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A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass

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Abstract

Introduction—Patients diagnosed with epithelial ovarian cancer (EOC) have improved outcomes when cared for at centers experienced in the management of EOC. The objective of this trial was to validate a predictive model to assess the risk for EOC in women with a pelvic mass.

Methods—Women diagnosed with a pelvic mass and scheduled to have surgery were enrolled on a multicenter prospective study. Preoperative serum levels of HE4 and CA125 were measured. Separate logistic regression algorithms for premenopausal and postmenopausal women were utilized to categorize patients into low and high risk groups for EOC.

Results—Twelve sites enrolled 531 evaluable patients with 352 benign tumors, 129 EOC, 22 LMP tumors, 6 non EOC and 22 non ovarian cancers. The postmenopausal group contained 150 benign cases of which 112 were classified as low risk giving a specificity of 75.0% (95% CI 66.9–81.4), and 111 EOC and 6 LMP tumors of which 108 were classified as high risk giving a sensitivity of 92.3% (95% CI=85.9–96.4). The premenopausal group had 202 benign cases of which 151 were classified as low risk providing a specificity of 74.8% (95% CI=68.2--80.6), and 18 EOC and 16 LMP tumors of which 26 were classified as high risk, providing a sensitivity of 76.5% (95% CI=58.8--89.3).

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Conclusion—An algorithm utilizing HE4 and CA125 successfully classified patients into high and low risk groups with 93.8% of EOC correctly classified as high risk. This model can be used to effectively triage patients to centers of excellence.

Introduction

Each year in the United States, approximately 289,000 women are hospitalized with an ovarian cyst or pelvic mass. As the incidence of surgery for suspected ovarian neoplasms is increasing, estimates indicate approximately 10% of all women in the United States will undergo surgery for an ovarian neoplasm (1). However, only a small percentage of these women will ultimately be diagnosed with an epithelial ovarian cancer (EOC), a malignancy that requires comprehensive surgical staging or aggressive cytoreductive surgery. Unfortunately, fewer than half of ovarian cancer patients have their initial surgery by gynecologic oncologists or surgeons that have specialty training in the surgical management of ovarian cancer and therefore many patients undergo inadequate surgical staging or receive suboptimal cytoreductive surgery at their initial surgery(2;3). A recent study indicate women who are operated on by surgeons who specialize in the management of EOC and at centers experienced in the management of patients with this disease have decreased morbidity and mortality and an increase in overall survival (4-7).

Currently, algorithms and triage protocols for the assessment of the probability of a woman with a pelvic mass harboring a malignancy are limited. The serum tumor marker CA125 has been evaluated in this role(8). However, CA125 is elevated in less than half of early stage EOC and is not expressed in approximately 20% of EOC resulting in decreased sensitivity (9;10). Equally problematic, CA125 is elevated in many benign gynecologic diseases that commonly affect premenopausal women and in many medical conditions that affect postmenopausal women resulting in a reduction of specificity (10). A risk assessment tool that accurately classifies patients into high and low risk groups for having an ovarian malignancy is critical for the ability to triage patients to centers of excellence.

A study examining a panel of serum biomarkers for the detection of malignancy in women presenting with a pelvic mass demonstrated that the addition of HE4 to CA125 improved the sensitivity and specificity over that of CA125 alone for the risk assessment of a malignancy in patients with a pelvic mass (11). We conducted a prospective multicenter clinical trial to validate a predictive model utilizing the dual marker combination of HE4 and CA125 to assess the risk for EOC in women presenting with a pelvic mass.

Methods

This was a prospective multicenter trial registered with the National Institute of Health clinical trial registry ([ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study/NCT00315692) identifier NCT00315692). Each site participating in the study obtained institutional review board approval from their respective institutions. To be eligible for enrollment patients were required to be 18 years of age or older and have a diagnosis of an ovarian cyst or a pelvic mass with a planned surgical intervention. Women with a prior bilateral oophorectomy were not eligible for enrollment. Prior to collection of biological samples and surgery, all patients were required to give full informed consent. All patients had radiologic imaging either by pelvic ultrasound (US), computed tomography scanning (CT) and/or magnetic resonance imaging (MRI) prior to surgery to document the presence of an ovarian cyst or pelvic mass. Immediately prior to surgery, blood and urine samples were obtained. Within 4 hours of collection, blood samples were centrifuged and the serum and plasma was collected and dispensed into multiple 5cc cryotubes and all samples frozen to -20°C . Serum CA125 concentrations were measured using the Architect CA125II assay (Abbott Diagnostics, Abbott Park, IL) and serum HE4 levels were

determined using the HE4 EIA assay (Fujirebio Diagnostics, Malvern, PA). All assays were run according to manufacturer's instructions, and appropriate controls were within the ranges provided by the manufacturer for all runs.

All patients underwent surgical removal of the ovarian mass or cysts, and if a patient was diagnosed with an EOC, surgical staging was required by protocol. Tissue specimens were obtained from all patients and centrally reviewed by three gynecologic pathologists to verify the diagnoses made by the site pathologists. All histological evaluations were done blinded to laboratory values for the biomarker assays and laboratory testing was done blinded to histological outcome. Serum levels for HE4, CA125II and the predictive probability determined for the protocol were withheld from the physicians and patients participating in the study.

Statistical Analysis

The primary endpoint of the clinical study was to classify patients with a pelvic mass into high risk or low risk groups for having EOC using the serum biomarkers CA125 and HE4, and to determine the accuracy of these classifications. Prior to the start of this trial, a pilot study conducted at Women and Infants' Hospital of Rhode Island (WIHRI) examining multiple markers in patients with a pelvic mass determined that the dual marker combination of HE4 and CA125 had the highest predictive value out of the 11 markers evaluated(11). The WIHRI pilot study used logistic regression analysis to classify the subjects into mutually exclusive low, moderate, and high risk groups. Using the results from the pilot study, the following assumptions were made for the pivotal study sample size calculations: Approximately 20% of the subjects presenting with a pelvic mass will be found to have ovarian cancer at the time of surgery; greater than 30% of the total number of subjects will fall into the low risk group; for the group of subjects without evidence of cancer (~80% of the evaluable subjects), ~45% would fall into the low risk group, ~45% would fall into the moderate risk group, and ~10% would fall into the high risk group. For the group of subjects with ovarian cancer (~20% of the evaluable subjects), ~5% would fall into the low risk group, ~15% would fall into the moderate risk group, and ~80% would fall into the high risk group.

With these assumptions, a chi-square test with a two-sided significance level of 0.05 would have >99% power to distinguish between the groups when the proportions in the three risk groups are distributed as described above if the total sample size was 500. Therefore, the minimum number of patients to be enrolled was set at 500, with the requirement that a minimum of 100 patients have histologically proven ovarian cancer.

Prior to the completion and analysis of the pivotal trial presented in this paper, a second pilot study was completed and separate logistic regression algorithms for premenopausal and postmenopausal women were developed to separate patients into low and high risk groups. The algorithms were developed using pooled data from a prospective pilot study conducted at Women and Infants' Hospital (N=219) and a retrospective case-control study conducted at Massachusetts General Hospital (N=236) of women who underwent surgery for pelvic mass. The two logistic regression formulae, which included model intercept terms adjusted to account for the sampling scheme in the case-control study, coefficients for the natural log (LN) of the HE4 values, and coefficients for the LN of the CA125 values, are:

$$\text{Premenopausal: Predictive Index (PI)} = -12.0 + 2.38 * \text{LN (HE4)} + 0.0626 * \text{LN (CA 125)}$$

$$\text{Postmenopausal: Predictive Index (PI)} = -8.09 + 1.04 * \text{LN (HE4)} + 0.732 * \text{LN (CA 125)}$$

$$\text{Predicted Probability (PP)} = \exp(\text{PI}) / [1 / \exp(\text{PI})]$$

The above equations derived from the WIHRI and MGH combined pilot study are the algorithms tested for validation in the current study.

For the purposes of analysis in this study, women were considered to be postmenopausal if they had not had a menstrual period for >1 year prior to their study blood draw or if they had an oophorectomy, or if they were >55 years old and the date of the last menstrual period was unknown. Women were considered to be premenopausal if they had a period within 1 year of the study blood draw or if they were <48 years old and the date of their last menstrual period was unknown. Menopausal status for women between the ages of 48 and 55 who had an unknown last menstrual period or a prior hysterectomy was determined by measurement of plasma follicle stimulating hormone (FSH) levels performed on a Architect platform (Abbott Diagnostics, Abbott Park, IL). Women with plasma FSH levels less than 22 mIU/ml were defined as premenopausal and all other women were classified as postmenopausal.

Using the serum CA125 and HE4 values, a predicted probability (PP) was calculated for each patient using the appropriate logistic regression formula based on their menopausal status, with the resulting PP values ranging from 0% to 100%. For both statistical and medical reasons, it was decided *a priori* that the study would demonstrate a clinically useful algorithm for differential diagnosis if the sensitivity at a specificity of 75% was greater than 80% for premenopausal and postmenopausal women combined. That is, the minimum performance for clinical usefulness would occur when 75% of patients with benign disease were correctly classified as low risk and the 95% confidence interval for classifying patients with malignancy as high risk would rule out any sensitivity of 80% or less.

A specificity of 75% in premenopausal and postmenopausal women was achieved when PP thresholds of > 13.1% and 27.7% were applied, respectively. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for premenopausal and postmenopausal women separately and in combination. Tumor marker levels between the premenopausal and postmenopausal women and between the benign and ovarian cancer patient groups were compared using the Wilcoxon rank-sum test (Mann-Whitney two sample statistic). For all statistical comparisons a level of $P < 0.05$ was accepted as statistically significant.

Results

A total of 566 patients were enrolled from 12 different geographic sites across the United States. Patient demographics and characteristics are illustrated in Table 1. Of the 566 patients enrolled onto the trial, 531 patients were evaluable, with 283 postmenopausal women and 248 premenopausal women. A total of 54 women had menopausal status determined by plasma FSH levels, 47 of which had a prior hysterectomy with preservation of at least one ovary. The mean age of the evaluable study cohort was 54 years old (range: 18 to 87), with a mean age for postmenopausal women of 65 years old (range: 42 to 87) and for premenopausal 41 years old (range: 18 to 59). There were 352 women with benign disease (150 postmenopausal and 202 premenopausal) and 179 women with a malignancy diagnosed in the study group. The histologic classification of benign and malignant disease and the site of origin are provided in Table 1.

There were 129 patients diagnosed with EOC (111 postmenopausal and 18 premenopausal). These EOC cases had the following histologic distribution; 83 serous, 16 endometrioid, 6 mucinous, 6 clear cell, 8 mixed, 3 carcinosarcomas, 5 undifferentiated, 1 transitional cell and 1 adenosquamous. There were 22 patients diagnosed with low malignant potential (LMP) tumors (6 postmenopausal and 16 premenopausal). Histologic classification of the LMP tumor revealed 14 serous, 7 mucinous and 1 endometrioid LMP tumors. There were 6 patients diagnosed with non EOC (4 granulosa cell tumors, 1 dysgerminoma and 1 leiomyosarcoma of the ovary) and 22 patients with non ovarian malignancies (15 gastrointestinal cancers, 1 serous cystadenomas with concurrent renal cell carcinoma, 1 serous cystadenoma with a concurrent colon cancer, 3 metastatic endometrial cancers, 1 malignancy of unknown primary and 1 spindle cell wolffian tumor). In EOC patients there were 17 stage I, 18 stage II, 84 stage III, 6 stage IV and 4 unstaged patients. In patients diagnosed with LMP tumors there were 8 stage I, 1 stage II, 3 stage III and 10 unstaged patients.

Analysis of serum tumor marker levels was performed for all patients as a group and for postmenopausal and premenopausal patients as separate groups. The median serum level for CA125 for all benign cases was 20.5 IU/mL (interquartile range (IR): 13 to 44.7). In postmenopausal women the median CA125 level for benign disease was 17.8 IU/mL (IR: 11.3 to 30.0) and in premenopausal women with benign disease the median CA125 level was 24.3 IU/mL (IR: 13.9 to 60.2). Median CA125 levels for all 179 cancer cases was 210.9 IU/mL (IR: 82.4 to 849.4) and for EOC and LMP tumors alone, the median CA125 levels were 317.1 IU/mL (IR: 99.6 to 960.2). CA125 serum levels for benign cases versus all cancers or EOC plus LMP tumors alone were significantly different in both the premenopausal and postmenopausal groups (all p-values <0.0001).

The median HE4 serum levels for all benign cases were 58.6 pM (IR: 46.0 to 75.4). For postmenopausal women, the median HE4 serum levels for benign disease were 70.8 pM (IR: 56.8 to 102.7) and in premenopausal women 51.2 pM (IR: 40.7 to 63.4). The median HE4 serum levels for all 179 cancers were 274.4 pM (IR: 89.2 to 783.4) and for EOC and LMP tumors alone, the median HE4 serum levels were 386.6 pM (IR: 122.6 to 941.0). HE4 serum levels for benign cases versus all cancers or EOC plus LMP tumors alone were significantly different in both the premenopausal and postmenopausal groups (all p-values <0.0001).

The dual marker algorithm stratified patients into low and high risk of malignancy groups using the designated predictive probability thresholds for premenopausal and postmenopausal women (Table 2). The high risk of malignancy group was defined as a predictive probability of >13.1% for premenopausal women and >27.7% for postmenopausal women. The sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the dual marker combination of HE4 and CA125 in the differentiation of women with benign disease versus EOC and LMP tumors are shown in Table 3.

An analysis of premenopausal and postmenopausal women with benign neoplasms (N=352) or with EOC and LMP tumors (N=151) classified 280 (55.7%) women into the low risk group and 223 (44.3%) women into the high risk group, resulting in a sensitivity of 88.7% (95% CI: 82.6 - 93.3%), a specificity of 74.7% (95% CI: 69.8 - 79.2%) and a NPV of 93.9% (95% CI: 90.5 - 96.4%) as illustrated in Table 3. The lower limit of the 95% confidence interval for sensitivity at 75% specificity is 82.6%, which clearly rules out sensitivities less than 80%. The algorithm incorrectly classified 9 patients with LMP tumors and 8 with EOC to the low risk group. Thus, out of the 129 patients with EOC, only 8 (6.2%) women were misclassified into the low risk group, providing a sensitivity of 93.8% (95% CI: 88.1%-97.3%) at a specificity of 75% (Table 4).

An analysis of postmenopausal patients with benign neoplasms (N=150) or with EOC and LMP tumors (N=117) classified 121 (45.3%) women into the low risk group and 146 (54.7%) women into the high risk group, resulting in a sensitivity of 92.3% (95% CI: 85.9 – 96.4%), a specificity of 74.7% (95% CI: 66.9 – 81.4%) and a NPV of 92.6% (95% CI: 86.3 – 96.5%) as illustrated in Table 3. Postmenopausal patients incorrectly classified to the low risk group included 3 patients with LMP tumors and 6 patients with EOC. Thus, out of the 111 postmenopausal patients with EOC, only 6 (5.1%) were misclassified into the low risk group providing a sensitivity of 94.6% (95% CI: 88.6-98.0%) at a specificity of 75% (Table 4).

An analysis of premenopausal patients with benign neoplasms (N=202) or with EOC and LMP tumors (N=34) classified 159 (67.4%) women into the low risk group and 77 (32.6%) women into the high risk group, resulting in a sensitivity of 76.5% (95% CI: 58.8 – 89.3%), a specificity of 74.8% (95% CI: 68.2 – 80.6%) and a NPV of 95.0% (95% CI: 90.3 – 97.8%) as reported in Table 3. Premenopausal patients incorrectly classified to the low risk group revealed 6 patients with LMP tumors and 2 patients with EOC. Thus, out of the 18 premenopausal patients with EOC, only 2 (11.1%) were misclassified into the low risk group providing a sensitivity of 88.9% (95% CI: 65.3-98.6%) at a specificity of 75% (Table 4).

An analysis of premenopausal and postmenopausal with benign neoplasms (N=352) or with any cancer or LMP tumor (N=179) achieved a sensitivity of 86.0% (95% CI: 80.1 – 90.8%) at a specificity of 74.7% (95% CI: 69.8 – 79.2%). In postmenopausal women only, the dual marker algorithm had a sensitivity of 92.5% (95% CI: 86.6 – 96.3%) at a specificity of 74.7% (95% CI: 66.9 – 81.4%) and in premenopausal women only, the dual marker algorithm had a sensitivity of 67.4% (95% CI: 52.0 – 80.5%) at a specificity of 74.8% (95% CI: 68.2 – 80.6%).

Discussion

The American Cancer Society estimates there will be 22,430 women diagnosed with ovarian cancer resulting in 15,280 deaths in the year 2007(12). Surgical debulking and comprehensive surgical staging are the hallmark of ovarian cancer management. Optimal debulking surgeries have been correlated with increased survival rates and surgical staging has also been shown to play a vital role in the management of women diagnosed with ovarian cancer (13-15). While patients diagnosed with surgical stage IA or IB epithelial ovarian cancer can often be treated and cured with surgery alone, approximately 30% of women who are thought to have early stage disease after their initial surgery and subsequently undergo comprehensive surgical staging will be up-staged and thus require chemotherapy for the appropriate treatment of their ovarian cancer (16).

For women diagnosed with EOC the experience of their surgeons and the institutions where they receive their initial treatment will affect the morbidity and survival rates for these patients(4-7;17). Despite these findings less than 50% of women with ovarian cancer currently have their initial surgery by a gynecologic oncologist, surgeons that are most likely to perform a complete surgical staging or optimal cytoreductive surgery (2;6;17;18). For these reasons, it is imperative that an accurate method for determining whether a pelvic mass likely represents a malignancy is used to triage women at high risk to centers of excellence for their treatment. Equally important, a successful triage tool will allow women at low risk for having a malignancy to stay in their community for their treatment with their primary gynecologist and supportive networks.

HE4 (WFDC2) is made up of two whey acidic protein (WAP) domains and a 4 disulfide core and has been shown to be over expressed by epithelial ovarian cancer tumors. The HE4 gene is part of a family of protease inhibitors that function in protective immunity, and is expressed primarily in the reproductive tract and upper airways and can be detected in the sera of patients(19-22). As well, HE4 is not elevated in many common benign gynecologic and medical conditions where CA125 is elevated(22). In premenopausal women CA125 suffers from a lack of specificity secondary to its tendency to be elevated in many common benign gynecologic and non gynecologic conditions. Because HE4 is not falsely elevated in many of these conditions it may complement CA125.

Moore et al. examined a panel of biomarkers and found the dual marker combination of HE4 and CA125 produced the highest sensitivity of the various tumor marker combinations and increased the sensitivity of CA125 alone(11). Maggino et al. examined the sensitivity and specificity of CA125 at various cutoffs (8). At an upper limit normal cutoff of 35U/ml, CA125 achieved a sensitivity of 78.3% and a specificity of 82%. Increasing the upper cutoff limit to 65U/ml, the sensitivity was decreased to 71.7% and the specificity was increased to 92.5%. Employing an upper cutoff limit of 65U/ml in postmenopausal women yields a sensitivity that is useful for the prediction of the presence of a malignancy for this age group. The dual marker combination improves upon CA125 alone without using predefined cutoffs for either serum tumor markers. As well, for the 20% of EOC that express little, if any, CA125, a single marker is not sufficient. Notably, HE4 levels are elevated in greater than 50% of tumors that do not express CA125 (11). Therefore, the addition of HE4 to CA125 enables the detection of malignancies in patients with tumors that do not express CA125 and will be missed by algorithms that employ CA125 alone. Equally important, a combination of HE4 and CA125 or HE4 alone has been shown to have greater sensitivity in patients with early stage disease compared with CA125(11).

Currently the risk of malignancy index (RMI) is the most utilized algorithm for predicting malignancy in women with a pelvic mass and utilizes a combination of serum CA125 levels, pelvic sonography and menopausal status(23). At an RMI score of 50, Jacobs et al report a specificity of 76.5% with a sensitivity of 95.1% similar to that achieved utilizing the dual marker algorithm alone. Recognizing the subjective nature of sonography, Bailey et al. examined the RMI algorithm in a diverse population of patients allowing for variation in sonography and differences in CA125 assays. These authors validated the RMI algorithm with a reported sensitivity of 87.4%, specificity of 56.8%, PPV of 86.8% and a NPV of 58.1% when the RMI cutoff was 200 for the detection of EOC and LMP tumors in patients with a pelvic mass (24). The current study, without the utilization of imaging in the risk assessment for malignancy, achieved a higher sensitivity and specificity when considering women of all ages and menopausal status. Operator experience and variability in reporting of morphologic features of an ovarian neoplasm contribute to inconsistencies seen from center to center and introduce subjective variables into algorithms employing ultrasound imaging. The advantage of a serum biomarker algorithm is the inherent objective nature of a biomarker test and the omission of subjective measurement and therefore facilitates for reproducibility from center to center and region to region.

Upon examination of patients that were misclassified into the low risk group, half of the patients were diagnosed with LMP tumors. In this study, LMP tumors were included in the analysis with EOC because of the historical recommendation that patients with LMP tumors should undergo surgical staging at the time of their initial surgery due to the risk that on final pathology their tumors may contain invasive ovarian cancer. Patients with LMP tumors alone on final pathology receive very little benefit from surgical staging, as they often do not require adjuvant treatment with chemotherapeutic agents and are followed with observation. Consequently, the misclassification of a patient with an LMP tumor to the low risk group

may be of little clinical significance as these patients would not need further surgical intervention if they were not staged at their initial surgery. Of the patients diagnosed with EOC, 94% were classified in the high risk category and would have been triaged to centers of excellence for their initial surgical care. Alternatively, 75% of patients with benign disease were classified as low risk for malignancy and would have been appropriately triaged to stay in their community for their surgical care.

The dual marker combination of HE4 and CA125 in the risk of malignancy algorithms presented in this paper can be used to classify women into high and low risk groups allowing for the effective triage of women to appropriate surgical centers for their care.

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Table 1

Patient demographics and tumor characteristics.

Parameter	Premenopausal (N)	Postmenopausal (N)	All Patients (N)	%
Race				
White	199	253	452	85.1
Black	24	19	43	8.1
Hispanic	12	4	16	3.0
Asian	7	3	10	1.9
Other	6	4	10	1.9
Total	248	283	531	100.0
Disease Status				
Benign				
Adenofibroma/Cystadenofibroma	6	16	22	6.3
Serous cystadenoma/cystadenoma	27	52	79	22.4
Mucinous Cystadenoma	9	13	22	6.3
Fibroma/Fibrothecoma	3	15	18	5.1
Endometriosis	42	2	44	12.5
Teratoma	18	11	29	8.2
Tubo-ovarian abscess/hydrosalpinx	8	6	14	4.0
Leiomyoma	16	3	19	5.4
Functional cyst/Hemorrhagic cyst	14	0	14	4.0
Simple/Paratubal	34	21	55	15.6
Normal	3	2	5	1.4
Other	22	9	31	8.8
Total	202	150	352	100
Cancer				
EOC	18	111	129	72.1
LMP	16	6	22	12.3
Non-EOC	6	0	6	3.4
Metastatic	5	9	14	7.8
Other Gynecologic	1	7	8	4.4
Total	46	133	179	100.0
EOC				
Grade 1	5	6	11	8.5
Grade 2	4	27	31	24.1
Grade 3	9	75	84	65.1
Unknown	0	3	3	2.3
Total	18	111	129	100.0
EOC				
Stage I	4	13	17	13.2
Stage II	2	16	18	14.0
Stage III	9	75	84	65.1

Parameter	Premenopausal (N)	Postmenopausal (N)	All Patients (N)	%
Stage IV	1	5	6	4.6
Unknown	2	2	4	3.1
Total	18	111	129	100.0

Table 2

Stratification of pelvic mass patients with benign diseases and cancer based on predictive probability.

Disease Status	Premenopausal		Postmenopausal		Combined	
	Low Risk	High Risk	Low Risk	High Risk	Low Risk	High Risk
Benign	151	51	112	38	263	89
LMP	6	10	3	3	9	13
EOC Stage I/II	1	5	4	25	5	30
EOC Stage III/IV	0	10	1	79	1	89
EOC Unstaged	1	1	1	1	2	2
Non-EOC	3	3	0	0	3	3
Other Gynecologic Cancers	1	0	1	6	2	6
Metastatic Cancers	3	2	0	9	3	11

Table 3
Distribution of patients into low risk and high risk groups: Benign vs. EOC and LMP Tumors.

Menopausal Status	Disease	Low Risk		High Risk		Total	Sensitivity	Specificity	PPV	NPV
		N	% ^I	N	% ^I	(N)				
Combined	Benign	263	93.9	89	39.9	352				
	Cancer	17	6.1	134	60.1	151	88.7%	74.7%	60.1%	93.9%
	Total	280	100	223	100	503				
Premenopausal	Benign	151	95.0	51	66.2	202				
	Cancer	8	5.0	26	33.8	34	76.5%	74.8%	33.8%	95.0%
	Total	159	100	77	100	236				
Postmenopausal	Benign	112	92.6	38	26.0	150				
	Cancer	9	7.4	108	74.0	117	92.3%	74.7%	74.0%	92.6%
	Total	121	100	146	100	267				

^I Percentage of cases within low risk group and within high risk group

Table 4

Percentage of EOC misclassified to low risk group.

Age Groups	LMP	EOC Stage			Total EOC	% EOC misclassified
		I	II	III & IV		
Postmenopausal	3	1	3	1	6/111	5.4%
Premenopausal	6	1	-	-	2/18	11.1%
All Ages	9	2	3	1	8/129	6.2%