

VIEWPOINT

Evolving Approaches in Research and Care for Ovarian Cancers

A Report From the National Academies of Sciences, Engineering, and Medicine

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Most women with ovarian cancer present at an advanced stage, when the case-fatality rate is high. Approximately 22 280 women are diagnosed with ovarian cancer in the United States each year; 60% are classified as advanced stage, and the overall 5-year survival for these women is 28%.¹ Reliable approaches for early detection of ovarian cancer have thus far been difficult to establish. The recently released report from the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine Committee on the State of the Science in Ovarian Cancer Research, titled *Ovarian Cancers: Evolving Paradigms in Research and Care*,² highlights key gaps in the evidence base of ovarian cancer research and underscores opportunities that could affect many women. This congressionally mandated report, sponsored by the Centers for Disease Control and Prevention, has its origins in the Gynecologic Cancer Education and Awareness Act—more commonly known as Johanna's Law, named for Johanna Silver Gordon, a schoolteacher who died of ovarian cancer.

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This report emphasizes the latest knowledge in research and recommends approaches that will benefit the outcome of women with or at risk for ovarian cancer.

Ovarian Cancer Is Not One Disease

Recent evidence suggests that most ovarian cancers do not arise in the ovary, as had been thought for decades.³ Instead, the most common and aggressive form of ovarian cancer, high-grade serous carcinoma (HGSC), is now thought to arise predominantly in the distal end of the fallopian tube.⁴ Other forms of ovarian cancer, including endometrioid, clear cell, and low-grade serous, likely arise from different sites and cells of origin including ovarian cysts and endometriosis, emphasizing the heterogeneity involved in the etiology

and risk of ovarian cancer. Until this time, clinicians and researchers have combined these varied subtypes of ovarian cancer into one disease, which has further complicated efforts toward understanding basic biology, prevention, and treatment. The Academies' committee recommends that research should account for the varied types of ovarian cancer and that a high priority should be given to the elucidation of the origins and pathogenesis of each subtype. To help reach this goal, classification schemes should reflect the morphologic and molecular heterogeneity of ovarian cancers, and standardized taxonomy should be widely adopted. To achieve this consensus, multiple stakeholders will need to address these complex issues in a collaborative, iterative, and dynamic process.

A Call for Expanded Screening and Prevention Research

To date, combined-modality screening with the CA-125 tumor marker and transvaginal ultrasonography have not been able to reliably detect ovarian cancer at early stages, when cure rates are remarkably high. The largest and recently reported screening trial from the United Kingdom (UKCTOCS) involved 202 638 women and used multimodality screening (MMS) with an algorithm to assess increases in CA-125 levels, which served as a trigger for transvaginal sonography as a secondary screen for abnormal biomarker results.⁵

This approach resulted in fewer unnecessary operations than sonography alone (2 per cancer diagnosed in the MMS group vs 10 in the sonography group) and a downstaging of disease with an increase in the detection of early-stage ovarian cancer (40% vs 24%). The 15% relative reduction in mortality seen in the MMS group and 11% in the sonography group were not significantly different than no screening in the primary analysis based on mortality rates of 0.29%, 0.30%, and 0.34% for the MMS, sonography, and no screening groups, respectively. The data suggested that most of the benefits of screening would occur between 7 and 14 years after initiation. Approximately 640 women would need to be screened annually for nearly 14 years to prevent 1 death from ovarian cancer. Further follow-up will be needed before definitive conclusions can be made regarding the efficacy of this approach to screening. Therefore, the committee recommended that future strategies should extend be-

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yond the current biomarkers and imaging modalities to reflect the pathobiology of each ovarian cancer subtype.

For more than 2 decades, it has been known that germline mutations in *BRCA1* and *BRCA2* are associated with an increased risk of breast and ovarian cancers. Professional societies and other organizations recommend that all women with invasive ovarian cancer undergo genetic testing for mutations in these genes. The primary purpose of this genetic testing is to identify unaffected family members who may be at increased risk for ovarian cancer and could use preventive measures such as risk-reducing surgery or chemoprevention to decrease the risk of developing the disease. Secondly, test results may help to stratify patients for newer targeted treatment approaches such as PARP (poly [ADP-ribose] polymerase) inhibition. However, many women with HGSC do not receive genetic counseling or undergo genetic testing owing to lack of knowledge by patients and clinicians or complex and inconsistent referral criteria, preventing the full benefit of risk reduction to be realized at present. Innovative strategies should be developed to increase the uptake of genetic testing and to share results among other at-risk family members. New approaches for surgical (eg, salpingectomy) and nonsurgical risk reduction should also be developed and studied in the context of risk-benefit balance.

Treatments Should Be Standardized and Disseminated

Over several decades, standards of care have been defined for the treatment of advanced-stage HGSC that include initial primary cytoreductive surgery followed by combination cytotoxic chemotherapy, often delivered intraperitoneally for patients whose disease is completely resected. Although treatment consistent with accepted guidelines has been associated with improved outcomes, less than half of patients with HGSC receive this treatment.⁶ To ensure the consistent implementation of current standards of care, studies should be directed toward reducing disparities in health care delivery and outcomes. Since no single model will be applicable to all patients and health care settings, additional research will be required to determine the best timing and type of initial sur-

gery for newly diagnosed women, including the appropriate use of neoadjuvant chemotherapy approaches. In addition, a better understanding of the mechanisms of disease recurrence and drug resistance will be essential to improving patient outcome. Exciting recent data have now paved the way for more effective pharmacologic and nonpharmacologic therapies and combinations of therapies that consider the unique biology and clinical course of ovarian cancer.⁷ In particular, immunologic and molecularly driven approaches specific to the different ovarian cancer subtypes performed by interdisciplinary teams should lead to efficient and information-rich clinical studies. Owing to the relative rarity of ovarian cancer and the distinct biology of the various subtypes, it will be important to develop and support more robust collaborative consortia to assess these new therapies.

Throughout the disease course, women will require long-term active disease management through supportive care and self-management strategies. The committee recommends that research efforts be directed toward identifying factors that put patients at high risk for poor outcomes and overcoming barriers to the systematic assessment of psychosocial effects of disease and treatment. Furthermore, complex factors influence the adoption of research results into clinical care, including the transfer of knowledge to all appropriate stakeholder groups. Effort should be directed toward the rapid dissemination and implementation of evidence-based information and practices to patients, families, physicians and other health care professionals, and advocates, using existing and newly developed dissemination modalities.

Although progress has been made in understanding ovarian cancers, especially over the last decade, additional research focused on the origins and mechanisms of disease will help to shape current and future approaches to prevention, screening and early detection, and treatment. Improved communication among patients, physicians and other clinicians, and researchers is also needed to recognize ovarian cancer as a compendium of many types of cancer involving the ovary. These efforts will help reduce the burden of ovarian cancer and result in improved survivorship and survival.

ARTICLE INFORMATION

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