chemotherapy. While 70-80% of patients achieve excellent response to primary cytoreductive surgery followed by platinum, taxane-chemotherapy, most of the patients suffer multiple recurrences and eventually die of the disease. Similar to EC, platinum resistance frequently emerges at relapse, and the response rate to second line cytotoxic agents ranges from 10 to 20%.

Biomarkers have paved the way to molecular classifications and as prognostic (patients' outcome independent of treatment) and predictive (patients' response to therapy) markers. The cellular response to DNA damage is critical for the maintenance of genomic integrity. The regulation of DNA repair gene transcription, the control of cell cycle progression, apoptosis via DNA damage checkpoints play a critical role in the development of cancer. ERCC1 is a single-stranded DNA endonuclease that forms a tight heterodimer with xeroderma pigmentosum complementation group F, and this complex is required for the excision of the damaged DNA. It has also been reported as a predictive marker for therapeutic efficacy and a prognostic marker of outcome in patients with lung and other cancers. Its expression, association, and clinical significance in endometrial and ovarian cancers remain uncertain. High expression of ERCC1 is associated with long survival in early stage lung cancer, independent of systemic therapy, but poor response to platinum therapy [8-13]. It has been reported that several biomarkers may serve as independent prognostic markers in endometrial and ovarian cancer patients, but to date, no good marker is available for screening or disease monitoring. Our study aims to investigate the clinical significance with ERCC1 in EC and EOC.

Material and Methods

Tissue samples and microarrays

The study was approved by the institutional review board of Wayne State University. All newly diagnosed endometrial and ovarian cancer patients were included after obtaining a written informed consent.

Formalin-fixed and paraffin embedded cases of endometrial cancer (n=421, 1995-2007) and epithelial cell ovarian cancer (n=198) were reviewed and tissue microarrays (TMAs) were prepared. Pathological stage and histological subtype were determined for each specimen by gynecological pathologists and updated according to 2009 FIGO criteria. Epithelial ovarian cancers were divided into three subtypes: borderline tumor (BLT), type I, and type II. Patient data were obtained by chart review and from the tumor registry.

TMAs were constructed with triplicate cores per case for endometrial and duplicate cores for ovarian cancers. Areas containing the most characteristic features were identified by two board certified pathologists using whole tissue sections stained with hematoxylin and eosin (H&E). Disagreements were discussed and resolved before tissue core collection. Areas on the block corresponding to the marked slides were then identified, and three 2 mm tissue cores were obtained. To ensure that the tissue core sufficiently represented the whole tissue section, every 10th section of the tissue array was stained with H&E and reviewed by pathologists to ensure that the pathologic diagnosis was current and matched the adjacent serial sections and that 50% or more of the valid cores remained intact. The design of each block was detailed in a map indicating the position and identification of each core.

Immunofluorescence histochemical staining

Immunofluorescence combined with automated quantitative analysis (AQUA) was used to evaluate the expression of the target molecules. Briefly, heat induced antigen retrieval was performed by incubating the tissue in a microwave oven with 1X PT Module Buffer 4 (10x stock, T-250-PMAX4, Thermo Scientific). Optimal concentrations of reagent samples were used to detect ERCC1 (rabbit polyclonal HPA029773, Atlas Antibodies). Mouse anti-human cytokeratin AE1/AE3 (M3515, Dako) was used as a marker for epithelial cells. The standardization, dilution, and optimization of the protocol had previously been developed and tested on control tissue microarrays before applying to test arrays as previously published [13].

Statistical analysis

The baseline characteristics were summarized with descriptive analyses for the endometrial and ovarian cancer patients separately. For AQUA measurements of ERCC1, the average levels of replicated cores were used. The threshold for high or low marker levels was determined from supervised greedy search for the lowest log-rank test p values on overall survival (OS). The potential cutoff was considered only if the resulting subgroups had more than 5 patients. A subgroup analysis for the endometrial cancer patients who only received surgery was also performed. The cutoff was optimized by identifying the local minimum of log-rank p values around the tentative cutoff from the analysis based on all endometrial cancer patients.

Associations between marker expressions and other baseline characteristics were evaluated by chi-square test, or Fisher's exact test, for small sample sizes of categorical variables and Wilcoxon rank-sum test for continuous variables. To further evaluate the prognostic role of ERCC1, Cox multivariable regression analysis was performed. The final model was obtained from a two-stage

approach. First, a univariate Cox regression at a significance level of 0.1 was performed to screen potential covariates such as age, race, tumor type, histology, FIGO grade, lymphovascular invasion, myometrium invasion, and cervix involvement**.** Second, a final Cox multivariable model was chosen by backward selection with likelihood ratio test while keeping ERCC1 in the model. All statistical analysis was performed with R version 3.0.2. P values of less than 0.05 were considered significant. All p values reported are raw p values without adjustment for multiple testing due to the exploratory nature of this study.

Results

Patient characteristics and clinical and pathological features

Out of the 421 EC cases, 304 with type-I tumors (72.2%) and 117 with type-II tumors (27.8%) were examined and verified by two independent pathologies (JZ, RA). The age ranged from 24 to 91 years with a mean age of 61 (**Table 1**), and 229 patients had been treated only with surgery. The median age of patients with type-II tumors was significantly higher than that of type-I patients (Kruskal-Wallis test, P< 0.001). Interestingly, we found that African American patients were more likely to have type-II tumors than white patients (Chi-square test, P<0.001) (**Figure 1**).

Kaplan-Meier survival curves and log rank tests indicated that type II, high FIGO grade, high FIGO stage, presence of lymphovascular invasion, and malignant mixed Mullerian tumor (MMMT) were associated with worse prognosis (log-rank P<0.001). The epithelial ovarian cancers (n=198 cases) were reviewed and divided into three main subtypes: BLT (44 cases, 22%), type I (29 cases, 15%) and type II (121 cases, 61%), and 4 cases (2%) were unclassified. The age of patients ranged from 16 to 89 years with a mean of 58 years (**Table 2**). Type II tumors were significantly more frequent among elderly white women (Fisher's exact test, p<0.001) as compared to African American women (**Table 3 and Figure 1**).

Immunofluorescence scores show significant differential expression of ERCC1 in endometrial cancer

ERCC1 expression was observed in 80% of tumor (337 cases) (**Figure 2A**). Kaplan Meier curves showed significant differences in OS between the groups with low and high levels of ERCC1 (log-rank P=0.013, **Figure 3A**). High ERCC1 levels were associated with good OS for type I tumors (log-rank P=0.014) and FIGO stage I-II tumors (log-rank P=0.037, **Figure 3A**). When using a Cox model adjusted for other covariates (age, race, tumor type, lymphovascular invasion, cervix involvement), high ERCC1 levels were associated with good OS (adjusted HR, 0.56; 95% CI, 0.33 to 0.95; P=0.031). Interestingly, African American patients had a worse prognosis as compared to white patients with a Cox model adjusted p value of 0.004 (**Table 2**).

Expression of ERCC1 in endometrial cancer patients without neoadjuvant radiochemotherapy

To eliminate the potential predictive impact of ERCC1 levels on chemotherapy and radiotherapy efficacy, all patients receiving neoadjuvant treatment were excluded from the analysis. Among the 229 patients with endometrial cancer who received solely surgical therapy, 185 cases demonstrated detectable levels of ERCC1. Kaplan Meier curves showed significant differences in OS between the groups of patients with low and high levels of ERCC1 (log-rank P=0.043). Subgroup log-rank testing demonstrated that type-I tumors and FIGO stage I-II tumors could each be subdivided further into good and poor survival groups based on low and high ERCC1 levels (log-rank P=0.024 for type I and 0.029 for stage I-II, **Figure 3B**). The difference of OS was also significant using a Cox model adjusted for the covariates age, race, and lymphovascular invasion. High ERCC1 levels were associated with better OS when compared to low ERCC1 levels (adjusted HR, 0.33; 95% CI, 0.16 to 0.68; P=0.002, **Table 4**).

Expression of ERCC1 in ovarian cancer

ERCC1 levels were not significantly associated with tumor type, histology, grade, or stage. A multivariable Cox regression model (ERCC1 levels, age, and peritoneal implants) demonstrated that only age and implants persisted as independent prognostic factors for poor OS. The hazard ratios of ERCC1 were similar to EC, but they were not statistically significant, which is probably due to the small sample size for ovarian cancers (**Figures 2B** and **4**) [14].

Discussion

Cancer of the uterine corpus and ovary has become the most common gynecologic malignancy in the United States. In 2015, uterine corpus and ovarian cancers are estimated to be responsible for 76,160 new cases and 24,350 deaths [15]. The incidence of endometrial and ovarian cancers in the general population is age-dependent and highest in elderly woman. However, the pathogenesis and molecular profiles of type I and type II endometrial and ovarian cancers are different. For example, type II EC represents an aggressive subtype of endometrial adenocarcinoma encompassing serous, clear cell, and grade 3 endometrioid histologic subtypes. It is associated with a distinctly different molecular signature, higher cancer-related deaths, and worse prognosis [16,17]. Obesity and diabetes are highly prevalent in type I and II ECs, especially in African American women, and in general, type II cancer is more predominant among African American women [18]. African-American women are significantly more likely to present with advanced-stage endometrial cancer, are more likely to have poorly differentiated tumors or tumors with an unfavorable histologic type, and are significantly less likely to undergo definitive surgery at all stages of disease [19]. The extent to which various socioeconomic, environmental, lifestyle, and genetic factors interact to account for this racial disparity in survival is poorly understood. In general, type II ECs has a lower incidence compared to type I and only accounts for 11% of ECs [20]. In our study, 117 out of 304 (27.79%) ECs were type II tumors; this could be due to our unique patient population. Located in downtown Detroit, our patient population is distinctly different from that of other cancer centers since 82% of Detroiters self-identify as black or African American. Our current data demonstrate that the median age of type II EC patients is significant older than the median age of type I patients

Table 1 Summary of patient characteristics and clinicopathological features in endometrial cancer patients.

Variable		Total Cases (n=421) No. (%)	Cases without Chemo/radiotherapy (n=229) No. (%)
Age	Median (range)	61 (24, 91)	60 (24, 91)
Race	Black	161 (38)	74 (32)
	White	260 (62)	155 (68)
Tumor type	I	304 (72)	187 (82)
	II	117 (28)	42 (18)
FIGO grade	1	111 (26)	98 (43)
	2	138 (33)	78 (34)
	3	172 (41)	53 (23)
FIGO stage	I-II	308 (73)	206 (90)
	III-IV	113 (27)	23 (10)
Histology	Mucinous	304 (72)	187 (82)
	Clear	14 (3)	6 (3)
	Serous	68 (16)	22 (10)
	MMMT	35 (8)	14 (6)
Cervix involvement	NO	314 (75)	207 (90)
	YES	107 (25)	22 (10)
Myometrial invasion	NO	101 (24)	92 (40)
	YES	320 (76)	137 (60)
Lymphovascular invasion	NO	259 (62)	187 (82)
	YES	162 (38)	42 (18)
ERCC1	Median (range)	2305 (63, 7608)	2298 (80, 6565)
	Missing	84	44

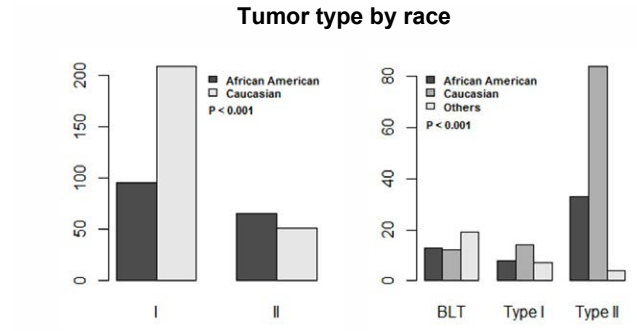

Figure 1 Association between race and tumor type. The chi-squared test p value and fisher test p value are less than 0.001 for endometrial cancer (left) and ovarian cancer (right).

Table 2 Multivariable Cox regression analysis of endometrial cancer all patients (n=421).

Variable		HR (95% CI)	P value
ERCC1	Low	ref.	0.031
	High	0.557 (0.328,0.947)	
Age		1.047 (1.029,1.067)	<0.001
Race	White	ref.	0.004
	Black	1.736 (1.189,2.536)	
Tumor type	I	ref.	<0.001
	II	2.291 (1.531,3.426)	
Lymphovascular invasion	No	ref.	<0.001
	Yes	2.204 (1.489,3.262)	
Cervix involvement	No	ref.	<0.001
	Yes	2.008 (1.358,2.970)	

(Kruskal-Wallis test, P<0.001) and that African American women have a significant higher proportion of type II EC tumors than white women (Chi-square test, P<0.001), which are consistent with previously published data [9,13]. Not surprisingly, type II EC, a high FIGO grade, FIGO stage, MMMT, and lymphovascular invasion were all associated with a worse prognosis (log-rank P<0.001) [16,21].

The search for better prognostic markers with high sensitivity and specificity for ECs and EOCs has been ongoing for decades. While there is some controversy regarding the roles of ERCC1 as predictive marker of therapeutic efficacy and prognostic marker of treatment-independent survival [9,22-25], most study results for patients with lung cancer suggest that patients with high levels of ERCC1 have a longer survival than patients with low levels. In contrast, as a predictive marker for treatment with platinum-based therapies, patients with low levels of ERCC1 typically have a longer survival than patients with high levels [9,10,13,26]. In the present work, we examined the expression of ERCC1 in archived cases of ECs and EOCs and association with demographic and clinicopathological characteristics. Looking at patients with EC treated with surgery, we found that expression of ERCC1 is more frequent (46%) in African Americans than in whites (40%). These differences, however, were not significant (p=0.540). While ERCC1 levels were not significantly associated with tumor type, histology, grade, and stage, high levels were associated with better OS when compared to low levels in both EC and EOC, which is consistent with our original findings in lung cancer and different from a report by Vanenput el al. [24]. This

Table 3 Summary of the patient characteristics and clinicopathological features in ovarian cancer patients.

Variable		Total Cases (n=198)
Age	Median	58 (range: 16-89)
Race	Black	55
	Caucasian	112
	Others	31
Tumor type	I	29
	II	121
	BLT	44
	Unclassified	4
Grade	1	12
	2	14
	3	117
	Others	55
Stage	I-II	55
	III-IV	137
	Missing	6
Implants	NO	42
	YES	123
	Missing	33
ERCC1	Median	2670
	Range(min,max)	(67, 5929)
	Missing	57

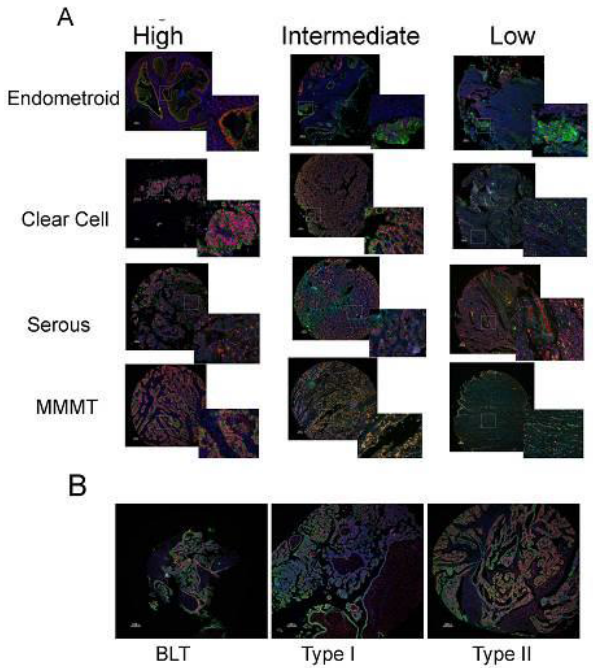

Figure 2 The expression of ERCC1 in endometrial (A) and ovary cancer (B). Red, ERCC1; green, cytokeratin; blue, nucleus.

difference is likely a result of differences in reagents and detection methodology used to evaluate ERCC1 levels. Furthermore, FIGO stage I-II tumors with high ERCC1 levels are associated with better OS than those with low levels (log-rank P=0.037). Our results raise the possibility that ERCC1 may also be used as a predictive marker of platinum-based efficacy in gynecologic cancers. The design and interpretation of clinical trials that incorporate ERCC1 levels into a treatment decision algorithm requires knowing ERCC1's prognostic impact [9]. Our results clearly demonstrate ERCC1's prognostic impact since the exclusion of patients that underwent pre-surgical chemo-radiotherapy demonstrated a significant survival advantage for patients with high ERCC1 levels.

Like endometrial cancer, recent morphologic, immunohistochemical, and molecular genetic studies have divided epithelial ovarian cancers based on a dualistic model of carcinogenesis into two broad categories designated types I and II. Type I tumors comprise low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas, and Brenner tumors. They are generally indolent, present in stage I (tumor confined to the ovary), and are characterized by mutations targeting specific signaling pathways, including KRAS, BRAF, ERBB2, CTNNB1, PTEN, PIK3CA, ARID1A, and PPP2R1A [27]. Type II tumors comprise high-grade serous, high-grade endometrioid, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas. They are aggressive, present in advanced stages, and have a high frequency of p53 mutations but rarely harbor the mutations detected in type I tumors [14,27,28] The relative importance of ovarian cancer risk factors may differ between African-American and Caucasian women, but at present, no clear association exists between tumor type and these racial groups. Our current data demonstrate that type II tumors were significantly more frequent among elderly white women (Fisher's exact test, $p<0.001$) as compared to African American women with Kaplan Meier curves showing no statistically significant difference in OS between type I and type II cancers. This unexpected result may reflect the therapy-related advantage with social and economic factors or small sample size of type I EOC.

In conclusion, this is the first analysis of ERCC1 in a large cohort of endometrial and ovarian cancers. We found high ERCC1 levels were associated with better OS when compared to low levels in both cancers (log-rank P=0.013 in endometrial and P=0.007 in ovarian cancer). While the mechanism is still unknown, our data suggest that ERCC1 can be an independent prognostic factor for patients with endometrial and ovarian cancers. Independent validation of our results is required.

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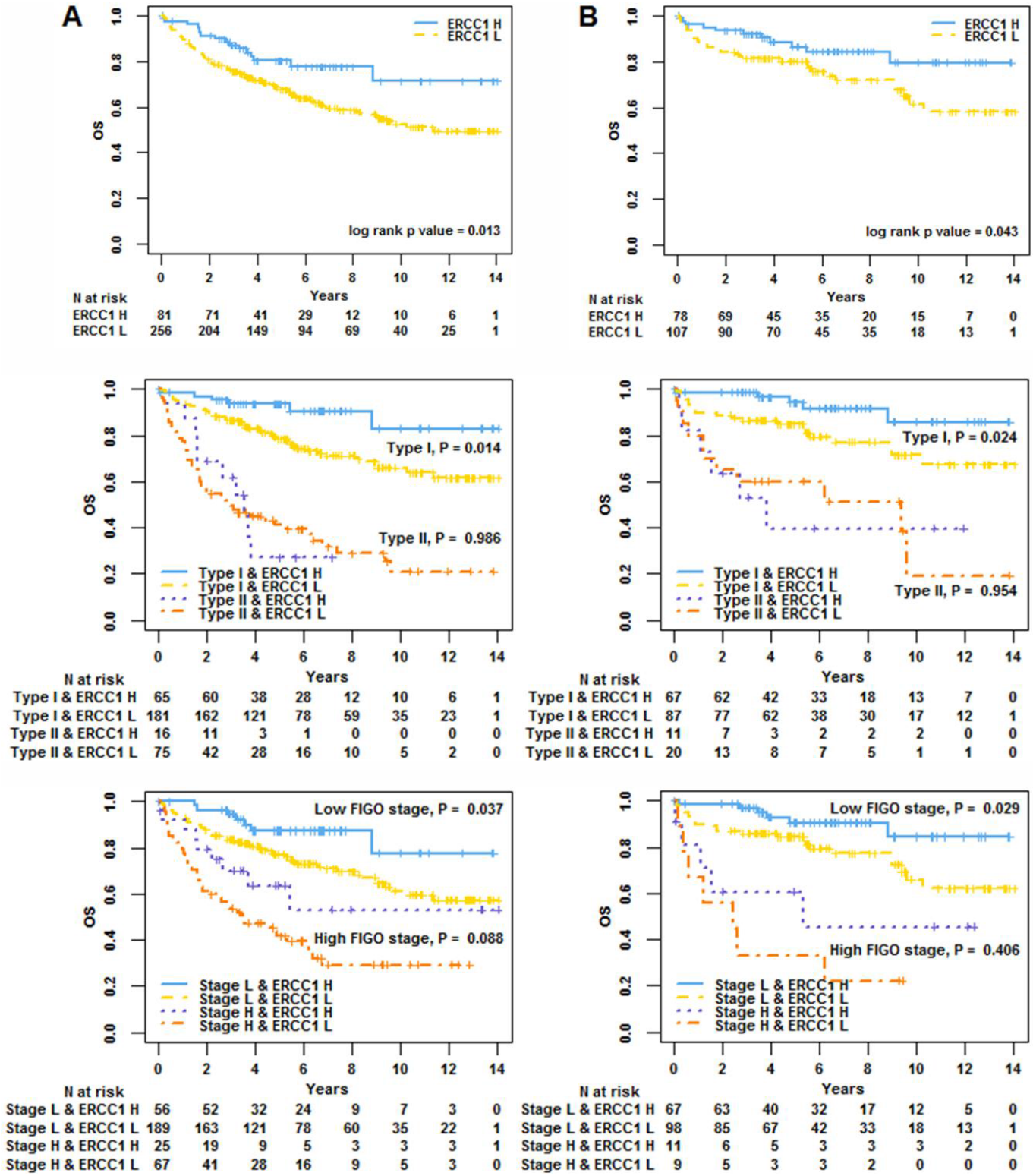

Figure 3 Kaplan-Meier overall survival estimates by ERCC1 expression categories for all EC patients (A) and EC patients with surgery only (B). Cut-off values of 3177 and 2538 were used to classify the patients into high and low ERCC1 expression for all EC and EC subgroup, respectively. Log-rank test was used to test the difference between low and high expression *vs* tumor type and stage.

Table 4 Multivariable Cox regression analysis of endometrial cancer patients with surgery only (n=229).

Variable		HR (95% CI)	P value
ERCC1			0.002
	Low	ref.	
	High	0.332 (0.164, 0.675)	
Age		1.102 (1.068,1.137)	<0.001
Race			0.005
	White	ref.	
	Black	2.471 (1.306,4.675)	
Lymphovascular invasion			<0.001
	No	ref.	
	Yes	3.218 (1.700,6.091)	

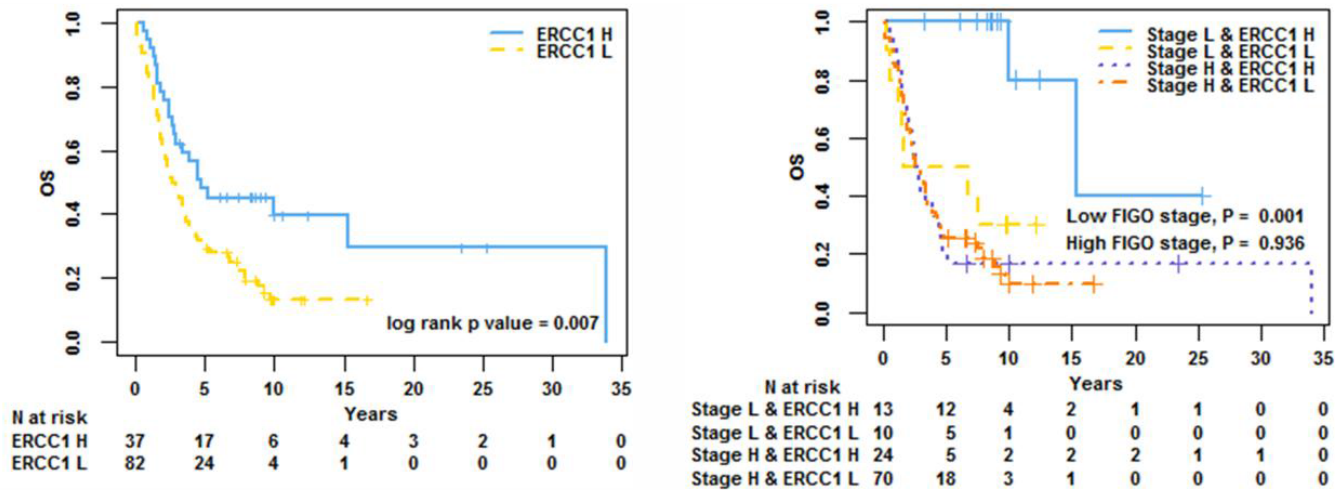

Figure 4 Kaplan-Meier overall survival estimates by ERCC1 expression categories in ovarian cancer. A cut-off value of 3359 was used to classify the patients into high and low ERCC1 expression. Log-rank test was used to test the difference between low and high expression *vs* stage.

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