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SPECIAL SECTION

PATIENT-CENTERED RISK ASSESSMENT FOR OVARIAN CANCER: INDIVIDUALIZING YOUR APPROACH

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Ovarian cancer: Risk assessment and patient management in the prevention of morbidity and mortality

Until screening approaches with good predictive values for ovarian cancer in average-risk women are developed, clinicians must rely on risk evaluation and watch for relevant signs and symptoms that require strategic follow-up testing

Neal M. Lonky, MD, MPH

In medicine, specifically gynecology, we are accustomed to a "screen, triage, and treat" secondary cancer prevention approach. The advent of the Pap smear, the subsequent discovery of the role of human papilloma virus (HPV) (and importantly its often-treatable precursors) testing in assessing risk for cervical cancer, health care access improvements (due to the myriad of insurance vehicles), and acceptable therapies for precursors and cancer have led to a dramatic reduction in cervical cancer incidence and mortality in industrialized countries.[1] Begun in the mid-20th century, this progress continues today.

HPV vaccine: A quantum leap in cancer prevention

HPV vaccination as primary prevention is a major breakthrough. With vaccination, a viral precursor can be immunologically blocked from causing carcinogenesis for the most prevalent HPV strains. This reduces not only cancer but also precursors and benign condyloma, which drain the health care economy for access to diagnosis and therapy in what I call the "revolving door of lower genital tract precursor emergence and regression."

HPV vaccination has not reached a desired rate in the United States due to social mores and other barriers to acceptance that deserve attention in a separate article. Where does that leave us when women present with concerning symptoms or family history and want impactful care that could potentially save their life? We should refocus our mind-set from screening, triage, and treatment to risk assessment and reduction of cancer sequelae. More importantly, we must educate women that the efforts that work for one cancer do not work for another cancer.

Dr. Lonky reports that he has received grant or research support from Merck & Co.

The conundrum of ovarian cancer detection

The American College of Obstetricians and Gynecologists' patient education page on ovarian cancer states that unlike the Pap test for cervical cancer and colonoscopy for colon cancer, there currently is no screening test to detect ovarian cancer in asymptomatic women.[2]

Ideally, a screening test should be able to detect ovarian cancer in, preferably, an early treatable stage. In fact, however, when average-risk women undergo screening—such as with transvaginal ultrasonography or a cancer antigen 125 (CA 125) test—many of those with abnormal results may undergo unnecessary surgery and experience resultant potential harm.[3] The potential harm outweighs the preventive utility in average-risk women.

This leaves the gynecologist to detect cancer at an early treatable stage or to tertiary prevention of mortality (not the cancer itself) from ovarian cancer. Beginning with clinical history and physical examination findings, some cases receive relevant triage ultrasonography and serum-based surveillance tests.

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With the advent of biomarkers revealing genetic risk factors, patients identified with mutations such as the *BRCA* gene or Lynch syndrome are offered adjunct surveillance with ultrasonography and other modalities to amplify the screening predictive value, because the disease prevalence in these groups improves the overall value of interventions.[4] This is where confusion may occur: the use of testing in screening versus in triage following a clinically identified relevant risk factor.

Fine-tuning ovarian cancer risk assessment

Sadly, since we do not have a primary prevention modality, like a vaccine, for ovarian cancer, we are left to find this cancer early instead of at a treatable precancerous stage. It is possible that, soon, we may have more powerful screening tests (high *negative* predictive value) and triage tools (high *positive* predictive value) to identify women at risk and avoid unnecessary surgeries.

We evaluate the challenges and opportunities of assessing risk for ovarian cancer in various patient scenarios in the roundtable discussion on page SS7, featuring Drs. Leslie Randall, Jason Wright, and Devansu Tewari. In addition, on page SS5, Dr. Jeanine Genkinger describes the epidemiology of ovarian cancer and explores the risks associated with gene mutations and risk assessment models. ■

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Ovarian cancer epidemiology for the practicing gynecologist

A targeted, 2-tiered approach to identify and monitor women at high risk for ovarian cancer holds promise for reducing false-positive results and improving mortality

Jeanine M. Genkinger, PhD, MHS

Ovarian cancer is considered a rare, but highly fatal, cancer unless it is detected early. In 2017, an estimated 22,440 cases of ovarian cancer occurred in the United States.[1] The most common (60%) and aggressive type of epithelial ovarian cancer is the high-grade serous type.[2] Overall, only 44% of women diagnosed with ovarian cancer survive more than 5 years post-diagnosis.[3,4] Yet, when ovarian cancer is detected at a localized stage (15% of cases), the 5-year survival rate is 94%.[3,4]

A number of reasons exist for the late diagnosis and high fatality rate, including few known modifiable risk factors, no effective screening tools, and lack of early diagnostic symptoms unique to ovarian cancer. Thus, approaches to prevent disease or identify it at earlier stages are critical to reduce the morbidity and mortality of this deadly disease.

Genetic and reproductive risk factors

Identifying known risk factors for ovarian cancer is crucial for early detection and risk assessment. Women with mutations in the *BRCA1* or *BRCA2* gene are at a much higher risk for developing ovarian cancer (16%–68% for *BRCA1* and 11%–27% for *BRCA2*).[5–16] Yet, a continuum of risk exists even for women with the same mutation, which contributes to difficulty in clinical decision making.

Women with a family history only have a much higher risk of ovarian cancer than the general population[17] such that having 1 affected first-degree relative increases a woman's risk 3-fold, and having multiple affected relatives increases a woman's risk 11-fold.[18]

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However, family history and/or genetic predisposition[19] accounts only for 5% to 10% of cases.[19,20] The majority of other risk factors for ovarian cancer are reproductive: older age at menarche, menopausal hormone use, and endometriosis.[21,22] By contrast, tubal ligation and oral contraceptive (OC) use are estimated to lower ovarian cancer risk by 30% to 50%, and parity, breastfeeding, and hysterectomy are additional known or suspected preventive factors.[23–28]

Risk assessment model utility

Currently, validated risk assessment models that integrate established risk factors exist for primary prevention. The Rosner model includes age at menopause, age at menarche, OC use, and tubal ligation; the concordance statistic (area under the receiver operator curve [AUC]) is 0.60.[29] The Pfeiffer model includes OC use, menopausal hormone therapy use, and family history of breast or ovarian cancer, with a discriminatory power of 0.59.[30] The Ovarian Cancer Association Consortium model includes 17 risk factors and 17 genome-wide significant single nucleotide polymorphisms (*BRCA1* and *BRCA2* mutations were not included); the AUC increased only to 0.66.[31] Due to their modest discriminatory power, these models have limited screening potential.[30]

Screening provides no mortality benefit

Currently, the US Preventive Services Task Force does not recommend screening for ovarian cancer.[32] Findings from recent large clinical trials of serum cancer antigen 125 (CA 125) and transvaginal ultrasonography demonstrated that these screening

modalities do not confer a benefit for mortality.[33–35] In fact, in the intervention arm participants had increased false-positive results, with at least 1 serious complication and/or adverse event.[33–35]

The major concern regarding CA 125 is that it may not be specific enough to ovarian cancer; in fact, CA 125 is elevated in benign conditions, such as pregnancy and menstruation, and is expressed in only about half of early-stage ovarian cancers.[36,37]

Targeted screening in high-risk patients has potential

These previous studies examining screening approaches were employed in average-risk women and may not represent the findings from a targeted approach in high-risk women. In the future, one suggestion for improved screening is a 2-tiered approach in which risk assessment models are used to identify high-risk women, who are then targeted for screening with a panel of markers that represent pathways to disease. This combined approach may reduce false-positives and improve mortality compared with using risk assessment or screening alone. Recent modeling supports this approach as effective for other diseases, such as breast cancer.[38–40] ■

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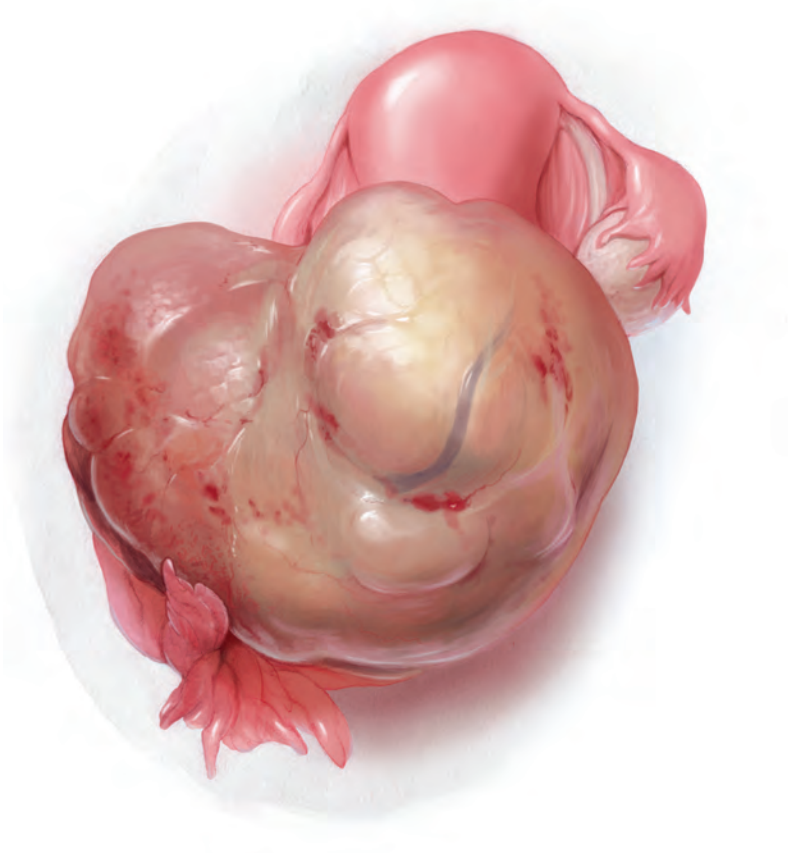
ROUNDTABLE

Optimal risk assessment and management of the potential ovarian cancer case

Expert guidance on individualizing an assessment approach for the patient at risk for ovarian cancer

Expert panel featuring Neal M. Lonky, MD, MPH, moderator; with Leslie M. Randall, MD; Devansu Tewari, MD; and Jason D. Wright, MD

In this roundtable discussion moderated by OBG Management Contributing Editor Neal M. Lonky, MD, MPH, 3 leading gynecologic oncologists use a case-based approach to discuss their strategies for assessing patients at risk for ovarian cancer. Considerations include patient age, history, genetic profile, and symptoms.



Assessing the premenopausal high-risk patient with positive family history, genetic concerns

Neal M. Lonky, MD, MPH: Your patient is at high risk for ovarian cancer due to a strong family history or genomic concerns. She is premenopausal and has no symptoms. What overall management approach would you take for this patient?

Leslie M. Randall, MD: For women with true genomic concerns, prevention is far preferred to surveillance. The specific high-risk genes are *BRCA1, BRCA2, RAD51C, RAD51D*, and *BRIP1,* plus Lynch syndrome (*MLH1, MSH2, MSH6, PMS1*, and *EpCAM*), and the minimum surgery for these women is a risk-reducing salpingo-oophorectomy (RRSO). RRSO is recommended between 30 and 35 years of age for *BRCA1* mutation carriers, and between 40 and 45 years for carriers of the other mutations listed, regardless of menopausal status. This is true for all age groups and in both symptomatic and asymptomatic patients.

If women have undiagnosed but suspected genetic mutations, they should be referred for genetic counseling and possible testing based on established criteria. Until better screening modalities are available, identifying these women for RRSO is our best method for improving ovarian cancer

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mortality. Screening, however, can be considered for mutation carriers who do not meet these age criteria, desire future childbearing, or are not yet willing to undergo RRSO, as well as for women with a strong family history who test negative for mutations in these genes.

There is no current standard recommendation for screening, but clinicians can start by educating patients regarding the symptoms of ovarian cancer and performing an annual pelvic examination. Further testing protocols include at least a yearly transvaginal ultrasound scan and a serum cancer antigen 125 (CA 125) test. This approach was not successful in the general population as reported by the Prostate, Lung, Colorectal and Ovarian (PLCO) screening project.[1] Screen-detected cancers in the PLCO were predominantly diagnosed in stages III or IV, and at the expense of false-positive results attributable to ultrasound findings that prompted unnecessary surgeries and subsequent complications.

An alternative strategy of reserving ultrasonography for women with a rising annual CA 125 level (termed "multimodal screening") was studied in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKTOCS).[2] While multimodal screening was associated with less unnecessary surgery, cancers were still diagnosed at an advanced stage. There was a trend for mortality reduction, however, for women who had normal screening for the initial 7 to 14 years of monitoring.

Finally, a third approach, the Risk of Ovarian Cancer Algorithm (ROCA), also employs a mathematical CA 125 trend model with increased frequency (measurement of CA 125 every 3 months).[3] In the high-risk, genomic concern population, this strategy showed improved sensitivity for early stage disease compared with historical methods, even before the CA 125 level was greater than 35 U/mL. The ROCA, however, requires further study in a larger cohort before it can be accepted as standard of care.

Jason D. Wright, MD: Appropriate risk assessment typically is the first step when considering screening for ovarian cancer. Women with a personal or family history of breast and ovarian cancer should undergo genetic counseling. For those who meet the criteria for genetic testing, testing for deleterious mutations of the *BRCA1* and *BRCA2* genes can be performed. Women with a *BRCA* mutation are considered at high risk and warrant heightened surveillance and consideration of risk-reducing surgery.

Many commercially available genetic tests now evaluate a panel of genes in addition to *BRCA1* and *BRCA2*. While those genes are associated with ovarian cancer, the risk is generally lower than that associated with *BRCA1* and *BRCA2*. Data on how best to manage patients with abnormalities in these lower-penetrance genes are more limited.

For a premenopausal woman who has not completed childbearing, transvaginal ultrasonography with serum CA 125 testing can be considered. The National Comprehensive Cancer Network currently endorses such screening in women with a *BRCA1* or *BRCA2* mutation starting at age 30 to 35 years.[4] It should be noted that the benefit of such screening is uncertain, and screening has not been shown to reduce mortality in these women. The frequency of screening is at the discretion of the clinician, but it is often performed at an interval of every 6 months.

Devansu Tewari, MD: The most important thing always to consider in someone presumed to have a high risk of ovarian cancer is the accuracy of their family history. Clearly a first-degree relative, such as a mother, daughter, or sister with ovarian cancer, or someone who has tested positive for a genetic mutation needs to be confirmed.

If the patient is considered at high risk based on family history alone, a referral to a geneticist is warranted to determine if testing is needed. Unfortunately, screening opportunities—other than routine gynecologic examinations—outside of a clinical trial are limited.

The postmenopausal high-risk patient with no symptoms of ovarian cancer

Dr. Lonky: What is your approach for a postmenopausal patient who has no symptoms?

Dr. Randall: My approach in the asymptomatic, postmenopausal patient is much like that for the premenopausal one: RRSO for known genetic mutation carriers, genetic testing for potential carriers, and the option to use ultrasound and CA 125 monitoring in the rest.

In women with significant family history (ovarian cancer in more than 1 first-degree relative), RRSO might be considered in those who are medically fit for surgery. Hysterectomy could be

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OVA1, combined with clinical assessment, has a 98% NPV providing a better pathway for managing potential malignancy in pelvic masses[1]

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Pelvic Mass on Ultrasound

Indicates Malignant

Cyst >10cm, papillary or solid components, irregularity, presence of ascites, high color Doppler flow.

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considered for women with indications such as high-grade cervical dysplasia, postmenopausal bleeding, or the need for tamoxifen therapy.[5] In addition, women with *BRCA1* mutations might be at higher risk for serous uterine cancers, and this should be discussed during surgical planning for RRSO.[6] Hysterectomy increases the risks of surgery, but these risks can be minimized by using a minimally invasive surgical approach.

Dr. Wright: Postmenopausal women with a *BRCA* mutation who have not undergone oophorectomy should strongly consider prophylactic RRSO. RRSO typically is recommended between the ages of 35 and 40 after the completion of childbearing. Since women with *BRCA2* mutations have later onset of ovarian cancer, RRSO can be delayed until 40 to 45 years of age in these patients.

Dr. Tewari: An asymptomatic patient without a genetic mutation should undergo routine annual gynecologic examinations. Screening outside of a clinical trial is not recommended. Women carrying a known genetic mutation, such as a *BRCA1* or *BRCA2* mutation, should have undergone risk-reducing surgery to remove the tubes and ovaries; those who have not already had RRSO should be counseled to do so. The issue related to hysterectomy needs to be discussed with these patients, given studies showing increased rates of uterine papillary serous cancers,[6] and if a personal history of breast cancer exists this may need to be factored in as well.

Suspicious symptoms in a premenopausal high-risk patient

Dr. Lonky: Please describe your management approach for a premenopausal patient who has current symptoms.

Dr. Randall: According to Goff and colleagues, symptoms that are concerning for ovarian cancer include pelvic and abdominal pain, urinary urgency and/or frequency, increased abdominal size and bloating, and early satiety present for less than 1 year and occurring more than 12 days per month.[7] Although not always specific to ovarian cancer, the presence of these symptoms increases the performance of diagnostic testing.

Dr. Wright: Yes, clinicians should have a heightened suspicion in women who have persistent symptoms that have been associated with ovarian cancer. This is particularly true for high-risk women with a *BRCA* mutation or those with a family history of ovarian cancer. These patients should undergo pelvic examination, transvaginal ultrasonography, and assessment of serum CA 125.

Dr. Randall: For these women, I start with abdominal and pelvic examinations, followed by abdominal and vaginal ultrasound with serum markers based on the presence and appearance of a pelvic mass. If the mass is large (>10 cm) and/or complex, in this age group I consider tumors of both epithelial and nonepithelial ovarian origin, in addition to colorectal cancer, and perform tests for CA 125, carcinoembryonic antigen (CEA), germ cell markers (lactate dehydrogenase [LDH], human chorionic gonadotropin [hCG], alpha-fetoprotein [AFP]), and sex cord/stromal markers (inhibin B and testosterone).

Large masses will need to be managed surgically, and unless they appear purely simple on ultrasound and all serum markers are normal, these should be managed by a gynecologic oncologist, especially in the setting of genomic concerns. If imaging shows a smaller mass or ascites alone, CA 125 and CEA typically are adequate markers, and the patient should be referred for gynecologic oncology evaluation and consideration for surgery. Benign diagnoses, such as endometriosis, pelvic abscess, and ectopic pregnancy, should not be excluded in this age group for fear of cancer.

Dr. Tewari: Any symptoms such as worsening abdominal or pelvic pain, bloating, urinary frequency, or gastrointestinal changes that do not improve should trigger a gynecologic examination followed by a transvaginal ultrasound to rule out a pelvic mass. If the patient carries a genetic mutation, I would include a CA 125 test to correlate with the imaging findings.

For known *BRCA1* and *BRCA2* genetic carriers, I would recommend prophylactic removal of both the tubes and the ovaries if childbearing has been completed (ages 35 to 40 years), and I would consider extending the age limit into the mid-40s for *BRCA2* carriers, given the later age of presentation.

Suspicious symptoms in a postmenopausal high-risk patient

Dr. Lonky: And how would you manage a postmenopausal patient who reports having current symptoms?

Dr. Tewari: I would follow the same approach for a symptomatic postmenopausal patient as for a premenopausal patient.

Dr. Wright: I agree. As with symptomatic premenopausal patients, we should be suspicious of ovarian cancer–related persistent symptoms in postmenopausal women, especially high-risk women who have a *BRCA* mutation or family history of ovarian cancer. Pelvic examination, transvaginal ultrasonography, and assessment of serum CA 125 are warranted.

Dr. Randall: I would mention that, in postmenopausal women, the risk of malignancy is greater for epithelial ovarian and nongynecologic primaries, such as colon and breast cancer. In addition, the risk for germ cell tumors is much lower than in premenopausal women, and that for sex cord stromal tumors is somewhat equivocal. Therefore, patients should have up-to-date breast and colon screening, and serum studies can be limited to CA 125 and CEA. In these patients, the threshold for gynecologic oncology referral and surgical evaluation should be low.

The premenopausal average-risk woman with symptoms

Dr. Lonky: Consider a woman at average risk for ovarian cancer who is premenopausal and has current symptoms. Please describe your management approach for this patient.

Dr. Wright: While ovarian cancer is often considered the "silent killer," some symptoms have been associated with ovarian cancer. As mentioned, women with ovarian cancer frequently describe symptoms of abdominal and pelvic pain, early satiety, bloating, and urinary urgency and frequency. Although these symptoms are common in the general population, women with ovarian cancer tend to experience them more frequently as well as persistently. An ovarian cancer symptom index has been developed; it includes pelvic and abdominal pain, urinary urgency and frequency, increased abdominal size, bloating, and difficulty eating or feeling full, with symptoms present for less than 1 year and for more than 12 days per month. While some studies have found that these symptoms are useful in detecting ovarian cancer, others have questioned the overall value of symptomatology.

Patients and clinicians should have a heightened suspicion for ovarian cancer when these symptoms are noted. When they do occur, evaluation can include pelvic and rectovaginal examination along with transvaginal ultrasound and measurement of serum CA 125. CA 125 is a nonspecific marker and is often elevated, particularly in premenopausal women. If the results of these tests raise concern for ovarian cancer, patients should be referred to a gynecologic oncologist or a physician with expertise in the diagnosis and management of ovarian cancer.

Dr. Randall: In this age group, other markers, such as human epididymis protein 4 (HE4) and a multivariate index assay (OVA1), might be helpful. HE4 is especially helpful when an elevated CA 125 is likely due to benign disease, such as endometriosis, adenomyosis, or leiomyomata. In these cases, HE4 is much less likely to be falsely elevated, and the Risk of Malignancy Algorithm (ROMA) can be used to calculate risk, but the HE4 level alone is sufficient to triage benign from malignant masses in low-risk patients.[8,9] OVA1 can be used to assist in the triage of pelvic masses planned for surgery due to size or symptomatology to benign gynecologic or gynecologic oncology surgeons. Of note, if the CA 125 is elevated, OVA1 also will be elevated and therefore less helpful than in cases where the CA 125 is normal.

Dr. Tewari: Without an abnormal finding on imaging, I would not order a CA 125 test given the high false-positive rate. If a mass is identified, its clinical features would determine if a CA 125 test is warranted as well as the next steps in surgical management.

Dr. Randall: Fortunately, premenopausal women at average risk for ovarian cancer typically have benign diagnoses, even when they are symptomatic. I would perform the same evaluation as in the high-risk patient, but I would have a higher threshold to suspect cancer, to refer to oncology, and to recommend or perform immediate surgical intervention.

The postmenopausal average-risk woman with symptoms

Dr. Lonky: Your average-risk patient is postmenopausal and has current symptoms. What is your management approach?

Dr. Randall: The approach in this age group is the same as that for the average-risk premenopausal

patient with symptoms, but cancer diagnoses including ovarian, endometrial, colon, or metastatic breast cancer are higher on the differential. Again, up-to-date breast and colon screening, endometrial biopsy for postmenopausal bleeding and abnormal uterine lining thickness, ultrasonography, and serum markers are the mainstays for evaluation.

Pre- and postmenopausal average-risk patients with no symptoms

Dr. Lonky: What is your approach for women who are at average risk for ovarian cancer and have no symptoms—whether they are premenopausal or postmenopausal?

Dr. Wright: Among average-risk women—whether they are premenopausal or postmenopausal—routine screening for ovarian cancer is not recommended. Overall, the prevalence of ovarian cancer in the general population is low. Therefore, even screening tests with a high specificity have a low predictive value for the detection of ovarian cancer, and they require evaluating a large number of women without cancer. This is problematic for ovarian cancer—which requires that women undergo surgery to diagnose a cancer.

Two large screening trials, one in the United States and one in the United Kingdom, evaluated the utility of screening average-risk women with CA 125 and transvaginal ultrasonography for the detection of ovarian cancer.[1,2] Neither trial was able to demonstrate a reduction in mortality with screening. Both trials noted that a significant number of women require surgical intervention to detect 1 case of ovarian cancer, and that surgery was associated with significant morbidity. Based on these data, the US Preventive Services Task Force considers the harms of screening to outweigh the benefits and classifies ovarian cancer screening as category D.

Dr. Randall: I agree, as shown in the PLCO and UKTOCS trials, the harms of screening currently outweigh any benefit.[1,2] Therefore, aside from screening for indications for genetic testing, I do not recommend any special testing in these age groups.

Dr. Tewari: The annual gynecologic examination gives ObGyns an opportunity to ask about symptoms that may be suggestive of ovarian cancer.

Other considerations

Dr. Lonky: Are there any other special case concerns to discuss?

Dr. Tewari: A lot of focus has centered around screening, which ignores the evidence for warranting increased symptom awareness. We need to convey to women the need to be aware of ovarian cancer symptoms, especially those listed in the ovarian cancer symptom index. Use of the symptom index has been associated with identifying the disease at earlier stages, which is important because that is when response and cure rates are higher.

Dr. Randall: I would like to mention additional imaging. Computerized tomography (CT) and magnetic resonance imaging (MRI) should be reserved for cases with abnormal ultrasound findings. CT with intravenous contrast has poor sensitivity for soft-tissue definition and is best employed to detect ascites, retroperitoneal lymphadenopathy, peritoneal carcinomatosis, and gastrointestinal or urinary tract obstruction. T2-weighted MRI with gadolinium contrast has excellent soft-tissue resolution and can be particularly helpful to differentiate ovarian and uterine masses in premenopausal women faced with surgery who desire to retain fertility.

Advanced imaging techniques, such as positron emission tomography (PET), increase costs significantly and often do not change management beyond that derived from CT or MRI studies. Therefore, PET should not be used routinely in the workup of these women.

Dr. Wright: Similar to liquid biopsies, there is interest in detecting ovarian cancer cells that are exfoliated through the lower genital tract. These cells could be obtained in a manner that is similar to collecting a specimen for a Pap test. A technology currently being developed by PapGene Inc uses cells collected from the cervix and examines them for molecular abnormalities. A pilot study found that the test identified 9 of 22 (41%) ovarian cancers. These types of tests are currently being evaluated as a potential modality to aid in the detection of ovarian cancer.

Dr. Lonky: Please explain what liquid biopsies are and how can they be used in gynecology.

Dr. Wright: Liquid biopsy is a test in which a blood sample is collected and analyzed to look for tumor cells. The hope with liquid biopsies is that ovarian cancer could be detected at an earlier

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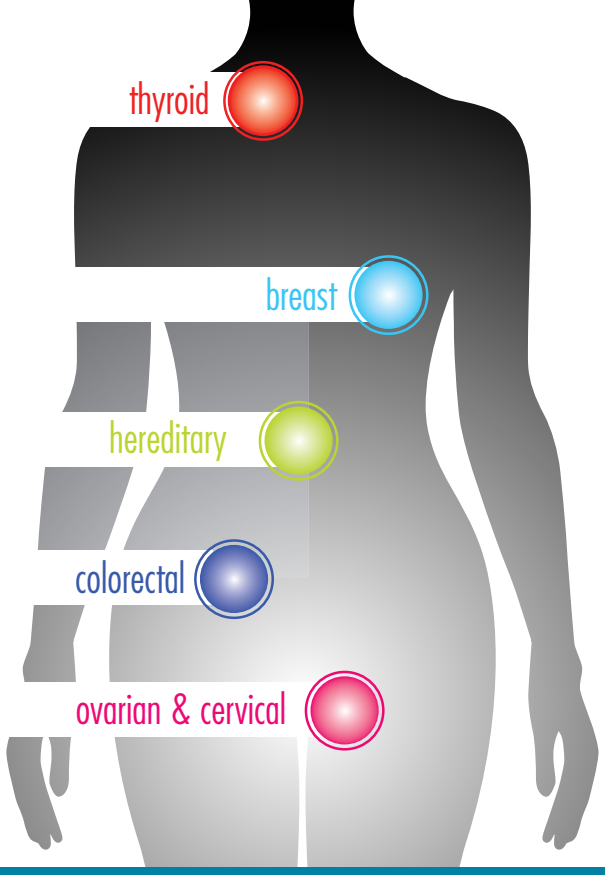

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stage. Liquid biopsy requires that tumor cells are present in the bloodstream and that these cells have molecular abnormalities that can be used to distinguish the tumor cells from normal cells. There currently are several promising technologies available, and many are undergoing testing and evaluation. At present, this is not a test that is used routinely in practice.

Dr. Tewari: Yes, they are the newest wave in next-generation sequencing. With no effective screening strategies for ovarian cancer to date, liquid biopsies serve as a potential future option. Although the technology of next-generation sequencing is improving by the minute, its role in gynecologic cancers at this time is more one of potential and promise than widespread acceptance. However, that day may not be far off as more and more studies are showing successful comparisons.

Dr. Randall: Liquid biopsies are attractive because not only do they save the patient the inconvenience, risk, and cost of a surgical or CT-guided percutaneous biopsy but also they are associated with a very quick turnaround time (days versus 3 to 4 weeks for tissue biopsy) for timely clinical decision making. If better markers of early stage gynecologic cancers of all types are validated, this technique has significant potential for screening, diagnosis, and monitoring of response to therapy. ■

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