The Importance of Test Positive Predictive Value in Ovarian Cancer Screening

Visintin et al. (1) have reported a multiplex (six biomarker), bead-based immunoassay system as a candidate for ovarian cancer screening in high-risk populations. This assay has recently been marketed as an ovarian cancer screening test by LabCorp, under the trade name OvaSure (2), citing the data in reference 1 as its scientific basis.

Visintin et al. (1) first tested 181 controls and 113 ovarian cancer cases to determine the initial panel of biomarkers that best discriminated between cases and controls (training set). The resulting panel was applied to an additional 181 controls and 43 ovarian cancer cases (test set). The published report is noteworthy for the performance characteristics attributed to this assay, based on the combined training and test sets, all ovarian cancers combined: sensitivity, 95.3%; specificity, 99.4%; positive predictive value (PPV), 99.3%; and negative predictive value, 99.2%.

However, the PPV estimate of 99.3% seems to have been based on a prevalence of ovarian cancer near 50%. The prevalence of ovarian cancer in any *screened* population will be *much* smaller than 50%. In a recently published correction to their article (3), Visintin et al. assumed that the prevalence of ovarian cancer in the screened population was 1 of 2,500 (0.04%) and recalculated the PPV to be only 6.5%. Disease prevalence has a critical effect on PPV through the following relationship (4):

$$PPV = \frac{Sensitivity \times Prevalence}{(Sensitivity \times Prevalence) + (1 - Specificity) \times (1 - Prevalence)}$$

Given that this assay is currently being marketed to health care providers and consumers as a validated ovarian cancer screening test, this difference is not academic. Ovarian cancer poses a unique challenge relative to the potential effect of false-positive screening test results. There are no reliable noninvasive diagnostic tests for early stage disease, and clinically significant early stage cancer may not be grossly visible at the time of exploratory surgery (5). Consequently, it is likely that some patients will only be reassured that their abnormal test does not indicate the presence of cancer by having their ovaries and fallopian tubes surgically removed and examined microscopically. A very low false-positive test rate (i.e., a high PPV) is essential if we are to minimize unnecessary surgery and induction of premature menopause, with its long-term nonneoplastic complications related to cardiovascular and bone health.

Because interested readers may not have seen the corrected PPV, we felt it important to highlight its clinical consequences. A PPV of 6.5% implies that only 1 in 15 women with a positive test result will, in fact, have ovarian cancer. The remaining 14 women will have experienced false-positive test results. Thus, many women with a positive screening test will suffer needless anxiety and potentially morbid diagnostic procedures, including bilateral salpingo-oophorectomy. Based on these and additional reasons, the Society of Gynecologic Oncology has made the following recommendation:

"*After reviewing OvaSure's materials, it is our opinion that additional research is needed to validate the test's effectiveness before offering it to women outside of the context of a research study conducted with appropriate informed consent under the auspices of an institutional review board.*" (6).

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