Diagnostic Markers for Ovarian Cancer Screening: Not Ready for Routine Clinical Use

To the Editor: Given the number of women who are diagnosed with ovarian cancer each year (1) and the poor survival after diagnosis, the development of an effective screening method would clearly be of public health benefit. Therefore, the results of the study by Visintin et al. (2, 3) of a serum biomarker test for ovarian cancer with a reported sensitivity of 95.3% and a specificity of 99.4% have important potential. However, we think that more research is needed before the test is accepted into clinical practice for screening in the general population or for women at “high risk” of ovarian cancer.

The reported positive predictive value of >99% in the Visintin study (2) was much higher than would be expected, even in a high-risk screening population, because of the high percentage of ovarian cancer in the test population (43 of 224, 19%). Among women screened annually in the general population aged 50 and over, we estimate that the annual incidence of ovarian cancer is 0.036% (1). For women aged 20 and over who have two first-degree relatives with ovarian cancer, the incidence is estimated to be 0.266% (1).2 and for women aged 20 and over who have tested positive for BRCA1 or BRCA2, it is between 0.137% and 0.683% (1).2,3 By using incidence to approximate prevalence (4), we estimate that the positive predictive values for the test would be approximately 5.4%, 29.8%, and between 17.9% and 52.2%, respectively, for women in each of those groups.

Although the poor predictive values for previously proposed screening tests for ovarian cancer have raised concern that harms from diagnostic surgery for false-positive test results outweigh the benefits of early detection in women with true positive results (3), the positive predictive values we estimate for women with a strong family history or with BRCA-positive tests suggest that benefits in these populations may outweigh harms. This possibility is particularly important because the only clinical option recommended by the U.S. Preventive Services Task Force for women who test positive for BRCA is prophylactic oophorectomy.4 A valid and useful screening test could potentially allow those women to delay or avoid surgery. However, several issues need to be addressed with additional research before such a biomarker test is translated for routine use (6–9).

First, the clinical setting for using the test needs to be defined (7). The authors note the possibility of screening women who are at high risk, but neither the level of risk nor the factors and methods that would be used to determine risk are identified. The performance characteristics of the biomarker test will depend on the level of risk among women screened, and the methods of stratifying by risk and identifying eligible women must be effective for the biomarker test to be effective (10).3 Second, more information is needed on the analytic validity of the test, particularly in terms of reproducibility and quality assurance (7).

Additional research on the clinical validity of the test is also clearly needed (7). The sensitivity estimates in this report, based on clinically diagnosed disease, may be misleading because the case group consists of women with early- and late-stage diagnoses (5). With only 13 women with stage I ovarian cancer in the study, any sensitivity and specificity estimates for women with early-stage disease are imprecise, with wide confidence intervals around those estimates. Identifying early-stage cancer is important because surgery has been found to be effective in women with stage IA and stage IB moderately differentiated or well-differentiated cancers, whereas chances of recurrence are much higher for cancers of stage IC and above.5

A second point related to clinical validity of the test evaluated by Visintin et al. is that research suggests that women at high risk of hereditary cancers may be more likely to have ovarian cancers with a poorer prognosis than are women in the general population (11). In addition, research on previous screening technologies suggests that cancers detected by screening may be more likely to have clinicopathologic features with a better prognosis than cancers diagnosed clinically (11). Therefore, to obtain valid estimates of sensitivity, specificity, and predictive values for screening women at high risk, research may need to be conducted within the specified high-risk populations, not among women in the general population.

Finally, further research is likely needed to evaluate the overall clinical utility of the test (7, 9). Given complex relations among screen detection, risk, and clinicopathologic features of ovarian cancers (11), carefully conducted research may be required to determine the effectiveness of treatments for screen-detected cancers in high-risk women and determine the overall balance of benefits and harms of screening (7, 9).

Given these issues, we are concerned that it is premature to market a screening test based on this research6 to populations at high risk of ovarian cancer. This concern is heightened by the possibility that some very high-risk women (e.g., those who are BRCA positive) may choose an inadequately evaluated screening test for surveillance over a well-evaluated option like oophorectomy. Therefore, we agree with the recommendation of the Society of Gynecologic Oncologists and the Food and Drug Administration that additional research is needed to fully evaluate the test before it is offered to women outside the research setting (12).7

On a final note, we suggest that for a screening test to be recommended for routine use in clinical practice, rigorous, systematic evidence reviews with published methods are needed (7, 9) to determine what is known about the overall balance of harms and benefits of the tests. In addition, recommendations are likely to be more credible if they are made by third-party panels minimizing conflicts of interest (7, 9).

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References

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