Tools of the Trade: Individualized Breast Cancer Risk Assessment

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Case Report

A 45-YEAR-OLD CAUCASIAN WOMAN presents to discuss her concern about her risk for breast cancer as she has breast cancer in her family. She is generally healthy. She is 163 cm tall and weighs 67.9 kg.

One month prior, she underwent stereotactic biopsy of the right breast following indeterminate calcifications on screening mammogram. Pathology was sclerosing adenosis. She has no other history of breast procedures, including reduction or augmentation. She underwent total abdominal hysterectomy with bilateral oophorectomy 2 years ago for fibroids and menorrhagia. She has not taken hormone therapy.

She is gravida 3 para 4 with age at first live birth of 25. She was 12 years old at menarche. Her family history of breast cancer includes her mother, diagnosed at age 50, who is alive and well and two paternal aunts diagnosed at ages 58 and 64 respectively. She has two healthy sisters. There is no ovarian cancer in the family. She is not of Jewish descent. Neither her mother nor other relatives have had genetic counseling or testing.

Which of the following do you recommend:

- A. Genetic counseling and annual screening mammography
- B. Annual screening mammography and exemestane
- C. Semiannual screening mammography and tamoxifen or raloxifene
- D. Annual breast magnetic resonance imaging (MRI) and tamoxifen or raloxifene
- E. Annual screening mammography, annual breast MRI, and tamoxifen or raloxifene

Discussion

In 2013, several guidelines for the treatment of women at high risk for breast cancer were issued and/or updated pertaining primarily to the need for genetic counseling and chemoprevention.

The U.S. Preventive Services Task Force (USPSTF) set a grade B recommendation for screening women with a validated calculator as a basis for referral for genetic counseling.¹ This assessment determines her level of risk for a known genetic mutation. In the United States, the Referral Screening

Tool (RST) and Pedigree Assessment Tool have been studied. The RST is a readily available, online calculator with high sensitivity.^{2,3} The calculation is based on Jewish ancestry, family history of breast and/or ovarian cancer in women, and male breast cancer.

The USPSTF had set guidelines for the use of chemoprevention in women at high risk for breast cancer in 2002. In 2013, the USPSTF updated these guidelines and now applies a grade B recommendation for the discussion and prescription of chemoprevention in women at high risk, but not in women at average risk (grade D designation).⁴

The American Society of Clinical Oncology (ASCO) also updated guidelines for chemoprevention of breast cancer in 2013, simplifying and consolidating the data regarding tamoxifen, raloxifene, and exemestane.⁵

In order to objectively counsel this woman and provide her with an individualized risk assessment, breast cancer risk calculation models must be used to guide discussion on risk reduction and enhanced surveillance strategies.

Several models are available:

- The Breast Cancer Risk Assessment Tool, commonly known as the Gail Model, calculates this woman's 5-year risk of breast cancer at 2.5%, compared with the population risk of 1% for her age. Her lifetime risk of breast cancer is 21.4% compared with the general U.S. population risk of 11.9%.⁶
- The International Breast Intervention Study (IBIS), or Tyrer-Cuzick, model calculates this patient's 10-year risk at 9.2% and lifetime risk at 43%.⁷

The Gail model was developed by Gail et al.⁸ using data from the Breast Cancer Detection Demonstration Project and later updated as the Gail 2 Model.⁹ The model uses age, race, menarche, age at first live birth, history of cancer in first degree relatives, history of breast biopsy, and history of atypical ductal hyperplasia to predict 5-year and lifetime risks. The Gail model is only used in women aged 35 years or older and cannot be applied to those with history of breast cancer, lobular carcinoma *in situ*, or ductal carcinoma *in situ*. It is the most commonly applied breast cancer risk assessment tool. In general, a score of $\geq 1.66\%$ for the 5-year risk is considered high. The Gail model has subsequently been updated for women of various ethnic backgrounds, including African Americans and Asian and Pacific Islanders. It is well

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suited for the determination of whether chemoprevention is indicated for breast cancer risk reduction.

The Tyrer-Cuzick model is based on data from the International Breast Intervention Study (IBIS) from the United Kingdom. This model can be employed to determine whether a woman is a candidate for annual screening MRI in conjunction with annual mammograms. Decision regarding screening MRI in women should be based on the 2007 American Cancer Society Guidelines.¹⁰ This woman qualifies because her lifetime risk of breast cancer is >20%–25%. The Tyrer-Cuzick tool is best suited to determine whether a woman qualifies for enhanced surveillance.

The efficacy of the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene has been demonstrated in several randomized, placebo-controlled trials. The two were directly compared in the Study of Tamoxifen and Raloxifene (STAR) trial, which demonstrated equivalent prevention of breast cancer at a risk reduction of approximately 50%. Raloxifene had fewer adverse events, particularly endometrial carcinoma/dysplasia and thromboembolic disease.¹¹ Evaluation of the data later, with prolonged follow-up, showed persistence of the decreased rates of adverse events with raloxifene, although tamoxifen demonstrated greater reduction in the incidence of breast cancer.¹² Tamoxifen has been approved by the Food and Drug Administration (FDA) and Health Canada for prevention in pre- and post-menopausal women (United States and Canada). Raloxifene is FDA approved for breast cancer prevention (United States) and can only be used post menopausally.

The aromatase inhibitors have also been assessed for chemoprevention. None of these agents are FDA approved for this use, though exemestane has been discussed as an alternative to the SERMs in the ASCO guidelines. The MAP.3 trial demonstrated that exemestane had a 65% risk reduction in invasive breast cancer after 3 years of follow-up. There was no significant difference between placebo and exemestane with regard to skeletal fractures or cardiovascular events.¹³ Adverse events with exemestane include vasomotor symptoms, musculoskeletal pain, and decrease in bone mineral density.¹⁴ More recently, anastrozole demonstrated a 53% reduction in the prospective, randomized, placebo controlled IBIS-2 trial. The anastrozole group reported higher rates of joint stiffness and vasomotor symptoms as well as higher blood pressures. There were not increased cardiovascular events or fractures.¹⁵

Answer: E

This patient is not in need of genetic counseling based on the RST. While this patient has three female relatives affected by breast cancer, only her mother was diagnosed at or before age 50. She has no additional familial cancer risk. The RST calculates her risk of genetic mutation at <5%, so she is not a candidate for genetic counseling. The patient's mother, however, should have risk assessment for genetic counseling based on her own breast cancer history.

This patient is at elevated risk for breast cancer based on the Gail Model and the Tyrer-Cuzick risk calculators, making her a candidate for chemoprevention (Gail $\geq 1.66\%$ five-year risk) and annual MRI ($\geq 20\%$ – 25% lifetime risk) in conjunction with annual mammograms. The Gail model factors associated with increased risk in this particular patient are her

history of previous biopsy and family history of breast cancer in a first-degree relative.

Options for chemoprevention include tamoxifen and raloxifene because she is surgically post-menopausal. Exemestane can also be considered and has a favorable risk-to-benefit ratio and safety profile but would be an off label use. Providers should provide a balanced assessment of the risks and benefits of the preventive therapies and incorporate a shared decision approach to individualize therapy.¹⁶

All high-risk women should continue to be screened with annual mammography. It is prudent to encourage women to be aware of breast changes during the normal activities of daily living and seek prompt evaluation of new breast concerns.¹⁷

The topic of screening and chemoprevention for high-risk patients is a complex one. Another option for this woman would be referral to a breast specialist or breast health center of excellence in which providers are familiar with the intricacies of these recommendations and therapies.

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