Published in final edited form as:

Gynecol Oncol. 2009 September ; 114(3): 480–485. doi:10.1016/j.ygyno.2009.05.045.

ESTROGEN AND PROGESTERONE RECEPTOR STATUS AND OUTCOME IN EPITHELIAL OVARIAN CANCERS AND LOW MALIGNANT POTENTIAL TUMORS

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Abstract

Objective—Receptors for estrogen (ER) and progesterone (PR) are prognostic indicators for a variety of endocrine tumors including breast and endometrial. This study was conducted to determine if ER and PR expression patterns are predictive of outcome in patients with epithelial ovarian cancer (EOC) or ovarian low malignant potential (LMP) tumors.

Methods—ER and PR protein levels were assessed by immunohistochemistry in 45 LMP and 89 EOC samples. Patterns of ER/PR expression (individually and combinations of ER−/PR−, ER+/PR−, ER/PR+, and ER+/PR+) were correlated with standard prognostic factors of overall survival (OS) in this patient population.

Results—For patients with EOC, the 5-year OS per ER−/PR+, ER+/PR−, ER+/PR+, and ER−/PR− expression were 83%, 79%, 61%, and 48%, respectively, and these differences were statistically significant. In multivariate analyses, ER/PR expression patterns were found to be independent predictors of OS, as were the classical prognostic factors of grade, stage, debulking, and chemotherapy response to treatment. In patients with mucinous LMP tumors, ER and PR were absent. Because no LMP patients died of disease during the studied period, no correlation analysis with OS could be performed.

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Conflict of Interest Statement. The authors declare that there are no conflicts of interest.

This work was presented at the 12th Biennial meeting International Gynecologic Cancer Society. Bangkok, Thailand, October 25–28, 2008.

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Conclusions—Patterns of ER/PR expression provide prognostic information in EOC. Additional studies evaluating hormonal inhibition may help personalize the therapy of patients with ovarian cancer.

Introduction

The “incessant ovulation” hypothesis postulates that repetitive cycles of ovulation-induced trauma followed by repair of the ovarian surface epithelium, without pregnancy-induced rest periods or use of contraception, contributes to ovarian cancer development [1,2]. This reparative process is controlled in normal ovaries by a variety of hormones, cytokines, growth factors and their receptors, acting in networks of autocrine and/or paracrine regulatory systems. Imbalance of these networks may contribute to the development of EOC. Steroid hormones, primarily estrogen and progesterone have been implicated in ovarian carcinogenesis [3]. Estrogens are major regulators of growth and differentiation in normal ovaries. The association between estrogen and cancer is linked to the mutagenic properties of estrogen and its derivatives in ovarian normal epithelial cells [4–6; rev. in 3]. In contrast, progesterone and its receptors exert protective effects by (1) decreasing the exposure to high levels of estrogen and suppressing ovulation; (2) antagonizing the growth-promoting effect of estrogen; and (3) inducing cell differentiation and apoptosis [3,7]. Loss of heterozygosity at the 11q23.3–24.3 region which contains the PR gene has been associated with an elevated risk for ovarian cancer and poorer prognosis [8,9]. Because high expression of ER and PR has been reported in EOC samples [10–16], we hypothesized that expression patterns of ER and PR may be related to tumor behavior, prognosis, or both.

Methods

Clinical specimens

This study was reviewed and approved by the Human Research Review Committee of the University of New Mexico Health Sciences Center. Formalin-fixed, paraffin embedded tumor specimens obtained from 134 patients diagnosed with LMP (n=45) or EOC (n=89) tumors, treated at the University of New Mexico Cancer Center between March 1996 and June 2005, were retrieved from the Human Tissue Repository. Sample size was constrained by the case availability. Eligible cases had to have a surgical debulking and a platinum-based treatment and a complete clinical data set. Samples were anonymized and forwarded to the laboratory, which was blinded to treatment and outcomes. Clinicopathologic factors (age, stage, grade, histopathology, performance status, cytoreduction, node status, and response to chemotherapy) were evaluated by reviewing medical charts and pathologic records. The extent of cytoreduction was defined as optimal if residual disease after surgery was smaller than 1 cm, or suboptimal if residual disease was larger than 1 cm [17]. Tissue slides were reviewed for histological classification and clinical outcome was followed from the date of surgery to the date of death or until June 2005. Survival rates were calculated as the percentage of subjects who survived. Deaths from other causes were censored.

Immunohistochemistry

Five- μ m sections were stained with ER (clone 6F11), and PR (clone 1A6) antibodies. ER and PR immunohistochemistry (IHC) was performed using the Ventana XT Benchmark stainer as described by the provider (Ventana Medical Systems, Inc., Tucson, AZ). Briefly, tissue sections were baked, deparaffinized in xylene, rehydrated in graded ethanol (100% and 95%), and rinsed in water. The slides were then incubated in fresh 3% H₂O₂ in phosphate-buffered saline (PBS) for 20 minutes followed by three 5-minute rinses in PBS. The slides were loaded on to an automated XT Benchmark stainer and detection was performed using the iVIEWTM DAB detection system (Ventana Medical Systems, Inc., Tucson, AZ). Endometrial tissue was

used as a positive control; the negative control was the same tissue incubated with matched isotypic antibody (Figure 1). Immunohistochemical stains were digitized using the Aperio system (Vista, CA). Grading of nuclear ER and PR staining was performed using an H-scoring system obtained by multiplying the epithelial cell intensity (graded as 0 negative, 1+ weak, 2+ moderate, or 3+ strong) by the percentage of positive epithelial cells (0–100%). For statistical analysis, the samples were grouped into negative (H values below or equal to the median) or positive (H values higher than the median). The two pathologists involved in staining interpretation were blinded to clinical information. Cases with discordant scores were re-evaluated to obtain a consensus score.

Statistical analysis

Fisher's exact tests were used to compare demographic, clinical, and pathological data between LMP and EOC subjects and H scores between samples. The Spearman test was used to assess correlations between ER and PR expression. Since there were no cancer-related deaths in patients with LMP tumors, only EOC cases were used in the univariate and multivariate analyses. The LIFETEST procedure was used to calculate survival curves according to the Kaplan-Meier method, and differences in survival were compared by the Log-rank test. Univariate and multivariate analyses of the effects of age at diagnosis, FIGO stage, histology, grade, performance status, debulking, and ER and PR protein levels on survival were performed using Cox's proportional hazards models. Inclusion was based on the significance of each variable as assessed by a likelihood ratio test comparing the multivariate model to the reduced model obtained by deleting variable(s) from the full model [18]. This approach employs a backward elimination strategy. For each ordinal variable, the lowest value was used as the reference in computing hazard ratios (HR), except for grade, because there were no deaths in patients with grade 1 disease; hence grade 2 was used as the reference value. Wald tests were used to test for significance of hazard ratios. Two-tailed P values less than 0.05 were considered statistically significant. SAS software (SAS Institute Inc, SAS/STAT User's Guide version 9.1, Cary NC SAS Institute Inc., 2003) was used to perform these analyses.

Results

Patient characteristics

Of the 134 patients included in this study, 47.7% were non-Hispanic whites, 34.3% Hispanics, 15.7% Native Americans, 1.5% Blacks, and 0.8% Asians. The median age was 54.1 ± 14.3 years (range, 17–87 years). All patients underwent standard surgical staging. This included hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy (total if diseased), systematic pelvic and para-aortic lymphadenectomy, and resection of as much visible tumor as was technically possible. All LMP patients underwent complete surgical staging. All 33 (37.1%) patients with Stage I or II EOC had optimal debulking except for one patient. Of the 56 patients with Stage III or IV disease, optimal cytoreduction was achieved in 29 (51.8%). Sixty two patients with EOC received at least one combination chemotherapy regimen either as neoadjuvant chemotherapy (1 to 4 cycles) followed by cytoreduction (six patients) or after cytoreductive surgery (56 patients) (Table 1). Twenty two patients received 1 to 5 different regimens of chemotherapy for recurrent disease. Six patients received tamoxifen as second or third line therapy. One had a complete response and one exhibited stable disease for 12 months. Both of them had tumors that expressed the ER+/PR+ pattern. Four progressed, and of these, only one had an ER+/PR+ pattern. All LMP patients and 64.0% of EOC patients survived during the observed 5-year period. Therefore, the 5-year survival analysis was only applied to the EOC cases. The characteristics of the patient population are provided in Table 1. The LMP cases were more commonly diagnosed at stage I (89%) and in younger patients (median age, 47.5 years; range, 17 to 82 years), and had a serous or mucinous histology. EOC cases were diagnosed in older patients (median age, 57.4 years; range, 21 to 87 years), at advanced stage

of disease (62.9%, stages III/IV), with high grade (60.7%, grade 3) and a serous histology (57.3%). The median H-scores for ER (90; range 0–300) and PR (10; range 0–300) were applied to patient characteristics. Representative immunostaining patterns obtained in the study cases are shown in Figure 1.

ER and PR expressions in LMP samples

Except for one case with endometrioid histology, LMP cases were either mucinous (N=22) or serous (N=22) (Table 1). The patterns of ER, PR, and ER/PR expressions are provided in Table 2. Mucinous cases were negative for ER and PR, while serous and endometrioid cases were positive ($P<0.001$; Table 2). There was a positive correlation between the ER and PR expression ($P<0.001$).

ER and PR expression in EOC samples

The majority of EOC cases were positive for ER (56%)(Table 1). There was no difference in ER and PR expression between grades 1, 2, and 3. Of 13 EOC grade 1 samples, 7 (54%) were positive for ER and 8 (62%) for PR. Of 76 grade 2 and 3 EOC, 43 (56.5%) were positive for ER and 35 (46%) for PR. A significant difference was noted in ER and PR expression across the histopathological categories (Table 3). As expected, the majority of serous and endometrioid cases were ER+ or PR+ (67.7% and 58.5%, respectively), the majority of mucinous and other EOC tumors were ER– or PR– (75% and 79.2%, respectively; $P<0.001$, and $P=0.02$, respectively). There was a positive correlation between ER and PR expression ($P<0.001$). While most serous and endometrioid cases were ER+/PR+ ($n=29$; 44.6%), the majority of mucinous and other EOC tumors was ER–/PR– ($n=15$; 62.5%) (Table 3). ER/PR expression patterns were not associated with age, race, stage, debulking, node status, and chemotherapy treatment.

The 5-year survival analysis for EOC cases, using the univariate Cox's proportional hazard ratios (HR) model, demonstrated that ER/PR expression patterns were predictors of survival along with grade, stage, performance status, and debulking ($P\leq 0.001$), while age and histology were not (Table 4). These predictors retained their significance in the multivariate analysis except for performance status (Table 4). Of note, chemotherapy treatment was not significant in the univariate analysis but it is a predictor of survival in the multivariate analysis. Figure 2 shows the Kaplan-Meier survival data by ER/PR expression patterns, demonstrating that the patients with ER–/PR+ showed a strikingly superior clinical outcome. The 5-year OS for ER–/PR+, ER+/PR–, ER+/PR+, and ER–/PR– were 83%, 79%, 61%, and 48%, respectively.

Discussion

The strength of our study resides in the homogenous patient population treated with optimal debulking procedures, full surgical staging, modern chemotherapy with platinum-based combinations, and the long follow-up of 60 months. The limitation lies in the retrospective aspect and the limited number of patients.

The prognosis and treatment of LMP differ from that of invasive EOC [19,20]. LMP tumors account for 10% to 20% of all epithelial ovarian malignancies and the 10-year overall survival for LMP patients is approximately 97% [19,21]. In our sample, we observed no deaths at 60 months. As expected, LMP cases predominated in young patients, were diagnosed at an early stage, and had either a serous or mucinous histology. PR expression was low in LMP mucinous tumors and unlikely to play a role in the carcinogenetic events leading to invasion. In contrast, serous LMP cases were positive for ER and PR [22]. Sixty-five percent of LMP serous/endometrioid cases were ER+/PR+, whereas 91% of mucinous LMP were ER–/PR– (Table 3). Chemotherapy has no efficacy against borderline tumors [23,24], but anecdotal reports

show that LMP tumors can be successfully treated with hormones. The only phase II clinical trial of hormones for LMP used oral letrozole, an aromatase inhibitor that depletes levels of estrogen available to the ER. Letrozole has a 30% anti-tumor activity in advanced or recurrent LMP tumors [25]. Identifying LMP patients susceptible to respond to hormone treatment could be beneficial. Our data showed that more than 60% of patients with serous LMP are ER and/or PR positive and potential candidates for hormonal treatments.

In patients with EOC, the multivariate analysis identified ER/PR expression patterns, grade, stage, debulking, and chemotherapy as independent prognostic factors (Table 4). Of note, no patients with grade 1 serous tumors that were ER and PR positive died during the study period. Our observation supports the concept that grade 1 serous tumors constitute a distinct clinical and perhaps biologic entity [26,27].

Epidemiological and experimental data suggest that estrogen is implicated in ovarian carcinogenesis [3,4]. ER expression, observed mainly in serous and endometrioid EOC (range from 50 to 90%), also supports a role for estrogens in ovarian tumorigenesis [11–16]. While ER over-expression has not been associated with prognosis [14–16], progesterone and its receptor have been shown to protect against the development of ovarian cancer [3,7,14,15]. In our study, we found that the ER–/PR+ pattern was expressed in 13.5% of patients, and this pattern was an independent positive prognostic factor in the multivariate analysis (Table 4). The ER/PR expression pattern was associated with histology (Table 3); however, histology was not a prognostic factor. No associations were found between the ER/PR expression patterns and ethnicity, grade, node status, debulking, or chemotherapy treatments. Another study confirmed that the ER–/PR+ expression pattern, present in 10% of tumors, conferred a significantly better prognosis and was associated with less ascites and lower tumor stage and grade [15].

An explanation for the observed differential effect of the ER/PR expression pattern on survival may be explained by the mutagenic properties of estrogen on the ovarian epithelial cells. The growth-stimulating and mutagenic activities of estrogen may be counter-balanced by the growth inhibitory (cell differentiation and apoptosis) effects of progesterone, leading to improved OS in the ER–/PR+ patients. ER+/PR– expressing patients had the second best OS, but patients expressing both ER and PR had a worse survival. This was a surprising observation for which we do not have a clear explanation. We are planning further studies to clarify the modulating role of PR on the oncogenic activity of estrogen. Patients whose tumor do not express ER and PR have the worst prognosis, a phenomenon also observed in breast cancer [28]. Why patients who have a tumor negative for both receptors fare worse has also not been elucidated.

There are many case reports of successful treatment of EOC with hormones. An old study of endometrioid carcinoma treated with medroxyprogesterone acetate (MPA) used as a first-line therapy after surgery or radiation, reported an overall response rate of 54%. ER+ and PR+ tumors demonstrated the highest (68%) regression but there was no tumor regression in patients with ER– and PR– tumors [29]. Letrozole yields an objective response of 15% to 26% in patients with advanced EOC, and the response was again associated with higher levels of ER expression [30–32], since letrozole inhibits the ER signaling pathway by interfering with estrogen synthesis. The overall response rate to hormonal therapy currently reported in patients with recurrent ovarian cancer is around 10%, but no systematic randomized studies have clearly defined the EOC population who could benefit from such treatments [33]. Tamoxifen, a selective estrogen receptor modulator with agonist/antagonist property, is a standard treatment for ER positive breast cancer as it inhibits the ER signalling pathway [34]. Estrogen and tamoxifen have the ability to induce PR expression and synergize with progestational drugs [33]. Therefore, we hypothesize that the ER/PR expression pattern, which has a prognostic

value in EOC as shown in this study, may help select patients who could benefit from hormonal therapy. Whether a personalized hormonal therapy would benefit patients with a specific ER/PR expression pattern should be addressed in a clinical trial.

In summary, we have found that the ER/PR expression pattern in EOC correlates with survival. We therefore suggest that the determination of ER/PR status by IHC offers prognostic information for patients diagnosed with EOC. Our results are hypothesis generating and should be confirmed in a prospective study. Whether the ER/PR patterns could be predictors of response to hormonal therapy is now being proposed in a SWOG GYN Working group as a prospective clinical trial.

Acknowledgments

Supported in part by the National Cancer Institute R01 CA118743 (ERP, HOS); NIH/NCI P30 CA118110, University of New Mexico School of Medicine; Dedicated Health Research Funds from the University of New Mexico School of Medicine (RAC grants C-2291-T to HAP, and C-2279 to HOS); a grant from the Stranahan Foundation (ERP); and by the DHHS/PHS/NIH/NCRR/GCRC Grant # 5M01 RR00997, Clinical and Translational Science Center, University of New Mexico Health Sciences Center.

We would like to thank the C. Martinez, A. Meisner (UNM Human Tissue Repository) for providing tissue samples and clinical data; Karen Buehler (Tricore), for technical support with the IHC assays; the Biostatistics Shared Resource of the Cancer Center, and Fernando Valenzuela (UNM, Albuquerque) for reviewing the manuscript and the anonymous reviewers for insightful comments.

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Figure 1.

Representative immunohistochemical staining of ER (A, C, E) and PR (B, D, F) in a serous papillary cystadenoma (A), serous papillary LMP (B) and a serous carcinoma (C,D) sample. These samples were positive for ER and PR using the H-score as described in the Materials and Methods. Endometrium (E and F) tissues were used as positive controls. Insets shows the positive tissues stained with matched isotype antibody. Slides were digitized using the Aperio digital system (20X).

Figure 2. Kaplan-Meier survival curves of overall survival time according to ER/PR expression patterns. The number of patients at risk of death from EOC is shown at 12, 24, 36 and 60 months for each ER/PR expression pattern.

Table 1

Characteristics of LMP and EOC cases.

Characteristics	Variable	45 LMP	89 EOC
		N (%)	N (%)
Age	Median, years	47.5	57.4
	range	17–82	21–87
	≤50 yrs	26 (57.8)	27 (30.3)
	>50 yrs	19 (42.2)	62 (69.7)
Histology	Serous	22 (48.9)	51 (57.3)
	Mucinous	22 (48.9)	15 (16.9)
	Endometrioid	1 (2.2)	14 (15.7)
	Other	0	9 (10.1)
Grade	0	45 (100)	0
	1	0	13 (14.6)
	2	0	22 (24.7)
	3	0	54 (60.7)
FIGO Stage	I	40 (88.9)	24 (27.0)
	II	3 (6.7)	9 (10.1)
	III	2 (4.4)	43 (48.3)
	IV	0	13 (14.6)
Performance Status	0	42 (95.5)	71 (80.7)
	1	2 (4.5)	17 (19.3)
Debulking	Optimal	45 (100)	66 (74.2)
	Suboptimal		23 (25.8)
Any chemo	No	44 (100.0)	27 (30.3)
	Yes	0	62 (69.7)
ER	Negative cases	30 (66.7)	39 (43.8)
	Positive cases	15 (33.3)	50 (56.2)
PR	Negative cases	24 (53.3)	46 (51.7)
	Positive cases	21 (46.7)	43 (48.3)
ER/PR patterns	ER–/PR–	24 (53.3)	27 (30.3)
	ER+/PR–	0	19 (21.4)
	ER–/PR+	6 (13.3)	12 (13.5)
	ER+/PR+	15 (33.3)	31 (34.8)

Characteristics	Variable	45 LMP	89 EOC
		N (%)	N (%)

LMP, low malignant potential; EOC, epithelial ovarian cancer

Table 2
Immunostaining by histopathology in LMP samples.

Histology	Serous N (%)	Endometrioid N (%)	Mucinous N (%)	P value [*]
ER				
Negative	8 (36.4)	0	22 (100.0)	<0.001
Positive	14 (63.6)	1 (100.0)	0	
PR				
Negative	4 (18.2)	0	20 (90.9)	<0.001
Positive	18 (81.8)	1 (100.0)	2 (9.1)	
ER/PR patterns				
ER-/PR-	4 (17.4)		20 (90.9)	<0.001
ER+/PR-	0		0	
ER-/PR+	4 (17.4)		2 (8.3)	
ER+/PR+	15 (65.2)		0	

* Fisher exact test.

Table 3

Immunostaining by histopathology in EOC samples.

Histology	Serous N (%)	Endometrioid N (%)	Mucinous N (%)	Other N (%)	P value *
ER					
Negative	17 (33.3)	4 (28.6)	13 (86.7)	5 (55.6)	<0.001
Positive	34 (66.7)	10 (71.4)	2 (13.3)	4 (44.4)	
PR					
Negative	23 (45.1)	4 (28.6)	12 (80.0)	7 (77.8)	<0.01
Positive	28 (54.9)	10 (71.4)	3 (20.0)	2 (22.2)	
ER/PR patterns					
ER-PR-		12 (18.5)		15 (62.5)	< 0.001
ER+/PR-		15 (23.1)		4 (16.7)	
ER-PR+		9 (13.9)		3 (12.5)	
ER+/PR+		29 (44.6)		2 (8.3)	

* Fisher exact text.

Table 4
Five-year survival Analysis: Univariate and Multivariate Cox's Proportional Hazards Models.

Variable	Univariate Model		Multivariate Model	
	P- value *	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Wald P- value
Grade	0.001			
1		0.00 (None **)	0.00	0.989
2		1.00 (Reference)	1.00 (Reference)	
3		1.01 (0.47, 2.18)	0.76 (0.32, 1.82)	0.540
Stage	< 0.001			
I + II		1.00 (Reference)	1.00 (Reference)	
III		6.02 (1.78, 20.4)	6.20 (1.68, 22.88)	0.006
IV		20.8 (5.50, 78.6)	7.56 (1.59, 36.04)	0.011
Performance status	0.001			
0-1		1.00 (Reference)	1.00 (Reference)	
2-4		3.84 (1.83, 8.06)	2.19 (0.82, 5.86)	0.118
Debulking	< 0.001			
Optimal		1.00 (Reference)	1.00 (Reference)	
Sub-Optimal		4.66 (2.31, 9.41)	2.63 (1.08, 6.43)	0.034
Chemotherapy	0.108			
No		1.00 (Reference)	1.00 (Reference)	
Yes,		0.55 (0.27, 1.12)	0.25 (0.10, 0.64)	0.004
ER/PR patterns	0.040			
ER+/PR-		1.00 (Reference)	1.00 (Reference)	
ER-/PR-		3.34 (1.10, 10.20)	4.12 (1.19, 14.30)	0.026
ER-/PR+		0.72 (0.13, 3.92)	0.98 (0.17, 5.70)	0.979
ER+/PR+		1.88 (0.61, 5.82)	2.78 (0.85, 9.09)	0.091

* Likelihood Ratio test compares reduced to full model; in the multivariate model, P-values and HRs are adjusted for the other factors in the model.

** Grade 1 had no events, so Grade 2 was used as the reference category.