Multivariate Index Assay Is Superior to CA125 and HE4 Testing in Detection of Ovarian Malignancy in African-American Women

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ABSTRACT

OBJECTIVE: To review and analyze the serum values of risk of ovarian malignancy algorithm (ROMA) and multivariate index assay (MIA) in subgroups of women who underwent surgery for adnexal masses to determine sensitivity, specificity, and positive and negative predictive values for the detection of malignancy in different ethnic populations.

METHODS: Serum samples from 2 prospective trials of 1029 women in which 274 women diagnosed with malignancy were analyzed for ROMA scores and MIA results. Biomarker data were obtained from the previous prospective studies that validated the MIA test. Of these, 250 women were Caucasian (C) and 24 were African-American (AA). Sensitivity, specificity, positive and negative predictive values, and confidence intervals for preoperative test results were calculated using DTComPair package of the R programming language. In premenopausal women, a ROMA value equal to or greater than 1.14 indicates a high risk of finding epithelial ovarian cancer. In premenopausal women, MIA values greater than 5.0 are associated with a greater risk of malignancy. In postmenopausal women, a ROMA value equal to or greater than 2.99 indicates a high risk of finding epithelial ovarian cancer. In postmenopausal women, MIA values greater than 4.4 are associated with a greater risk of malignancy.

RESULTS: Primary ovarian malignancy was diagnosed in 179 cases (167 C/12 AA) and metastatic disease to the ovary in an additional 27 cases (22 C/5 AA). Overall results are shown below.

CONCLUSIONS: Our results demonstrate that ROMA in AA women with adnexal masses have lower sensitivity for the detection of malignancy than does MIA. Implementation of MIA in the evaluation of adnexal masses will increase the sensitivity of the detection of malignancy compared with ROMA, with the most marked results in AA women.

KEYWORDS: ethnicity, risk of ovarian malignancy algorithm (ROMA), multivariate index assay

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Introduction

Evaluation of women with an adnexal mass is clinically challenging. The ability to predict benign or malignant masses is clinically important. Preoperative tumor marker testing, as well as ultrasound characteristics, has been used. Appropriate surgical referral to a gynecologic oncologist based on imaging and tumor markers can be undertaken. Data have shown that treatment by a gynecologic oncologist results in more complete staging, higher rates of complete tumor removal, and better overall survival.[1]

Four recent publications have shown differences in ethnic populations of CA 125 levels. Study populations have included healthy postmenopausal women, women with BRCA mutations, and women with ovarian cancer.[2–5] In each of these studies, lower values of CA 125 were demonstrated in African-American women or non-white women. As CA 125 is a major component of risk of ovarian malignancy algorithm (ROMA), we investigated a database from 2 prospective studies, for an assessment of ethnic bias on ROMA and the multivariate index assay (MIA).[6,7] We compared the sensitivity of ROMA with that of MIA in both Caucasian women and African-American women.

Materials and Methods

Review of the database from the prospective studies from the OVA500[6] and the OVA1[7] studies identified 274 out of a total of 1029 women who were diagnosed with malignancy and for whom both ROMA and MIA were available.

Multivariate index assay incorporates CA 125 II, transferrin, transthyretin (prealbumin), apolipoprotein A1, and beta-2 microglobulin. The individual biomarker results are used to generate an ovarian malignancy risk score using a proprietary algorithm.[7] Numerical results range from 0.0 to10.0 and risk of malignancy was stratified as follows:

- Premenopausal
  Low probability of malignancy (MIA < 5.0);
  High probability of malignancy (MIA ≥ 5.0).

- Postmenopausal
  Low probability of malignancy (MIA < 4.4);
  High probability of malignancy (MIA ≥ 4.4).

Risk of ovarian malignancy algorithm is a qualitative serum and plasma test that combines CA 125, HE4, and menopausal status into a numerical risk score to determine the risk of ovarian malignancy. In premenopausal women, a ROMA value equal to or greater than 1.14 indicates a high risk of finding epithelial ovarian cancer.

In postmenopausal women, a ROMA value equal to or greater than 2.99 indicates a high risk of finding epithelial ovarian cancer.

Inclusion criteria for the patients in this database have been described previously.[6,7] Briefly, samples were drawn from women greater than or equal to 18 years, with a documented pelvic mass planned for surgical intervention and no history of malignancy in the previous 5 years.[6,7] Institutional review boards approved both the studies where the data were obtained.[6,7]

Sensitivity, specificity, and positive and negative predictive values along with 95% confidence intervals (CIs) for preoperative test results were calculated using DTComPair package of the R programming language.

Results

Serum samples from 274 of the 1029 women diagnosed with malignancies were analyzed for both ROMA and MIA. Of these, 250 women were Caucasian (C) and 24 were African-American (AA). Of the total subjects, 873 were Caucasian and 156 were African-American, making the prevalence 28.6% and 15.4%, respectively. Patient demographics are shown in Table 1.

Primary ovarian malignancy was diagnosed in 179 cases (167 C/12 AA) and metastatic disease to the ovary in an additional 27 cases (22 C/5 AA). Borderline or low malignant potential tumors accounted for 52 patients (47 C/5 AA). Non-primary tumors with no ovarian involvement were found in 16 women (14 C/2 AA).

Multivariate index assay demonstrated an overall sensitivity for the detection of malignancy of 93.2% (95% CI: 90.0-96.3) for Caucasian women and 79.1% (95% CI: 62.9-95.4) for African-American women. ROMA gave a sensitivity of 82.9% (95% CI: 62.9-95.4) in Caucasian women, but only 54.5% (95% CI: 33.7-75.3) in African-American women (Table 2).

Discussion

Tumor markers such as prostate-specific antigen (PSA) have been shown to have different levels based on ethnicity. Four recent papers have discussed the differences in CA 125 levels in different ethnic populations. Pauler et al[2] studied 18 748 healthy postmenopausal women with CA 125 levels as part of the St Bartholomew's/Royal London Hospital ovarian cancer screening trial. They found that race is a significant predictor of normal CA 125 levels with an average CA 125 II concentration from African (median: 9.0; 95% range: 4.0-26.0 units/mL) to be lower than that in Caucasian women (median: 14.2; range: 6.0-41.0 units/mL; $P < .001$).

Skates et al[3] reported on 3692 women with a finding that premenopausal women with an Asian background had 24% lower CA 125 levels than those of other ethnicity. Postmenopausal black women had a 22% reduction in predicted CA 125 levels. The population studied was women with BRCA mutations.

Cramer et al[4] studied 805 women prior to treatment for ovarian cancer. Differences were found in women of Jewish ancestry who had higher CA 125 levels than in other women with non-mucinous ovarian cancer.

Babic et al[5] reviewed pretreatment CA 125 in 13 studies participating in the Ovarian Cancer Association Consortium. A total of 5091 women with invasive epithelial ovarian cancer had CA 125 measurements. Non-white race was associated with a 13% lower CA 125 level than in white women with ovarian malignancy.

Given the disparities in CA 125 levels in different ethnic populations, we explored the sensitivity of ROMA and MIA in the detection of ovarian malignancy in women with a radiographic finding of an adnexal mass. In all cases, MIA was more sensitive than ROMA in both Caucasian and African-American women. Sensitivity for detection in African-American women by ROMA levels is low. Whereas MIA is less sensitive in the African-American population, in Caucasian women it is still better than ROMA. Due to the small number of African-American women in the population, 95% CIs are overlapping.

As CA 125 is a component of MIA, we would expect some decreased sensitivity in African-American women.

Multivariate index assay in this cohort is more sensitive than ROMA to detect malignancy in the entire population studied. However, it is most pronounced in African-American women in which ROMA has lower sensitivity for the prediction of ovarian malignancy. Adoption of MIA will improve referral of women with ovarian malignancy to the proper surgeon, particularly African-American women.

This is the first publication to investigate the sensitivity of ROMA and MIA for ovarian malignancy based on ethnic difference. Similar data for CA 125 and MIA have been presented at the Middle Atlantic Gynecologic Oncology Society in October 2018.

A limitation of our study is the small number of African-American women in the 2 prospective studies that are database uses for analysis leading to lack of statistical evidence of superiority. However, given the biological basis of lower CA 125 in African-American women, we feel that these results are clinically significant to alert practitioners of the possible false negatives of ROMA in African-American women. We are exploring research to add additional African-American women to the database to confirm these results.

Table 1. Population demographics.

	CAUCASIAN SUBJECTS			AFRICAN-AMERICAN SUBJECTS		
	ALL MALIGNANCIES	PREMENOPAUSAL SUBJECTS	POSTMENOPAUSAL SUBJECTS	ALL MALIGNANCIES	PREMENOPAUSAL SUBJECTS	POSTMENOPAUSAL SUBJECTS
Age (years)						
N	250	69	181	24	15	9
Mean (SD)	58.0 (12.9)	44.1 (8.4)	63.3 (10.0)	48.5 (13.1)	41.5 (9.1)	60.2 (10.1)
Median	57	47	61	48.5	42	62
Range (min, max)	20, 92	20, 58	41, 92	25, 75	25, 53	43, 75
Pathology diagnosis, n (%)						
Primary ovarian malignancy	167 (66.8)	43 (62.3)	124 (68.5)	12 (50.0)	9 (60.0)	3 (33.3)
Low malignant potential (borderline)	47 (18.8)	16 (23.2)	31 (17.1)	5 (20.8)	2 (13.3)	3 (33.3)
Non-primary with metastatic involvement of the ovaries	22 (8.8)	7 (10.1)	15 (8.3)	5 (20.8)	3 (20.0)	2 (22.2)
Non-primary ovarian malignancies with no involvement of the ovaries	14 (5.6)	3 (4.3)	11 (6.1)	2 (8.3)	1 (6.7)	1 (11.1)
Stage, n (%) (primary ovarian malignancies)						
Stage I	55 (32.9)	14 (32.6)	41 (33.1)	7 (58.3)	6 (66.7)	1 (33.3)
Stage II	23 (13.8)	8 (18.6)	15 (12.1)	1 (8.3)	1 (11.1)	0 (0.0)
Stage III	78 (46.7)	17 (39.5)	61 (49.2)	3 (25.0)	2 (22.2)	1 (33.3)
Stage IV	8 (4.8)	3 (7.0)	5 (4.0)	1 (8.3)	0 (0.0)	1 (33.3)
Not given	3 (1.8)	1 (2.3)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values and 95% confidence interval (CI) analysis of ovarian malignancies for MIA and ROMA.

	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	PPV (95% CI)	NPV (95% CI)
MIA Caucasian	93.2 (90.0–96.3)	45.3 (41.3–49.2)	40.8 (36.7–44.8)	94.2 (91.6–96.9)
ROMA Caucasian	82.9 (78.0–87.7)	75.4 (71.9–78.9)	57.5 (52.2–62.8)	91.6 (89.1–94.1)
MIA AA	79.1 (62.9–95.4)	66.6 (58.6–74.7)	30.1 (18.8–41.4)	94.6 (90.0–99.2)
ROMA AA	54.5 (33.7–75.3)	85.0 (78.8–91.2)	38.7 (21.5–55.8)	91.5 (86.5–96.5)

Abbreviations: AA, African-American; MIA, multivariate index assay; ROMA, risk of ovarian malignancy algorithm.

Author Contributions

All authors were active in the analysis and writing of the article.

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