ONCOLOGY

# The effect of ovarian imaging on the clinical interpretation of a multivariate index assay

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**OBJECTIVE:** The purpose of this study was to investigate the relationship between imaging and the multivariate index assay (MIA) in the prediction of the likelihood of ovarian malignancy before surgery.

**STUDY DESIGN:** Subjects were recruited in 2 related prospective, multiinstitutional trials that involved 44 sites across the United States. Women had ovarian imaging, biomarker analysis, and surgery for an adnexal mass. Ovarian tumors were classified as high risk for solid or papillary morphologic condition on imaging study. Biomarker and imaging results were correlated with surgical findings.

**RESULTS:** Of the 1110 women who were enrolled with an adnexal mass on imaging, 1024 cases were evaluable. There were 255 malignant and 769 benign tumors. High-risk findings were present in 46% of 1232 imaging tests and 61% of 1024 MIA tests. The risk of malignancy increased with rising MIA scores; similarly, the likelihood of malignancy was higher for high-risk, compared with low-risk, imaging. Sensitivity and specificity for the prediction of malignancy were 98% (95% CI, 92—99) and 31% (95% CI, 27—34) for ultrasound or MIA; 68% (95% CI, 58—77) and 75% (95% CI, 72—78) for ultrasound and MIA, respectively. For computed tomography scan or MIA, sensitivity was 97% (95% CI, 92—99) and specificity was 22% (95% CI, 16—28); the sensitivity and specificity for computed tomography scan and MIA were 71% (95% CI, 62—79) and 70% (95% CI, 63—76). Only 1.6% of ovarian tumors were malignant when both tests indicated low risk. A logistic regression model to predict risk of malignancy is presented.

**CONCLUSION:** An understanding of how pelvic imaging influences the MIA score can help clinicians better interpret the malignant risk of an ovarian tumor.

**Key words:** imaging, multivariate index assay, OVA1, ovarian tumor

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Ovarian cancer is the leading cause of gynecologic cancer death in the United States, and fewer than 40% of women diagnosed with ovarian cancer will be cured.[1] One of the recognized challenges is how to identify at-risk ovarian tumors for referral before the initial surgery. More than 15 years ago, the National Institutes of Health released a consensus statement that declared that a woman with an ovarian mass at high risk for malignancy should be given the option of having her surgery performed by a gynecologic oncologist.[2] Many subsequent ovarian cancer publications have established that outcomes are improved with the involvement of a specialist[3-7]; yet, 2 of every 3 women in the United States are not referred to a gynecologic oncologist for their primary ovarian cancer surgery.[7] There are several plausible explanations for the low referral rate; among them is that the low sensitivity of existing algorithms fails to alert the evaluating physician before surgery. This may be particularly important for premenopausal women who rarely are considered to be at risk for ovarian malignancy but who account for up to 20% of all ovarian cancers.[1,8]

In 2006, Myers et al,[4] who published a pooled statistical analysis for algorithms that were used to evaluate an adnexal

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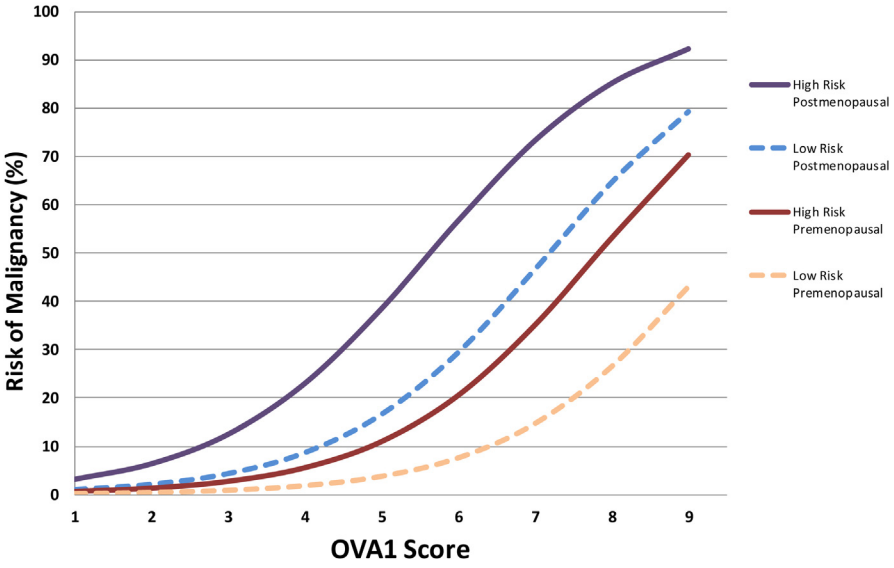
FIGURE 1
**Predicted risk of malignancy over range of OVA1 scores by ultrasound result and menopausal status**

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mass, concluded that a combined strategy of imaging with biomarker was superior to either one alone. Until recently, cancer antigen 125 (CA125) has been the most used biomarker to evaluate women with an ovarian tumor. Unfortunately, the sensitivity of CA125 is reported to be 50% in early-stage disease[9] and has a 20-25% false-negative rate in advanced-stage cancers. In premenopausal women, CA125 has a sensitivity of 50-74%, with a specificity reportedly as low as 26% for ovarian malignancy.[4] OVA1 (multivariate index assay [MIA]) is a sensitive biomarker test specifically for use in the preoperative evaluation of ovarian tumors. In the leading publication, physician assessment plus MIA identified 86% of malignancies that were missed by CA125, and its clinical performance was consistent in early- and late-stage cancers.[10] These findings were confirmed recently with a subsequent prospective investigation by Bristow et al.[11] There are circumstances in which an ovarian tumor has a high-risk MIA score but a low-risk imaging study. In this situation, there are no published data to assist providers in making informed decisions about surgery.

This study was undertaken to better understand the relationship between ovarian imaging and the MIA in the preoperative evaluation of an adnexal mass.

## Materials and Methods

Subjects were enrolled prospectively at 44 sites across the United States (Figure 1) and included primary care women's health clinics, obstetrics and gynecology groups, gynecologic oncology practices, community and university hospitals, and health maintenance organizations. These data were merged from 2 published national trials.[10,11] Both trials had identical inclusion and exclusion criteria. The inclusion criteria included female age ≥18 years, a documented ovarian tumor with planned surgery within 3 months of imaging, agreeable to phlebotomy, and signed informed consent. The exclusion criteria were age <18 years, no planned surgical intervention, declined phlebotomy, or a malignancy diagnosis in the last 5 years, with the exception of a nonmelanoma skin cancer. *Menopause* was defined as the absence of menses for at least 12 months or age ≥50 years when not stated. Institutional review board approval was obtained from each site. All data were collected on standardized case report forms.

The methods for blood collection and specimen handling have been reported previously.[10,11] Biomarker measurements were performed by Quest Diagnostics, Inc (Chantilly, VA); blinded validation testing was done at Johns Hopkins Medical Institutions (Baltimore, MD) and Specialty Laboratories (Valencia, CA).

### The MIA test

The OVA1 test, which has been cleared by the Food and Drug Administration and is commercially available (Quest Diagnostics, Madison NJ), incorporates CA125-II, transferrin, transthyretin (prealbumin), apolipoprotein A1, and beta 2 microglobulin. The OvaCalc software program (Vermillion Inc, Austin, TX) combines the values for each assay and uses a proprietary algorithm to generate an ovarian malignancy risk index score for each. The numeric result ranges from 0.0−10.0, with the following clinical report:

Premenopausal: low risk for malignancy, <5.0; high risk for malignancy, ≥5.0; Postmenopausal: low risk for malignancy, <4.4; high risk for malignancy, ≥4.4.

### Ovarian imaging

Preoperative imaging results, which included computed tomography (CT), ultrasound scans, or magnetic resonance imaging, were collected prospectively and analyzed retrospectively. Enrolling physicians were allowed to choose the type of imaging to be performed. Magnetic resonance imaging results were omitted from the analysis because of low numbers (n = 43). High-risk imaging criteria were selected based on univariate analysis of the study group. The following variables are statistically predictive of ovarian malignancy ($P <$ .001 for each): solid tumor components or papillary ovarian morphologic condition (odds ratio [OR], 4.2; 95% confidence interval [CI], 3.0−5.8), ascites (OR, 8.0; 95% CI, 5.3−12.1), and metastatic implants (OR, 28.3; 95% CI, 9.9−80.8). Ascites and metastatic implants are correlated highly with advanced disease; however, because the