ABSTRACT

Although BRCA1 and BRCA2 pathogenic or likely pathogenic variants are a well-established cause of hereditary ovarian cancer, recent studies have brought other homologous recombination repair pathway genes into the limelight. The current NCCN Guidelines reflect the most up-to-date, evidence-based data relating to the risk management of patients who are carriers of BRCA1/2 and/or other variants. Risk-reducing bilateral salpingo-oophorectomy is the current standard of care, but a recommendation for salpingectomy alone may be on the horizon.

“BRCA1 and BRCA2 [pathogenic or likely pathogenic variants] are the most common cause of hereditary ovarian cancer, but...in the past several years, we have learned a lot more about the other genetic contributions,” commented Leigha Senter, MS, CGC, Professor, Clinical Internal Medicine; Associate Director, Division of Human Genetics, The Ohio State University, and member of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Panel for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. At the NCCN 2023 Annual Conference, she discussed the current variants of concern, testing principles, and risk management strategies for hereditary ovarian cancer.

BRCA-Related Ovarian Cancer

“We know, and have known for a long time, that pathogenic and likely pathogenic variants in BRCA1 and BRCA2 are the most common cause of hereditary ovarian cancer,” Ms. Senter remarked. Individuals with a family or personal history of multiple cases of early-onset breast cancer, ovarian cancer, breast and ovarian cancers in the same individual, bilateral breast cancer, male breast cancer, pancreatic cancer, and/or prostate cancer may be at a higher risk for hereditary breast and ovarian cancer syndrome.

“For a long time, professional organizations, including NCCN, have recommended that all patients diagnosed with ovarian cancer be offered genetic counseling and testing to include BRCA1 and BRCA2 at minimum,” she remarked. “Those endorsements continue to be made by [other] professional organizations, including the Society of Gynecologic Oncology and ASCO.”

Implementation of these recommendations, however, seems to have fallen short in clinical practice. According to Ms. Senter, some studies have shown that fewer than half of patients diagnosed with ovarian cancer are offered testing or have it performed. Lack of physician referral, minimal access to clinical genetic services, lack of perceived benefit, worry about insurability or cost, and disease-related burden have been found to hamper genetic evaluation efforts. Some of the studies have shown really effective ways of getting around these barriers,” she commented. “Although barriers to treatment are all different, a lot of them come back to the fact that we need to make [obtaining testing] easier for patients, [establish it as] part of their routine clinical care, and meet patients where they are.”

Histologic data suggested that although some cases of epithelial ovarian cancer may be classified as endometrioid (BRCA-related, 14%; sporadic, 13%) or clear cell (2% vs 7%, respectively), more than half (68% vs 60%) are of the serous subtype. Of note, mucinous histology was observed in none of BRCA-related ovarian cancers compared with 5% of those with sporadic origin—this trend has been observed in subsequent studies, further highlighting the rarity of the mucinous subtype in patients harboring variants of the BRCA gene.

Some of the earliest studies of BRCA-related risk demonstrated an increase in the likelihood of developing cancer among those harboring variants of this gene. However, as more families were tested and followed, clinicians gained a more refined understanding of the risks associated with the different types of BRCA variants. Two recent large analyses, in particular, have produced a robust analysis of the likelihood of developing ovarian cancer with BRCA1 versus BRCA2 variants.

There are also published data describing the age-related risk of ovarian cancer in individuals with BRCA pathogenic variants. A longitudinal cohort study of patients who developed ovarian cancer after enrollment showed that
8 who harbored a BRCA1 variant and 0 with a BRCA2 variant were diagnosed with ovarian cancer at age <40 years. This study and others have allowed us to better refine the risk-reduction recommendations regarding BRCA1 and BRCA2 [variant] carriers,” Ms. Senter remarked. “It has allowed for BRCA2 [variant] carriers to potentially delay the timing of risk-reducing surgery.”

**Beyond BRCA: Other Pathologic or Likely Pathologic Variants**

Although BRCA1 and BRCA2 variants are established as the most common hereditary cause of ovarian cancer, other genetic factors have been found to contribute to its development. An analysis by Couch et al also demonstrated that 18% of patients with ovarian cancer who underwent next-generation sequencing harbored pathologic germline variants. Of this population, 15% had BRCA1/2 alterations, 3% had non-BRCA homologous recombination repair pathway gene alterations (BRIP1, RAD51C, RAD51D, PALB2, and BARD1), and 0.4% had mismatch repair gene alterations.

“Over the past 5 to 10 years, we have learned a lot more about what having a mutation in one of these [non-BRCA homologous recombination repair pathway] genes means,” commented Ms. Senter. “We continue to learn about the lifetime risk.” She added that “the recommendations for consideration or actually doing the surgery to reduce ovarian cancer risk have also evolved over time.”

She noted that, although the NCCN Guidelines have been updated to recommend risk-reducing surgery for patients with certain non-BRCA variants of homologous recombination repair pathway genes, this intervention may not be appropriate in some cases. Clinicians should weigh the potential trade-offs of premature menopause versus likelihood of developing ovarian cancer prior to making surgical decisions.

**Risk-Reducing Surgery for BRCA Pathologic or Likely Pathologic Variant Carriers**

“The reason we have to rely on risk-reducing surgery is that ovarian cancer screening is not standard and not typically relied upon,” Ms. Senter remarked. “The standard is risk-reducing bilateral salpingo-oophorectomy at this time.”

Results from a meta-analysis have demonstrated that BRCA variant carriers who underwent salpingo-oophorectomy appear to have a significantly reduced risk of developing ovarian cancer. These efficacy data support the NCCN Guidelines recommendation of this intervention for patients with BRCA variants between the ages of 35 and 40 years; however, in some cases, those harboring BRCA2 variants may delay surgery until they are between the ages of 40 and 45 years (Figure 1).1

Although undergoing concurrent surgery is a personal choice, according to Ms. Senter it is important to keep in mind that serial sectioning of the ovaries should be performed, which may identify occult malignancy and inform adjuvant therapy decisions. Counseling for those considering salpingo-oophorectomy should address the risks associated with surgical menopause, including cardiovascular disease, osteoporosis, cognitive impairment, and all-cause mortality.1

“Additional days, we are talking a lot about salpingectomy,” commented Ms. Senter. “There is a large body of evidence showing that most or potentially all epithelial ovarian cancers actually arise in the tubal epithelium.” Based on a retrospective review of an unselected population, salpingectomy with (hazard ratio [HR], 0.06; 95% CI, 0.03–0.12) and without

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**OVARIAN/UTERINE CANCER**

- Recommend RRSO, typically between 35 and 40 years, and upon completion of childbearing. Because ovarian cancer onset in patients with BRCA2 P/LP variants is an average of 8–10 years later than in patients with BRCA1 P/LP variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with BRCA2 P/LP variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
- Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, hormone replacement therapy (HRT), and related medical issues.
- Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that individuals are still at risk for developing ovarian cancer. In addition, in premenopausal individuals, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
  - ± hysterectomy
  - Specialized pathology protocol – serial sectioning
  - May increase risk for cardiovascular disease, osteoporosis, cognitive impairment, all-cause mortality

**Figure 1.** BRCA Pathogenic/Likely Pathogenic Variant-Positive Management: Standard risk reducing bilateral salpingo-oophorectomy. NCCN Clinical Practice Guideline in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; Version 2.2023 [BRCA-A 2 of 3].

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(HR, 0.67; 95% CI, 0.54–0.83) the addition of oophorectomy and hysterectomy was found to reduce the risk of developing ovarian and tubal cancers.14

Insufficient prospective data have hindered the adoption of salpingectomy alone as a standard of care, and thus clinical trials of interval salpingectomy and delayed oophorectomy are ongoing.1 The SOROCk trial will evaluate the risk-reducing potential of salpingectomy with or without delayed oophorectomy compared with traditional bilateral salpingo-oophorectomy in carriers of a BRCA1 variant (ClinicalTrials.gov identifier: NCT04251052).

“This study could provide the prospective data that we need to potentially change—or at least confirm that it shouldn’t change—the recommendation for risk reduction in patients with BRCA variants,” Ms. Senter concluded.

Disclosures: Ms. Senter has disclosed receiving consulting fees from and serving on the product/speakers bureau for AstraZeneca Pharmaceuticals LP; and serving as a scientific advisor for GlaxoSmithKline.

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References