How to better identify and manage women with elevated breast cancer risk

This case-based review details screening and management strategies that can maximize the care you provide to women at heightened risk.

PRACTICE RECOMMENDATIONS
- Assess breast cancer risk in all women starting at age 35. (C)
- Perform enhanced screening in all women with a lifetime risk of breast cancer > 20%. (A)
- Discuss chemoprevention for all women at elevated risk for breast cancer. (B)

Strength of recommendation (SOR)
- A: Good-quality patient-oriented evidence
- B: Inconsistent or limited-quality patient-oriented evidence
- C: Consensus, usual practice, opinion, disease-oriented evidence, case series

Breast cancer is the most common invasive cancer in women in the United States; it is estimated that there will be 287,850 new cases of breast cancer in the United States during 2022 with 43,250 deaths.1 Lives are extended and saved every day because of a robust arsenal of treatments and interventions available to those who have been given a diagnosis of breast cancer. And, of course, lives are also extended and saved when we identify women at risk and provide early interventions. But in busy offices where time is short and there are competing demands on our time, proper assessment of a woman’s risk of breast cancer does not always happen. As a result, women with a higher risk of breast cancer may not be getting appropriate management.2,3

Familiarizing yourself with several risk-assessment tools and knowing when genetic testing is needed can make a big difference. Knowing the timing of mammograms and magnetic resonance imaging (MRI) for women deemed to be at high risk is also key. The following review employs a case-based approach (with an accompanying ALGORITHM) to illustrate how best to identify women who are at heightened risk of breast cancer and maximize their care. We also discuss the chemoprophylaxis regimens that may be used for those at increased risk.

CASE
Rachel P, age 37, presents to establish care. She has an Ashkenazi Jewish background and wonders if she should start doing breast cancer screening before age 40. She has 2 children, ages 4 years and 2 years. Her maternal aunt had unilateral breast cancer at age 54, and her maternal grandmother died of ovarian cancer at age 65.

Risk assessment
The risk assessment process (see ALGORITHM) must start with...
either the clinician or the patient initiating the discussion about breast cancer risk. The clinician may initiate the discussion with a new patient or at an annual physical examination. The patient may start the discussion because they are experiencing new breast...
symptoms, have anxiety about developing breast cancer, or have a family member with a new cancer diagnosis.

**Risk factors.** There are single factors that convey enough risk to automatically designate the patient as high risk (see **TABLE 1**). These factors include having a history of chest radiation between the ages of 10 and 30, a history of breast biopsy with either lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia (ADH), past breast and/or ovarian cancer, and either a family or personal history of a high penetrant genetic variant for breast cancer.

In women with previous chest radiation, breast cancer risk correlates with the total dose of radiation. For women with a personal history of breast cancer, the younger the age at diagnosis, the higher the risk of contralateral breast cancer. Precancerous changes such as ADH, LCIS, and ductal carcinoma in situ (DCIS) also confer moderate increases in risk. Women with these diagnoses will commonly have follow-up with specialists.

**Risk assessment tools.** There are several models available to assess a woman’s breast cancer risk (see **TABLE 2**). The Gail model (https://bcrisktool.cancer.gov/) is the oldest, quickest, and most widely known. However, the Gail model only accounts for first-degree relatives diagnosed with breast cancer, may underpredict risk in women with a more extensive family history, and has not been studied in women younger than 35. The International Breast Cancer Intervention Study (IBIS) Risk Evaluation Tool (https://ibis-risk-calculator.magview.com/), commonly referred to as the Tyrer-Cuzick model, incorporates second-degree relatives into the prediction model—although women may not know their full family history. The Breast Cancer Surveillance Consortium (BCSC) model (https://tools.bcsc-scc.org/BC5yearRisk/intro.htm) is the only model that includes breast density in the prediction algorithm. The choice of tool depends on clinician comfort and individual patient risk factors. There is no evidence that one model is better than another.

**CASE**

Ms. P’s clinician starts with an assessment using the Gail model. However, when the result comes back with average risk, the clinician decides to follow up with the Tyrer-Cuzick model in order to incorporate Ms. P’s multiple second-degree relatives with breast and ovarian cancer. (The BCSC model is not an option for Ms. P because she’s never had a mammogram and thus does not have a breast density measurement to include in the model.)

### Genetic testing

The National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing if a woman has a first- or second-degree relative with pancreatic cancer, metastatic prostate cancer, male breast cancer, breast cancer at age 45 or younger, 2 or more breast cancers in a single person, 2 or more people on the same side of the family with at least 1 diagnosed at age 50 or younger, or any relative with ovarian cancer (see **TABLE 3**). Before ordering genetic testing, it is useful to refer the patient to a genetic counselor for a thorough discussion of options.

Results of genetic testing may include high-risk variants, moderate-risk variants, and variants of unknown significance (VUS), or be negative for any variants. High-risk variants for breast cancer include **BRCA1**, **BRCA2**, **PALB2**, and cancer syndrome variants such as **TPS3**, **PTEN**, **STK11**, and **CDH1**. These high-risk variants confer sufficient risk that women with these mutations are automatically categorized in the high-risk group. It is estimated that high-risk variants account for only 25% of the genetic risk for breast cancer.

**BRCA1/2** and **PTEN** mutations confer greater than 80% lifetime risk, while other
high-risk variants such as TP53, CDH1, and STK11 confer risks between 25% and 40%. These variants are also associated with cancers of other organs, depending on the mutation.17

Moderate-risk variants—ATM and CHEK2—do not confer sufficient risk to elevate women into the high-risk group. However, they do qualify these intermediate-risk women to participate in a specialized management strategy.5,9,13,18

VUS are those for which the associated risk is unclear, but more research may be done to categorize the risk.9 The clinical management of women with VUS usually entails close monitoring.

In an effort to better characterize breast cancer risk using a combination of pathogenic variants found in broad multi-gene cancer predisposition panels, researchers have developed a method to combine risks in a “polygenic risk score” (PRS) that can be used to counsel women (see “What is a polygenic risk score for breast cancer?” on page 203).19-21 PRS predicts an additional 18% of genetic risk in women of European descent.21

### TABLE 2

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk factors included</th>
<th>Comments</th>
<th>Available at</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gail</td>
<td>• Race/ethnicity&lt;br&gt;• First-degree relatives with breast cancer&lt;br&gt;• Age at menarche&lt;br&gt;• Age at first live birth&lt;br&gt;• History of ≥ 1 breast biopsy</td>
<td>• Designed in 1989&lt;br&gt;• Includes DCIS&lt;br&gt;• Not accurate for women with previous cancer or chest radiation&lt;br&gt;• Does not account for distant family history (ie, second-degree relatives)</td>
<td><a href="https://bcrisktool.cancer.gov/">https://bcrisktool.cancer.gov/</a></td>
</tr>
<tr>
<td>Tyrer-Cuzick (IBIS)</td>
<td>• Race/ethnicity&lt;br&gt;• First-, second-degree relatives with breast cancer (includes age of onset)&lt;br&gt;• Age at menarche&lt;br&gt;• Age at first live birth&lt;br&gt;• Hormone therapy&lt;br&gt;• BMI&lt;br&gt;• History of breast biopsy</td>
<td>• Includes more extensive family history&lt;br&gt;• Includes high-risk ethnicity</td>
<td><a href="https://ibis-risk-calculator.magview.com/">https://ibis-risk-calculator.magview.com/</a></td>
</tr>
<tr>
<td>Breast Cancer Surveillance Consortium (BCSC)</td>
<td>• Race/ethnicity&lt;br&gt;• Family history of first-degree relative&lt;br&gt;• History of breast biopsies&lt;br&gt;• Breast density</td>
<td>• Only model to include breast density*</td>
<td><a href="https://tools.bcsc-scc.org/BC5yearRisk/intro.htm">https://tools.bcsc-scc.org/BC5yearRisk/intro.htm</a></td>
</tr>
</tbody>
</table>

* Breast density is the amount of fibroglandular tissue on mammography; high breast density is a risk factor for breast cancer.

### TABLE 3

<table>
<thead>
<tr>
<th>Genetic testing criteria</th>
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</thead>
<tbody>
<tr>
<td>• First- or second-degree relative with any of the following:</td>
<td></td>
</tr>
<tr>
<td>o Pancreatic cancer</td>
<td></td>
</tr>
<tr>
<td>o Metastatic prostate cancer</td>
<td></td>
</tr>
<tr>
<td>o Male breast cancer</td>
<td></td>
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<tr>
<td>o Breast cancer ≤ age 45</td>
<td></td>
</tr>
<tr>
<td>o ≥ 2 breast cancer primaries in a single individual</td>
<td></td>
</tr>
<tr>
<td>o ≥ 2 individuals with breast cancer primaries on the same side of the family</td>
<td></td>
</tr>
<tr>
<td>- At least 1 diagnosed ≤ age 50</td>
<td></td>
</tr>
<tr>
<td>• Any relative with ovarian cancer</td>
<td></td>
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</tbody>
</table>
|��风险变体如TP53，CDH1和STK11具有25％到40％的风险。这些变体也与其它器官的癌症相关，具体取决于突变。17

中等风险变体—ATM和CHEK2—不赋予足够的风险将女性提升为高风险组。然而，它们确实使这些中间风险的女性有资格参与专门的管理策略。5,9,13,18

VUS是那些关联风险不明的，但更多的研究可能用于分类风险。9这些女性的临床管理通常包括紧密监测。

为了更好地利用多基因癌症易感性扫描仪中发现的多种致病性变体来量化乳腺癌风险，研究人员开发了一种方法来组合风险，形成“多基因风险评分”（PRS），该评分可用于指导女性（见“什么是乳腺癌的多基因风险评分？”在第203页）。19-21

PRS预测了欧洲裔女性额外18％的遗传风险。21

### 表2

<table>
<thead>
<tr>
<th>模型</th>
<th>风险因素包含</th>
<th>评论</th>
<th>可访问地址</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gail</td>
<td>• 种族/民族&lt;br&gt;• 一级或二级亲属与乳腺癌&lt;br&gt;• 月经初潮年龄&lt;br&gt;• 第一胎生育年龄&lt;br&gt;• ≥1次乳腺活检</td>
<td>• 1989年设计&lt;br&gt;• 包括DCIS&lt;br&gt;• 不适用于以前癌症或胸部放疗的女性&lt;br&gt;• 不考虑远亲家系史（即，二级亲属）</td>
<td><a href="https://bcrisktool.cancer.gov/">https://bcrisktool.cancer.gov/</a></td>
</tr>
<tr>
<td>Tyrer-Cuzick（IBIS）</td>
<td>• 种族/民族&lt;br&gt;• 一级、二级亲属与乳腺癌（包括发病年龄）&lt;br&gt;• 月经初潮年龄&lt;br&gt;• 第一胎生育年龄&lt;br&gt;• 生育激素&lt;br&gt;• BMI&lt;br&gt;• 乳腺活检史</td>
<td>• 包括更广泛的家族史&lt;br&gt;• 包括高风险民族</td>
<td><a href="https://ibis-risk-calculator.magview.com/">https://ibis-risk-calculator.magview.com/</a></td>
</tr>
<tr>
<td>Breast Cancer Surveillance Consortium（BCSC）</td>
<td>• 种族/民族&lt;br&gt;• 直系亲属病史&lt;br&gt;• 乳腺活检史&lt;br&gt;• 乳房密度</td>
<td>• 只有模型包含乳房密度*</td>
<td><a href="https://tools.bcsc-scc.org/BC5yearRisk/intro.htm">https://tools.bcsc-scc.org/BC5yearRisk/intro.htm</a></td>
</tr>
</tbody>
</table>

* 乳房密度是乳腺照相术中纤维腺组织的量；高乳房密度是乳腺癌的风险因素。

### 表3

<table>
<thead>
<tr>
<th>遗传测试标准</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 一级或二级亲属与以下任何一项：</td>
<td></td>
</tr>
<tr>
<td>o 胰腺癌</td>
<td></td>
</tr>
<tr>
<td>o 远端前列腺癌</td>
<td></td>
</tr>
<tr>
<td>o 男性乳腺癌</td>
<td></td>
</tr>
<tr>
<td>o 乳腺癌 ≤ 45岁</td>
<td></td>
</tr>
<tr>
<td>o ≥2例乳腺癌在单一个体中</td>
<td></td>
</tr>
<tr>
<td>o ≥2例乳腺癌在同一个体的两侧</td>
<td></td>
</tr>
<tr>
<td>- 至少1例诊断 ≤ 50岁</td>
<td></td>
</tr>
<tr>
<td>• 任何与卵巢癌相关的亲属</td>
<td></td>
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</tbody>
</table>
Using the assessment results, the clinician talks to Ms. P about her lifetime risk for breast cancer. The Gail model indicates her lifetime risk is 13.3%, just slightly higher than the average (12.5%), and her 5-year risk is 0.5% (average, 0.4%). The IBIS or Tyrer-Cuzick model, which takes into account her second-degree relatives with breast and ovarian cancer and her Ashkenazi ethnicity (which confers increased risk due to elevated risk of BRCA mutations), predicts her lifetime risk of breast cancer to be 20.4%. This categorizes Ms. P as high risk.

Enhanced screening recommendations for women at high risk

TABLE 4 summarizes screening recommendations for women deemed to be at high risk for breast cancer. The American Cancer Society (ACS), NCCN, and the American College of Radiology (ACR) recommend that women with at least a 20% lifetime risk have yearly magnetic resonance imaging (MRI) and mammography (staggered so that the patient has 1 test every 6 months) starting 10 years before the age of onset for the youngest affected relative but not before age 30. For carriers of high-risk (as well as intermediate-risk) genes, NCCN recommends annual MRI screening starting at age 40. BRCA1/2 screening includes annual MRI starting at age 25 and annual mammography every 6 months starting at age 30. Clinicians should counsel women with moderate risk factors (elevated breast density; personal history of ADH, LCIS, or DCIS) about the potential risks and benefits of enhanced screening and chemoprophylaxis.

Risk-reduction strategies

Chemoprophylaxis

The US Preventive Services Task Force (USPSTF) recommends that all women at increased risk for breast cancer consider chemoprophylaxis (B recommendation) based on convincing evidence that 5 years of treatment with either a synthetic estrogen reuptake modulator (SERM) or an aromatase inhibitor (AI) decreases the incidence of estrogen receptor positive breast cancers. (See TABLE 5 for absolute risk reduction.) There is no benefit for chemoprophylaxis in women at average risk (D recommendation). It is unclear whether chemoprophylaxis is indicated in women with moderate increased risk (ie, who do not meet the 20% lifetime risk criteria). Chemoprophylaxis may not be effective in women with BRCA1 mutations, as they often develop triple-negative breast cancers.

Accurate risk assessment and shared decision-making enable the clinician and patient to discuss the potential risks and benefits of chemoprophylaxis. The USPSTF did not find that any 1 risk prediction tool was better than another to identify women who should be counseled about chemoprophylaxis. Clinicians should counsel all women taking AIs about optimizing bone health with adequate calcium and vitamin D intake and routine bone density tests.

Surgical risk reduction

The NCCN guidelines state that risk-reducing bilateral mastectomy is reserved for individuals with high-risk gene variants and individuals with prior chest radiation between ages 10 and 30. NCCN also recommends discussing risk-reducing mastectomy with all women with BRCA mutations.

Bilateral mastectomy is the most effective method to reduce breast cancer risk and should be discussed after age 25 in women with BRCA mutations and at least 8 years after chest radiation is completed. There is a reduction in breast cancer incidence of 90%. Breast imaging for screening (mammography
### Table 4

<table>
<thead>
<tr>
<th>Who</th>
<th>Recommendation</th>
<th>When</th>
<th>Recommended by</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20% lifetime risk</td>
<td>Annual MRI and mammography screening*</td>
<td>Starting 10 years before onset of youngest affected relative Not before age 30</td>
<td>ACR, ACS, NCCN</td>
</tr>
<tr>
<td>BRCA1/2 mutation carriers</td>
<td>Annual MRI and mammography screening*</td>
<td>MRI at age 25 Mammography at age 30</td>
<td>NCCN</td>
</tr>
</tbody>
</table>

ACR, American College of Radiology; ACS, American Cancer Society; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network.

* Staggered every 6 months.

### Table 5

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Eligible women</th>
<th>Special considerations</th>
</tr>
</thead>
</table>
| Tamoxifen (SERM) | 20 mg/d | Premenopausal, postmenopausal | • 7 fewer invasive breast cancers (CI, 4-12) per 1000 women over 5 years 23  
• Only medication indicated in premenopausal women  
• Increased risk of VTE (5 extra cases per 1000 women over 5 years) 23 endometrial cancer (4 extra cases per 1000 women over 5 years) 23 and cataracts  
• Menopausal symptoms |
| Raloxifene (SERM) | 60 mg/d | Postmenopausal | • 9 fewer invasive breast cancers (CI, 3-15) per 1000 women over 5 years 23  
• Menopausal symptoms  
• Increased risk of VTE (7 extra cases per 1000 women over 5 years) 23  
• Decreases the risk of vertebral fractures |
| Exemestane (AI) | 25 mg/d | Postmenopausal | • 16 fewer invasive breast cancers (CI, 8-24) per 1000 women over 5 years 23  
• Up to 50% risk of arthralgias and joint pain  
• Menopausal symptoms  
• Decreased BMD |
| Anastrozole (AI) | 1 mg/d | Postmenopausal | • 16 fewer invasive breast cancers (CI, 8-24) per 1000 women over 5 years 23  
• Up to 50% risk of arthralgias and joint pain  
• Menopausal symptoms  
• Decreased BMD |

AI, aromatase inhibitor; BMD, bone mineral density; SERM, synthetic estrogen reuptake modulator; VTE, venous thromboembolism.

or MRI) is not indicated after risk-reducing mastectomy. However, clinical breast examinations of the surgical site are important, because there is a small risk of developing breast cancer in that area.26

Risk-reducing oophorectomy is the standard of care for women with BRCA mutations to reduce the risk of ovarian cancer. It can also reduce the risk of breast cancer in women with BRCA mutations.27
CASE

Based on her risk assessment results, family history, and genetic heritage, Ms. P qualifies for referral to a genetic counselor for discussion of BRCA testing. The clinician discusses adding annual MRI to Ms. P’s breast cancer screening regimen, based on ACS, NCCN, and ACR recommendations, due to her 20.4% lifetime risk. Discussion of whether and when to start chemoprophylaxis is typically based on breast cancer risk, projected benefit, and the potential impact of medication adverse effects. A high-risk woman is eligible for 5 years of chemoprophylaxis (tamoxifen if premenopausal) based on her lifetime risk. The clinician discusses timing with Ms. P, and even though she is finished with childbearing, she would like to wait until she is age 45, which is before the age at which her aunt was given a diagnosis of breast cancer.

Conclusion

Primary care clinicians are well positioned to identify women with an elevated risk of breast cancer and refer them for enhanced screening and chemoprophylaxis (see ALGORITHM). Shared decision-making with the inclusion of patient decision aids (https://decisionaid.ohri.ca/AZsearch.php?criterion=breast-cancer) about genetic testing, chemoprophylaxis, and prophylactic mastectomy or oophorectomy may help women at intermediate or high risk of breast cancer feel empowered to make decisions about their breast—and overall—health. JFP

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References