Hereditary Breast/Ovarian Cancer Syndrome

A Primer for Obstetricians/Gynecologists

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KEYWORDS

• BRCA1 • BRCA2 • Hereditary breast cancer • Hereditary ovarian cancer
• Genetic testing • Clinical management

KEY POINTS

- Families with hereditary breast and ovarian cancer (HBOC) syndrome are at substantially greater risk for breast and ovarian cancer than the general population.
- Genetic cancer risk assessment is important to identify high-risk families.
- Effective, evidence-based preventive strategies are available to reduce the risk of cancer and overall morbidity and mortality.
- Women's health providers knowledgeable about HBOC can greatly improve the lives of HBOC families.

INTRODUCTION

Breast cancer remains the most common female cancer, affecting approximately 1 in 8 women over the course of their lifetime.[1] Of the more than 200,000 of breast cancers that occur in the United States each year, most are considered sporadic, 15% to 20% are familial, and 5% to 10% are hereditary.[1–3] **Table 1** shows the general distinctions between these three classifications of genetic risk for breast cancer. Ovarian cancer affects fewer women over the course of their lifetimes (1 in 70), but it remains associated with late detection and high mortality, and 20% to 25% of epithelial ovarian cancers may have a hereditary cause.[1,4]

Hereditary cancers are associated with inherited, primarily dominant, mutations in cancer-predisposing genes, including tumor suppressor, DNA mismatch repair, and oncogenes. The cancers are characterized by early age of onset, multifocal or bilateral disease, and high penetrance, with lifetime risks typically 5-fold to 10-fold that of the general population. Hereditary breast/ovarian cancer syndrome (HBOC) accounts for

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Table 1
Classifications of genetic risk for breast cancer[a]

Sporadic	Familial	Hereditary
Single occurrence in family	Two or more first-degree or second-degree affected relatives	Multiple affected individuals in multiple generations
Late age of onset (after 60 y)	Onset typically after 50 y	Early age of onset (often less than 50 y)
Unilateral	Primarily unilateral or late-onset bilateral	Bilateral/multifocal disease
Lack of other cancers in the family, or only common cancers of late onset	Evidence of skipped generations, no clear inheritance pattern	Presence of ovarian cancer, male breast cancer, Jewish ancestry (suggests *BRCA1/2*); multiple other unusual and/or early onset malignancies
Primarily caused by age an other nongenetic factors	Multiple minor/moderate inherited genetic factors interacting with environment	Single major cancer susceptibility gene mutation, autosomal dominant inheritance

[a] Classifications are general and overlap can be seen, especially in small families with few female members (ie, limited family history).

approximately 2% to 7% of all breast cancers, and 10% to 15% of all ovarian cancers.[5–8] HBOC is associated with germline mutations in the *BRCA1* or *BRCA2* genes, isolated in 1994 and 1995 respectively.[9,10] Approximately 1 in 400 individuals in the general population, and 1 in 40 individuals of Ashkenazi Jewish descent, carry a mutation in one of these genes.[8,11–13]

Over the 2 decades since these genes were discovered and clinical testing has become available, a wealth of evidence has accumulated documenting the personal, familial, and population health advantages of identifying individuals at risk for HBOC, providing genetic counseling and testing, and offering enhanced surveillance and surgical risk reduction options. This article provides an overview of current knowledge and practice regarding HBOC. Practical information regarding collecting a family history, cancer genetic counseling, and testing is followed by a discussion of specific cancer risks in HBOC, cancer prognosis and treatment, screening recommendations, and risk reduction strategies. This resource for women's health providers, will assist in the identification of women and families affected by HBOC, and their clinical management.

THE IMPORTANCE OF FAMILY HISTORY

Despite the increasing availability of direct-to-consumer genetic testing and multigene panels, a detailed family history remains the most important and easily affordable tool for identifying individuals at familial or hereditary risk for breast, ovarian, or other cancers. Collecting a family history to identify possible HBOC should, at minimum, include the following:

- History of breast and/or ovarian cancer (cancer of the peritoneum and fallopian tubes should be considered a part of the spectrum of HBOC) in all:
  - First-degree relatives (parents, siblings, children), and
  - Second-degree relatives (aunts/uncles, grandparents, nieces/nephews)