



**EDUCATIONAL OBJECTIVE:** Readers will recognize the risk of breast cancer in patients with hereditary cancer syndromes and arrange appropriate referrals for them

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# Managing patients at genetic risk of breast cancer

## ABSTRACT

Hereditary syndromes that increase the risk of breast cancer are not common, but it is critical to recognize and manage them appropriately. This paper reviews the management of patients with the most common hereditary breast cancer syndromes, ie, hereditary breast and ovarian cancer syndrome, hereditary diffuse gastric cancer, Cowden syndrome (*PTEN* hamartoma tumor syndrome), Peutz-Jeghers syndrome, and Li-Fraumeni syndrome.

## KEY POINTS

In addition to breast cancer, hereditary cancer syndromes increase the risk of other malignancies, with the patterns of malignancy varying by causative genetic mutation.

Genetic counselors, medical breast specialists, surgical breast specialists, gynecologic oncologists, and others can help, but the primary care provider is the nucleus of the multidisciplinary team.

Management of these patients often includes surveillance, chemoprevention, and prophylactic surgery.

All decisions about surveillance, chemoprevention, and surgical risk reduction should be shared with the patient.

**W**HILE MOST CASES OF BREAST CANCER are sporadic (ie, not inherited), up to 10% are attributable to single-gene hereditary cancer syndromes.<sup>1-4</sup> People with these syndromes have a lifetime risk of breast cancer much higher than in the general population, and the cancers often occur at a much earlier age.

With genetic testing becoming more common, primary care physicians need to be familiar with the known syndromes, associated risks, and evidence-based recommendations for management. Here, we review the management of cancer risk in the most common hereditary breast cancer syndromes, ie:

- Hereditary breast and ovarian cancer syndrome<sup>5</sup>
- Hereditary diffuse gastric cancer
- Cowden syndrome (*PTEN* hamartoma tumor syndrome)
- Peutz-Jeghers syndrome
- Li-Fraumeni syndrome.

## ■ IT TAKES A TEAM, BUT PRIMARY CARE PHYSICIANS ARE CENTRAL

Women who have a hereditary predisposition to breast cancer face complex and emotional decisions about the best ways to manage and reduce their risks. Their management includes close clinical surveillance, chemoprevention, and surgical risk reduction.<sup>1,4</sup>

Referral to multiple subspecialists is an important component of these patients' preventive care. They may need referrals to a cancer genetic counselor, a high-risk breast clinic, a gynecologic oncologist, and counseling services. They may also require referrals to gastroenterologists, colorectal surgeons, endocrinologists, and endocrine surgeons, depending on the syndrome identified.

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TABLE 1

## Hereditary breast cancer syndromes

Syndrome	Gene	Breast cancer risk	Other cancer risks	Incidence
Hereditary breast and ovarian cancer	<i>BRCA1</i> <i>BRCA2</i>	43% <sup>17</sup> –85% <sup>8</sup>	Ovarian, male breast, prostate, pancreatic, melanoma ( <i>BRCA2</i> )	1:400–800 <sup>7,18</sup>
Cowden	<i>PTEN</i>	77%–85% <sup>11,12,19</sup>	Uterine, renal cell, colorectal, thyroid, melanoma	1:200,000 <sup>13</sup>
Li-Fraumeni	<i>TP53</i>	Undefined, but > 20%	Sarcoma, brain, adrenocortical carcinoma, others. Up to 100% all-site lifetime cancer risk	1:20,000 <sup>27</sup>
Peutz-Jeghers	<i>STK11</i>	45%–54% <sup>14,15</sup>	GI tract, pancreas, lung, gonadal, adenoma malignum of the cervix	1 in 50,000–200,000 <sup>16</sup>
Hereditary diffuse gastric cancer	<i>CDH1</i>	39%–52% <sup>a,9,10</sup>	Gastric (diffuse)	Unknown; 1%–3% of gastric cancers <sup>20</sup>

<sup>a</sup> Lobular breast cancer

Find a genetic counselor at [www.nsgc.org](http://www.nsgc.org)

Consultation with a certified genetic counselor is critical for patients harboring mutations associated with cancer risk. The National Society of Genetic Counselors maintains a directory of genetic counselors by location and practice specialty at [www.nsgc.org](http://www.nsgc.org). The counselor's evaluation will provide patients with a detailed explanation of the cancer risks and management guidelines for their particular condition, along with offering diagnostic genetic testing if appropriate. Women with germline mutations who plan to have children should be informed about preimplantation genetic diagnosis and about fertility specialists who can perform this service if they are interested in pursuing it.<sup>6</sup>

Screening and management guidelines for hereditary breast cancer syndromes are evolving. While subspecialists may be involved in enhanced surveillance and preventive care, the primary care physician is the central player, with both a broader perspective and knowledge of the patient's competing medical issues, risks, and preferences.

In addition to breast cancer, the risk of other malignancies is also higher, with the

pattern varying by syndrome (Table 1).<sup>7–20</sup>

The management of these additional risks is beyond the scope of this review; however, primary care physicians need to be familiar with these risks to provide adequate referrals.

### WHO IS AT INCREASED RISK OF BREAST CANCER?

In considering recommendations to reduce the risk of breast cancer, it is useful to think of a patient as being at either high risk or average risk.

The risk of breast cancer in women in the general population is about 12%, and most cases of breast cancer occur in patients who have no known risk factors for it. “High risk” of breast cancer generally means having more than a 20% lifetime risk (ie, before age 70) of developing the condition.

Even without a hereditary cancer syndrome, a combination of reproductive, environmental, personal, and family history factors can confer a 20% lifetime risk. But for women with hereditary syndromes, the risk far exceeds 20% regardless of such risk factors. It is likely

that interactions with reproductive, environmental, and personal risk factors likely affect the individual risk of a woman with a known genetic mutation, and evidence is emerging with regard to further risk stratification.

In an earlier article in this journal, Smith and colleagues<sup>21</sup> reviewed how to recognize heritable breast cancer syndromes. In general, referral for genetic counseling should be considered for patients and their families who have:

- Early-onset breast cancers (before age 50)
- Bilateral breast cancers at any age
- Ovarian cancers at any age
- “Triple-negative” breast cancers (ie, estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor 2-nonamplified (HER2-negative))
- Male breast cancer at any age
- Cancers affecting multiple individuals and in multiple generations.
- Breast, ovarian, pancreatic or prostate cancer in families with Ashkenazi Jewish ancestry

## HEREDITARY BREAST CANCER SYNDROMES

### Hereditary breast and ovarian cancer syndrome

The most common of these syndromes is hereditary breast and ovarian cancer syndrome, caused by germline mutations in the tumor-suppressor genes *BRCA1* or *BRCA2*.<sup>7</sup> The estimated prevalence of *BRCA1* mutations is 1 in 250 to 300, and the prevalence of *BRCA2* mutations is 1 in 800.<sup>1,4</sup> However, in families of Ashkenazi Jewish ancestry, the population frequency of either a *BRCA1* or *BRCA2* mutation is approximately 1 in 40.<sup>1,4,6</sup>

Women with *BRCA1* or *BRCA2* mutations have a lifetime risk of breast cancer of up to 87%, or 5 to 7 times higher than in the general population, with the risk rising steeply beginning at age 30.<sup>1,5,8</sup> In addition, the lifetime risk of ovarian cancer is nearly 59% in *BRCA1* mutation carriers and 17% in *BRCA2* mutation carriers.<sup>22</sup>

A meta-analysis found that *BRCA1* mutation carriers diagnosed with cancer in one breast have a 5-year risk of developing cancer in the other breast of 15%, and *BRCA2* muta-

tion carriers have a risk of 9%.<sup>23</sup> Overall, the risk of contralateral breast cancer is about 3% per year.<sup>3,4,24</sup>

*BRCA1* mutations are strongly associated with triple-negative breast cancers.<sup>1,3,4</sup>

### Hereditary diffuse gastric cancer

Hereditary diffuse gastric cancer is an autosomal-dominant syndrome associated with mutations in the *CDH1* gene, although up to 75% of patients with this syndrome do not have an identifiable *CDH1* mutation.<sup>9,25,26</sup> In cases in which there is no identifiable *CDH1* mutation, the diagnosis is made on the basis of the patient’s medical and family history.

Hereditary diffuse gastric cancer is associated with an increased risk of the lobular subtype of breast cancer as well as diffuse gastric cancer. The cumulative lifetime risk of breast cancer in women with *CDH1* mutations is 39% to 52%,<sup>6,9–11,25</sup> and their lifetime risk of diffuse gastric cancer is 83%.<sup>9</sup> The combined risk of breast cancer and gastric cancer in women with this syndrome is 90% by age 80.<sup>9</sup>

### Cowden syndrome (*PTEN* hamartoma tumor syndrome)

Cowden syndrome (*PTEN* hamartoma tumor syndrome) is caused by mutations in *PTEN*, another tumor-suppressor gene.<sup>11</sup> The primary clinical concerns are melanoma and breast, endometrial, thyroid (follicular or papillary), colon, and renal cell cancers. Women with a *PTEN* mutation have a twofold greater risk of developing any type of cancer than men with a *PTEN* mutation.<sup>12</sup> The cumulative lifetime risk of invasive breast cancer in women with this syndrome is 70% to 85%.<sup>11–13</sup>

### Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is an autosomal dominant polyposis disorder caused, in most patients, by a mutation in the serine/threonine kinase tumor-suppressor gene *STK11*.<sup>14</sup>

Patients with Peutz-Jeghers syndrome have higher risks of gastrointestinal, breast, gynecologic (uterine, ovarian, and cervical), pancreatic, and lung cancers. In women, the lifetime risk of breast cancer is 44% to 50% by age 70, regardless of the type of mutation.<sup>6,14,15</sup> Breast cancers associated with Peutz-Jeghers syndrome are usually ductal, and the mean age at diagnosis is 37 years.<sup>16</sup>

**Women with *BRCA1* or *BRCA2* mutations have a lifetime risk of breast cancer of up to 87%**

## Li-Fraumeni syndrome

Li-Fraumeni syndrome is an autosomal-dominant disorder caused by germline mutations in the *TP53* gene, which codes for a transcription factor associated with cell proliferation and apoptosis.<sup>27</sup>

These mutations confer a lifetime cancer risk of 93% in women (mainly breast cancer) and 68% in men.<sup>1,27</sup> Other cancers associated with *TP53* mutations include sarcomas, brain cancer, leukemia, and adrenocortical tumors. Germline *TP53* mutations are responsible for approximately 1% of all breast cancers.<sup>1,4</sup>

Breast cancers can occur at a young age in patients with a *TP53* mutation. Women with *TP53* mutations are 18 times more likely to develop breast cancer before age 45 compared with the general population.<sup>4</sup>

It is important to consider a *TP53* mutation in premenopausal women or women less than 30 years of age with breast cancer who have no mutations in *BRCA1* and *BRCA2*.<sup>1</sup>

## MANAGING PATIENTS WITH GENETIC PREDISPOSITION TO BREAST CANCER

Management for patients at high risk fall into three broad categories: clinical surveillance, chemoprevention, and surgical risk reduction. The utility and benefit of each depend to a large degree on the patient's specific mutation, family history, and comorbidities. Decisions must be shared with the patient.

## CLOSE CLINICAL SURVEILLANCE

Consensus guidelines for cancer screening in the syndromes described here are available from the National Comprehensive Cancer Network at [www.nccn.org](http://www.nccn.org) and are summarized in **Table 2**.<sup>26,28</sup> While the guidelines are broadly applicable to all women with these conditions, some individualization is required based on personal and family medical history.

In general, screening begins at the ages listed in **Table 2** or 10 years earlier than the age at which cancer developed in the first affected relative, whichever is earlier. However, screening decisions are shared with the patient and are sometimes affected by significant out-of-pocket costs for the patient and anxiety resulting from the test or subsequent test findings, which must all be considered.

## Breast self-awareness and clinical breast examination

Although controversial in the general population, breast self-examination is recommended for patients carrying mutations that increase risk.<sup>6</sup>

A discussion about breast self-awareness is recommended for all women at the age of 18. It should include the signs and symptoms of breast cancer, what feels “normal” to the patient, and what is known about modifiable risk factors for breast cancer. The patient should also be told to report any changes in her personal or family history.

Clinical breast examinations should be done every 6 months, as some cancers are found clinically, particularly in young women with dense tissue, and confirmed by diagnostic imaging and targeted ultrasonography.

## Radiographic surveillance

Mammography and magnetic resonance imaging (MRI) are also important components of a breast cancer surveillance regimen in women at high risk. Adherence to a well-formulated plan of clinical and radiographic examinations increases early detection in patients who have a hereditary predisposition to breast cancer.

MRI is more sensitive than mammography and reduces the likelihood of finding advanced cancers by up to 70% compared with mammography in women at high risk of breast cancer.<sup>29–31</sup> The sensitivity of breast MRI alone ranges from 71% to 100%, and the sensitivity increases to 89% to 100% when combined with mammography. In contrast, the sensitivity of mammography alone is 25% to 59%.<sup>29</sup> MRI has also been shown to be cost-effective when added to mammography and physical examination in women at high risk.<sup>5,32</sup>

Adding MRI to the breast cancer screening regimen has been under discussion and has been endorsed by the American Cancer Society in formal recommendations set forth in 2007 for patients with known hereditary cancer syndromes, in untested first-degree relatives of identified genetic mutation carriers, or in women who have an estimated lifetime risk of breast cancer of 20% or more, as determined by models largely dependent on family history.<sup>33</sup>

But MRI has a downside—it is less specific than mammography.<sup>29,33</sup> Its lower speci-

Think about other highly penetrant genetic mutations in a young breast cancer patient with no mutation in *BRCA1* or *BRCA2*

TABLE 2

## Summary of breast cancer screening guidelines

Modality	Hereditary breast and ovarian cancer syndrome and hereditary diffuse gastric cancer <sup>a</sup>		Cowden syndrome ( <i>PTEN</i> hamartoma tumor syndrome)		Li-Fraumeni syndrome		Peutz-Jeghers syndrome	
	Onset (years)	Timing	Onset (years)	Timing	Onset (years)	Timing	Onset (years)	Timing
Breast self-awareness and examination	18	Monthly	18	Monthly	18	Monthly	18	Monthly
Clinical breast examination	25	Every 6–12 months	25 <sup>b</sup>	Every 6–12 months	20–25 <sup>b</sup>	Every 6–12 months	25	Semiannually
Mammography	30 <sup>c</sup>	Annually	30–35 <sup>b</sup>	Annually	30 <sup>c</sup>	Annually	30	Annually
Breast MRI	25 <sup>c</sup>	Annually	30–35 <sup>b</sup>	Annually	20–29	Annually	25	Annually

<sup>a</sup> The National Comprehensive Cancer Network recommends following hereditary breast and ovarian cancer syndrome management for breast cancer risk in hereditary diffuse gastric cancer

<sup>b</sup> Or 5–10 years before the earliest known breast cancer in the family, whichever is earlier

<sup>c</sup> Individualized on the basis of family history

Information from references 6, 26, and 28.

ficity (77% to 90% vs 95% with mammography alone) leads to additional radiographic studies and tissue samplings for the “suspicious” lesions discovered. From 3% to 15% of screening breast MRIs result in a biopsy, and the proportion of biopsies that reveal cancer is 13% to 40%.<sup>33</sup> Furthermore, by itself, MRI has not been shown to reduce mortality in any high-risk group.

Mammography remains useful in conjunction with MRI due to its ability to detect breast calcifications, which may be the earliest sign of breast cancer, and ability to detect changes in breast architecture. A typical screening program (Table 2) should incorporate both modalities, commonly offset by 6 months (eg, mammography at baseline, then MRI 6 months later, then mammography again 6 months after that, and so on) to increase the detection of interval cancer development.

### Chemoprevention

Chemoprevention means taking medications to reduce the risk. Certain selective estrogen receptor modulators and aromatase inhibitors

decrease the risk of invasive breast cancer in healthy women at high risk. These drugs include tamoxifen, which can be used before menopause, and raloxifene, anastrozole, and exemestane, which must be used only after menopause.

Because data are limited, we cannot make any generalized recommendations about chemoprevention in patients with hereditary breast cancer syndromes. Decisions about chemoprevention should take into account the patient’s personal and family histories. Often, a medical oncologist or medical breast specialist can help by discussing the risks and benefits for the individual patient.

**Tamoxifen** has been the most studied, mainly in *BRCA* mutation carriers.<sup>6,34–37</sup> As in the general population, tamoxifen reduces the incidence of estrogen receptor-positive breast cancers by 50%.<sup>36–38</sup> It has not been shown to significantly reduce breast cancer risk in premenopausal women with *BRCA1* mutations,<sup>37</sup> most likely because most cancers that occur in this group are estrogen receptor-negative. In patients with a history of breast cancer, however, tamoxifen has been shown to reduce the

**Guidelines for screening in hereditary cancer syndromes are at [www.nccn.org](http://www.nccn.org)**



risk of developing contralateral breast cancer by 45% to 60% in both *BRCA1* and *BRCA2* mutation carriers.<sup>6,35</sup>

There is also little evidence that giving a chemopreventive agent after bilateral salpingo-oophorectomy reduces the risk further in premenopausal *BRCA* mutation carriers.<sup>35</sup> These patients often receive hormonal therapy with estrogen, which currently would preclude the use of tamoxifen. Tamoxifen in postmenopausal women is associated with a small increased risk of venous thromboembolic disease and endometrial cancer.<sup>38</sup>

**Oral contraceptives** reduce the risk of ovarian cancer by up to 50% in *BRCA1* mutation carriers and up to 60% in *BRCA2* mutation carriers.<sup>6</sup> However, data conflict on their effect on the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers.<sup>39</sup>

Decisions about chemoprevention with agents other than tamoxifen and in syndromes other than hereditary breast and ovarian cancer syndrome must take into consideration the existing lack of data in this area.

## ■ SURGICAL PROPHYLAXIS

Surgical prophylactic options for patients at genetic risk of breast cancer are bilateral mastectomy and bilateral salpingo-oophorectomy.

### Prophylactic mastectomy

Bilateral risk-reducing mastectomy reduces the risk of breast cancer by at least 90%<sup>24,39,40</sup> and greatly reduces the need for complex surveillance. Patients are often followed annually clinically, with single-view mammography if they have tissue flap reconstruction.

Nipple-sparing and skin-sparing mastectomies, which facilitate reconstruction and cosmetic outcomes, are an option in the risk-reduction setting and have been shown thus far to be safe.<sup>41–43</sup> In patients with breast cancer, the overall breast cancer recurrence rates with nipple-sparing mastectomy are similar to those of traditional mastectomy and breast conservation treatment.<sup>41</sup>

In patients at very high risk of breast cancer, risk-reducing operations also reduce the risk of ultimately needing chemotherapy and radiation to treat breast cancer, as the risk of developing breast cancer is significantly lowered.

The timing of risk-reducing mastectomy depends largely on personal and family medical history and personal choice. Bilateral mastectomy at age 25 results in the greatest survival gain for patients with hereditary breast and ovarian cancer syndrome.<sup>5</sup> Such precise data are not available for other hereditary cancer syndromes, but it is reasonable to consider bilateral mastectomy as an option for any woman with a highly penetrant genetic mutation that predisposes her to breast cancer. Special consideration in the timing of risk-reducing mastectomy must be given to women with Li-Fraumeni syndrome, as this condition is often associated with an earlier age at breast cancer diagnosis (before age 30).<sup>1</sup>

Family planning, sexuality, self-image, and the anxiety associated with both cancer risk and surveillance are all factors women consider when deciding whether and when to undergo mastectomy. A survey of 12 high-risk women who elected prophylactic mastectomy elicited feelings of some regret in 3 of them, while all expressed a sense of relief and reduced anxiety related to both cancer risk and screenings.<sup>24</sup> Another group of 14 women surveyed after the surgery reported initial distress related to physical appearance, self-image, and intimacy but also reported a significant decrease in anxiety related to breast cancer risk and were largely satisfied with their decision.<sup>44</sup>

### Prophylactic salpingo-oophorectomy

In patients who have pathogenic mutations in *BRCA1* or 2, prophylactic salpingo-oophorectomy before age 40 decreases the risk of ovarian cancer by up to 96% and breast cancer by 50%.<sup>1,37,45</sup> This operation, in fact, is the only intervention that has been shown to reduce the mortality rate in patients with a hereditary predisposition to cancer.<sup>46</sup>

We recommend that women with hereditary breast and ovarian cancer syndrome strongly consider prophylactic salpingo-oophorectomy by age 40 or when childbearing is complete for the greatest reduction in risk.<sup>1,5</sup> In 2006, Domchek et al<sup>46</sup> reported an overall decrease in the mortality rate in *BRCA1/2*-positive patients who underwent this surgery, but not in breast cancer-specific or ovarian cancer-specific mortality.

Discuss breast self-awareness with all women patients at age 18

On the other hand, removing the ovaries before menopause places women at risk of serious complications associated with premature loss of gonadal hormones, including cardiovascular disease, decreased bone density, reduced sexual satisfaction, dyspareunia, hot flashes, and night sweats.<sup>47</sup> Therefore, it is generally reserved for women who are also at risk of ovarian cancer.

Hormonal therapy, ie, estrogen therapy for patients who choose complete hysterectomy, and estrogen-progesterone therapy for patients who choose to keep their uterus, reduces menopausal symptoms and symptoms of sexual dissatisfaction and has not thus far been shown to increase breast cancer risk.<sup>1,34</sup> However, this information is from nonrandomized studies, which are inherently limited.

It is important to address and modify risk factors for heart disease and osteoporosis in women with premature surgical menopause, as they may be particularly vulnerable to these conditions.

## HEREDITARY BREAST CANCER IN MEN

Fewer than 1% of cases of breast cancer arise in men, and fewer than 1% of cases of cancer in men are breast cancer.

Male breast cancer is more likely than female breast cancer to be estrogen receptor- and progesterone receptor-positive. In an analysis of the Surveillance, Epidemiology, and End Results registry between 1973 and 2005, triple-negative breast cancer was found in 23% of female patients but only 7.6% of male patients.<sup>2</sup>

Male breast cancer is most common in

families with *BRCA2*, and to a lesser degree, *BRCA1* mutations. Other genetic disorders including Li-Fraumeni syndrome, hereditary nonpolyposis colorectal cancer, and Klinefelter syndrome also increase the risk of male breast cancer. A genetic predisposition for breast cancer is present in approximately 10% of male breast cancer patients.<sup>2</sup> Any man with breast cancer, therefore, should be referred for genetic counseling.

In men, a *BRCA2* mutation confers a lifetime risk of breast cancer of 5% to 10%.<sup>2</sup> This is similar to the lifetime risk of breast cancer for the average woman but it is still significant, as the lifetime risk of breast cancer for the average man is 0.1%.<sup>1,2</sup>

Five-year survival rates in male breast cancer range from only 36% to 66%, most likely because it is usually diagnosed in later stages, as men are not routinely screened for breast cancer. In men with known hereditary susceptibility, National Comprehensive Cancer Network guidelines recommend that they be educated about and begin breast self-examination at the age of 35 and be clinically examined every 12 months starting at age 35.<sup>48</sup> There are limited data to support breast imaging in men. High-risk surveillance with MRI screening in this group is not recommended. Prostate cancer screening is recommended for men with *BRCA2* mutations starting at age 40, and should be considered for men with *BRCA1* mutations starting at age 40.

No specific guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family.

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