Screening for Ovarian Cancer: What We Know, What We Need to Know

The majority of women with ovarian cancer present with advanced-stage disease. Women with early-stage ovarian cancer have a much better chance of achieving a cure than do women with late-stage disease. This

Dr. Hensley and colleagues have provided an excellent and thorough summary of the disappointing state of affairs surrounding early detection of ovarian cancer. They review imaging modalities and circulating biomarkers, and considering the low prevalence of the disease in the general population, they conclude that screening for ovarian cancer is not appropriate for women at usual risk. The authors caution physicians using currently available screening modalities for women at high risk of ovarian cancer to take care to educate patients about the limitations of these techniques. Moreover, they advise physicians to consider these limitations when weighing the various alternatives for managing ovarian cancer risk.

Circulating Molecular and Biochemical Markers

In their article, Dr. Hensley and colleagues call attention to the need for better markers of early ovarian cancer and improved means of identifying women at increased risk of developing the disease—all areas of current intensive investigation. Ongoing studies continue to evaluate various technical improvements in the sensitivity of transvaginal ultrasound, and early clinical trials are now assessing novel strategies for obtaining cells of ovarian origin for detailed analyses. The development and validation of circulating molecular and biochemical markers for the early detection of cancers, including ovarian cancers, are the focus of the recently established Early Detection Research Network (EDRN)—a consortium for collaborative research funded through the National Cancer Institute’s Division of Cancer Prevention. Investigator-initiated projects in the EDRN focus on the identification of novel biomarkers of early cancers and cancer risk. These biomarkers can undergo validation in designated and funded laboratories and clinical evaluation in characterized sample cohorts. The EDRN is intended to speed the evaluation of potential markers, as well as the process by which a new biomarker enters the clinical arena. Additional data are eagerly awaited on a particular marker, lysophosphatidic acid (LPA). Early reports suggest that this marker indicates the presence of early ovarian cancer—though concerns about specificity have been raised.[1,2] If this marker lives up to its early potential, it may lead Dr. Hensley and colleagues to revise their recommendations.

Genetic Testing for Breast and Ovarian Cancers

Women at highest risk for ovarian cancer are currently identified through their personal and family cancer histories, and increasingly, through genetic tests. Women with germ-line mutations in the BRCA1 and BRCA2 genes for the hereditary breast/ovarian cancer syndrome have the highest risks—20% to 40% for the BRCA1 gene and 10% to 20% for the BRCA2 gene.[3,4] Women with mutations in the mismatch repair genes associated with the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome are also at increased genetic risk, as are women carrying germ-line mutations in the RB1 gene.[5,6]

However, not all genes for hereditary ovarian cancer have been identified. Therefore, female members of families with multiple cases of ovarian cancer, breast and ovarian cancers, or HNPCC in whom no currently evaluable gene mutation has been identified would also be considered to be at increased risk for ovarian cancer, based on family history and the absence of useful genetic information.

Women with high ovarian cancer risk are those for whom improved screening strategies are most likely to be beneficial—and most urgently needed. However, only 5% to 10% of ovarian cancers are believed to have a strong hereditary component.[7] Therefore, while efforts continue to identify additional ovarian cancer susceptibility genes, it is also important to identify other significant risk
factors and to better evaluate exposures that have been questioned, such as infertility treatments.

**Oral Contraceptives as Chemopreventives**

Oral contraceptives have been shown to reduce ovarian cancer risk in the general population and among women with mutations in the *BRCA1* or *BRCA2* genes. As chemopreventive agents, oral contraceptives have the advantage of being acceptable to a large number of women and of providing a realistic intervention option for young women who wish to retain their fertility. Oral contraceptives are generally safe as well; however, there is concern that they may increase the competing risk of breast cancer among women with *BRCA1* and *BRCA2* mutations. The efficacy of oral contraceptives as ovarian cancer chemopreventives has not been specifically evaluated in other high-risk populations.

**Conundrum of Late-Stage Ovarian Cancer**

The urgency of the research agenda in ovarian cancer detection and prevention comes in part from the inadequacy of current therapeutic interventions against cancers that are most often detected in late stages. Despite the addition of platinum compounds and the taxanes to the therapeutic armamentarium in recent years, survival rates for advanced ovarian cancer remain poor. The particularly devastating, suffering death from advanced ovarian cancer is one consideration that led to consensus panel recommendations for prophylactic bilateral oophorectomy among women at high risk on the basis of familial or genetic factors at the completion of childbearing. Although the efficacy of the procedure at reducing the risk of ovarian cancer is increasingly demonstrated in ongoing studies, the challenges of hormone replacement therapies in these young women—many of whom also have increased breast cancer risk—cannot be minimized. The introduction of the laparoscopic procedure has reduced the risks for surgical recovery from oophorectomy, although the optimal components of the procedure (eg, should the fallopian tubes be included? how important are peritoneal washings?) have not been conclusively addressed. In general, surgical preventive strategies are too expensive and impractical for large-scale application, even among women with a single affected relative.

**Conclusions**

Dr. Hensley and colleagues conclude that ovarian cancer screening with currently available modalities cannot be recommended for the general population. However, they do cautiously endorse transvaginal sonography with or without Doppler and CA-125 measurement for women at high risk for the disease. They remind readers to perform these tests in the first 10 days of the menstrual cycle to minimize the problem of false-positive results due to ovulation. Concerns about false-positive elevations in CA-125 have led several groups to defer use of the biomarker until after menopause.

The authors appropriately encourage the enrollment of high-risk women into prospective trials of current modalities, to clarify the many remaining questions about managing ovarian cancer risk. The development of improved screening modalities for women at usual and high risk is among the priorities of a multifaceted ovarian cancer research agenda. Early-stage ovarian cancer is a curable disease. A screening strategy that could reliably identify women with early disease would be a major advance in this challenging field.

**References:**


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