The Genetics of Breast Cancer

What the Surgical Oncologist Needs to Know

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KEYWORDS

• BRCA1 • Genetics • TP53 • Breast cancer • Ovarian cancer

KEY POINTS

- Surgeons need to understand the implications of germline predisposition to breast cancer, as revealed by increasingly more complicated next-generation sequencing–based tests.
- The rapid pace of change will continue to challenge paradigms for genetic cancer risk assessment (GCRA).
- Germline predisposition to breast cancer and GCRA can influence the medical and surgical management of breast cancer risk as well as strategies for screening and for risk reduction.

INTRODUCTION

Genetic cancer risk assessment (GCRA) is an established multidisciplinary practice that can be applied to the recognition/detection of hereditary forms of breast and ovarian cancer, to enable enhanced surveillance, risk-appropriate surgical management, and targeted therapy for metastatic disease.[1,2] Most breast cancer is hormone receptor positive, diagnosed after the age of 50 years old, and multifactorial in cause.[3]

Distinguishing features that suggest the subset of breast cancers associated with inherited predisposition include:

- Early age at onset
- Increased prevalence of bilateral breast cancer
- Association with ovarian cancer
- Family history of breast or ovarian cancer

Inheritance plays a role in the development of all human cancers to varying degrees. Hereditary forms of breast cancer constitute only 5% to 7% of breast cancer cases

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overall. However, the magnitude of the risk that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation (up to 85% lifetime risk for *BRCA1*) justifies the intense interest in predictive testing. There is a growing roster of identified breast cancer susceptibility genes, and next-generation sequencing (NGS) technologies have enabled diagnostic testing for an ever broader spectrum of relatively rare and incompletely understood causal variants.[4] Although less common than breast cancer, ovarian cancer is relatively more lethal, and several breast cancer associated genes are also associated with elevated ovarian cancer risk.[5] In addition, breast cancer can be a minor component of other genetic syndromes such as diffuse hereditary gastric cancer.[6,7] This article summarizes germline predisposition to breast cancer and how GCRA can influence the medical and surgical management of breast cancer risk as well as strategies for screening and for risk reduction.

THE PRIME EXEMPLAR: HEREDITARY BREAST AND OVARIAN CANCER ASSOCIATED WITH *BRCA1* AND *BRCA2* MUTATIONS

Consider the following clinical scenario illustrated in **Fig. 1**. The consultand (indicated by an *arrow*) was 45 years old and unaffected at the time of consultation, although she was certain she would develop cancer. She was contemplating both prophylactic mastectomy and oophorectomy because her mother and 2 of her sisters died of breast or ovarian cancer. She was also concerned about her own daughter's risk. A mutation in *BRCA1* (4184del4) had been found in her sister just before her death from breast cancer at age 50. After extensive counseling, the consultand decided to pursue genetic testing for the familial mutation. Fortunately, testing revealed that she did not carry the mutation. She canceled the surgical procedures after being told that her risk for breast or ovarian cancer was no more than that of the general population (11% and 1.6%, respectively). Moreover, she was relieved to learn that her daughter was not at increased risk either, because she had not inherited the familial mutation and thus could not pass it on to her. Other family members also came forward for testing. Her 47-year-old sister was found to carry the familial mutation (indicated by + in the **Fig. 1**). Before counseling and testing, she was so anxious about her cancer risk that she was unable to examine her own breasts. However, despite the bad news about her carrier status, she was empowered to pursue appropriate interventions from the surveillance and preventive surgery options presented. Genetic testing had a real impact on health care decisions in this carefully counseled high-risk family and presumably reassured some individuals and spared them from unnecessary procedures.

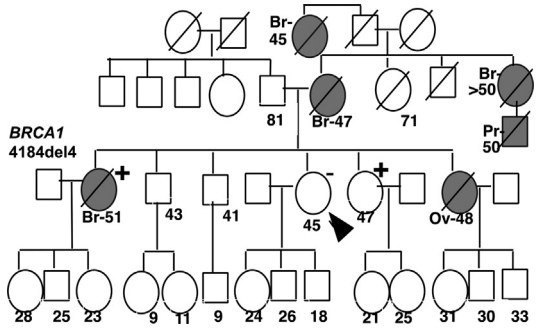

Fig. 1. Pedigree for family with hereditary breast and ovarian cancer.