

Pros and Cons of Screening for *BRCA* Mutations

Marissa Howard-McNatt

Estimates suggest that about 80% of breast cancers and 90% of ovarian cancers are sporadic [1]; only 5% to 10% of breast cancers are hereditary. Hereditary mutations of the *BRCA1* and *BRCA2* genes account for 60% of inherited breast and ovarian cancers [1]. According to data from the National Cancer Institute [2], the risk of a *BRCA2* mutation carrier developing breast cancer by age 70 years is 45%, and her risk of developing ovarian cancer is 11%–17%; *BRCA1* mutation carriers have a slightly higher risk of breast cancer (55%–65%) and a higher risk of ovarian cancer (39%).

Until recently, the management of breast cancers resulting from a *BRCA* mutation did not differ from management of sporadic tumors. However, genetic information is now important in planning surgeries and adjuvant therapies, and genetic testing for *BRCA* mutations is increasingly being used for risk assessment. This article will examine the pros and cons of such testing and discuss how it can affect patient care.

Genetic Consultation

In multidisciplinary breast centers, genetic counselors play a vital role by identifying and evaluating women who are at high risk for hereditary breast cancer syndromes. The US Preventive Services Task Force guideline on genetic risk assessment and *BRCA* testing strongly recommends that high-risk individuals be referred for genetic counseling and possible testing [3]. Genetic counseling and testing provide many benefits to the patient and to the health care team [1]. First, counseling and testing help to identify high-risk individuals who do not have cancer; these women will benefit from early screening and consultation. For a woman with a known cancer, counseling and testing may help her decide whether to undergo a bilateral mastectomy at the time of her cancer surgery, or whether to opt for careful surveillance of the remaining breast tissue. Finally, testing can alleviate the anxiety of not knowing one's carrier status.

The risks of genetic testing include the inability of such testing to detect all mutations, the unclear efficacy of some interventions, and the possibility of psychosocial or financial harm [1]. Genetic counselors can inform patients

about Title I of the Genetic Information Nondiscrimination Act of 2008 [4], which provides protection against discrimination based on genetic information in health insurance underwriting decisions. However, that protection covers only group and individual health insurance; it does not apply to life insurance, disability insurance, or long-term care insurance [4].

Management

Women who test positive for a *BRCA* mutation have several options for reducing their risk of developing cancer. These include surveillance, chemoprevention, and surgical risk reduction.

For *BRCA* mutation carriers, early detection strategies include annual or semiannual clinical breast examination by a physician or allied health professional, annual mammography beginning at age 25 years, and/or annual breast magnetic resonance imaging (MRI) [5]; if both breast MRI and mammography are being performed, the breast MRI should be performed 6 months after the yearly mammogram. The benefit of a clinical breast examination is under debate, as such exams have not been shown to improve the rate of cancer detection. Nonetheless, patients say that they find the exam reassuring, and it gives the provider an opportunity to discuss the patient's care [6].

Mammography has been shown to decrease the breast cancer mortality rate; however, its sensitivity is estimated to be only about 36% in *BRCA1* or *BRCA2* mutation carriers [7]. In contrast, the sensitivity of MRI screening in women with a familial or genetic predisposition is nearly 80% [7, 8]. The pros of breast cancer surveillance with MRI are that it is noninvasive and it has no long-term side effects. The cons are that it has not been shown to reduce the risk of breast cancer-related death in *BRCA* mutation carriers, and it carries an increased risk of false-positive results, which can lead to additional imaging or biopsies.

Breast cancer chemoprevention is offered in the form of tamoxifen and raloxifene, with the latter being used for postmenopausal women. The Study of Tamoxifen and Raloxifene (STAR) [9] showed that these selective estrogen receptor modulators (SERMs) lowered the risk of developing invasive breast cancer by about 50%. However, SERMs

cation selection versus outcomes for patients who are all treated with clopidogrel. For example, the genotype-guided strategy could test everyone in that study group for *CYP2C19* polymorphisms and use ticagrelor instead of clopidogrel for poor metabolizers, because ticagrelor is not dependent on metabolic activation (Figure 2). Clopidogrel would be the default medication choice for those without variant alleles because of its well-established evidence of effectiveness [21], substantially lower cost, and slightly lower risk of minor bleeding [36]. NCMJ

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do not completely eliminate the risk of developing breast cancer, and data regarding their effectiveness in *BRCA* mutation carriers are limited.

Bilateral prophylactic mastectomy has been shown to reduce breast cancer risk in women with a family history of breast cancer. The risk reduction in *BRCA* mutation carriers has been shown to be 90% in women with intact ovaries and 95% in those who have undergone prophylactic oophorectomy [10]. Many women who choose bilateral mastectomy also opt for immediate breast reconstruction with implants or autologous tissue. The advantage of prophylactic mastectomy is that it greatly reduces the risk of developing breast cancer. The disadvantages include the need for extra surgeries with breast reconstruction, possible surgical complications (eg, bleeding and infections), and psychosexual concerns. However, studies have shown that most women are satisfied with their surgical choice and do not experience poor body image after surgery [11, 12].

In addition to prophylactic mastectomy, *BRCA* mutation carriers may consider prophylactic oophorectomy. Bilateral prophylactic salpingo-oophorectomy is associated with an 85% reduction in the risk of developing gynecologic cancer among *BRCA1* mutation carriers [13].

Breast specialists and genetic counselors play an important role in guiding patients with an increased risk for developing breast cancer through genetic testing and treatment options. There are pros and cons to each risk-reduction strategy, but the more informed a patient is, the better her outcome and overall satisfaction will be. **NCMJ**

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