

# Clinical Watch

FROM CSAC, THE CLINICAL AND SCIENTIFIC AFFAIRS COUNCIL OF THE AAPA

## GENETICS

# Hereditary breast and ovarian cancers

### ▶WHO SHOULD READ THIS?

PAs who work in primary care settings, obstetrics and gynecology, oncology, and surgery and who take care of patients who may be at risk for developing hereditary breast and ovarian cancers (HBOC).

### ▶WHAT'S NEW?

Since 1996, testing has been available for mutations in two genes, *BRCA1* and *BRCA2*, that are associated with an increased risk of developing breast and ovarian cancers. Testing to determine a patient's genetic risk for specific cancers has become widely available only recently, and now HBOC testing is being marketed directly to patients.

### ▶WHY IS THIS IMPORTANT?

Breast and ovarian cancers are the second and fifth leading causes of cancer deaths among women in the United States, respectively. The American Cancer Society estimates that in 2007, there were more than 180,000 new cases of and 40,000 deaths due to breast cancer, and that there were 22,000 new cases of and 15,000 deaths due to ovarian cancer.<sup>1</sup>

The estimated prevalence of *BRCA* mutations are about 1 in 300 to 500 in the general population,<sup>2</sup> and these mutations are estimated to account for up to 7% of breast cancers and up to 14% of ovarian cancers.<sup>3</sup>

### ▶HOW DO YOU IDENTIFY THOSE AT RISK FOR HBOC?

In part, through a comprehensive family history, which should be established for all patients.<sup>4,5</sup> The family history should include cancer diagnoses on both the maternal and paternal sides. The cancer type, age at diagnosis, and current age if alive are important to determine for each family member affected. For deceased relatives, age at death and the specific cause of death should be included. History of occupational and environmental exposures, if known, should also be collected for the pedigree. Race/ethnicity and country of origin should be determined for grandparents and parents.

### ▶WHEN SHOULD *BRCA* TESTING BE ORDERED?

Patients who have already had breast or ovarian cancer, or who have a known *BRCA* mutation in a family member, have increased susceptibility to HBOC and may be referred for genetic counseling and testing. For women without a personal history of

### TAKE-HOME POINTS

- Genetic testing is now available and recommended in selected instances for patients at risk for hereditary cancers, including breast and ovarian cancers.
- Patients with a family history consistent with a genetic mutation associated with HBOC should be offered genetic counseling.
- Patients testing positive for *BRCA1* or *BRCA2* mutations are at significant lifetime risk of developing breast and/or ovarian cancers and should be counseled regarding management options.
- Knowledge needed to diagnose and manage cancers such as HBOC is changing rapidly and requires ongoing vigilance to provide the highest possible level of care.

breast or ovarian cancer and without a known mutation, the US Preventive Services Task Force (USPSTF) recommends referral for genetic counseling and evaluation for *BRCA* testing when the family history indicates high risk.<sup>6</sup> Any one of the following indicates increased risk of an inherited *BRCA* mutation:

- Two first-degree relatives with breast cancer, one of whom received a diagnosis before age 50 years
- Three or more first- or second-degree relatives with breast cancer, regardless of age at diagnosis
- A combination of both breast and ovarian cancers among first- and second-degree relatives
- Two or more first- and second-degree relatives with ovarian cancer, regardless of age at diagnosis
- A history of male breast cancer diagnosed at any age
- A first-degree relative with bilateral breast cancer, especially if diagnosed at an early age
- A first- or second-degree relative with both breast and ovarian cancer at any age
- Women of Ashkenazi Jewish ancestry with a family history of breast or ovarian cancer.

The USPSTF recommends against routine referral for women whose history is not associated with increased risk for *BRCA* mutations. For more information on *BRCA1/2* testing, the National Library of Medicine's GeneTests Web site has an extensive review useful to clinicians (<http://www.genetests.org/query?dz=brca1>).

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## ▶WHO PAYS FOR BRCA TESTING, AND WHAT ARE THE COSTS?

Genetic testing for HBOC is often covered by medical insurance plans, but this should be confirmed before any test is ordered. The cost ranges from \$300 to \$3,000, depending on the level of testing performed. In addition to the cost of the test itself, increased costs are incurred through follow-up referrals and care.

## ▶WHAT ARE THE HARMS OF TESTING FOR HBOC?

Adverse effects may include anxiety and depression. There is evidence that genetic counseling can mitigate these effects. The potential for discrimination and loss of insurance and the impact of a positive result on family members have been described but not well researched.

## ▶WHAT KIND OF GENETIC COUNSELING SHOULD BE PERFORMED AND BY WHOM?

Both pretest and posttest genetic counseling should be provided. The assessment of genetic risk, decision to test, interpretation of results, and ensuing clinical decisions are extremely complicated concepts. Patients need counseling and education from an appropriately trained health care provider. PAs without the appropriate knowledge and skills should refer patients to another professional with expertise in hereditary cancers, typically a genetic counselor or medical geneticist. PAs with training and experience in HBOC syndromes may choose to manage the patient themselves. This choice should be based upon their knowledge base, practice time constraints, and the availability of genetic expertise within the local community.

## ▶HOW ARE TEST RESULTS INTERPRETED?

PAs must remember that *BRCA* testing determines risks for breast and ovarian cancers, not individual outcomes. A positive test result does not mean a per-

son will get cancer; likewise, a negative test result does not mean a person will not get cancer.

A *positive* result occurs when a specific mutation in *BRCA1* or *BRCA2* is identified. This confers an increased risk of HBOC regardless of whether a known mutation exists in a family member. A *negative* result (no mutations that were tested for were found) must be interpreted with caution and has different meanings, depending on whether a known mutation has been previously identified in a family member. If a known mutation has been found in a family member but is not found in the patient, the patient has not inherited this specific *BRCA* mutation but still has at least the risk for breast or ovarian cancer of a member of the general population. If there is no known mutation in an affected family member, a patient with a negative test result may still be at increased risk for HBOC because of a not yet identified mutation. An *uncertain* (also *inconclusive* or *ambiguous*) result implies that a variant of a *BRCA* gene mutation is found but that the clinical significance of this variation is not known. This result can be most troubling for both the patient and the clinician; it requires individualized recommendations that each have significant implications.<sup>5</sup>

## ▶WHAT DOES IT MEAN IF THE TEST IS POSITIVE?

For the general population, the lifetime risk is approximately 13% for breast cancer and 1.7% for ovarian cancer. Cancer risk estimates for *BRCA* mutation carriers vary, but a review of 22 studies estimated a 45% to 65% risk of breast cancer by age 70 years. These same mutations may confer an 11% to 39% risk of ovarian cancer by age 70 years.<sup>7</sup> Patients with *BRCA1* and *BRCA2* mutations are at markedly increased risk of developing breast and ovarian cancer when compared with the general population.

Women who test positive for *BRCA1* or *BRCA2* mutations have three options: surveillance, chemoprevention,

or prophylactic surgery. The risks and benefits of each option should be discussed carefully with the patient. No randomized controlled trials have assessed the efficacy of intensive cancer surveillance. Chemoprevention trials with tamoxifen (Nolvadex) have demonstrated decreased breast cancer rates in treatment groups but also higher rates of endometrial cancer and thromboembolic events in treated women. No randomized trials of surgical interventions have been conducted. However, several studies have shown that prophylactic bilateral mastectomy confers a 90% reduction in risk of breast cancer in women with either a strong family history or documented *BRCA1* or *BRCA2* mutations<sup>8,9</sup> and an 85% to 96% reduction in ovarian cancer.<sup>10,11</sup> JAAPA

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