

Breast cancer prevention and Tx: An evidence-based guide

When to begin screening mammography may be the latest controversy, but it's not the only uncertainty regarding breast health and cancer care. We've culled the latest evidence to help you do what's best.

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*The authors reported no
potential conflict of interest
relevant to this article.*

PRACTICE RECOMMENDATIONS

□ Offer screening magnetic resonance imaging (MRI) to patients with a known BRCA 1 or 2 mutation, a strong family history of breast cancer, or a lifetime risk of breast cancer >20% to 25%. **(B)**

□ For early-stage breast cancer, lumpectomy and sentinel node mapping with excision is the preferred method for staging. **(A)**

□ Monitor patients receiving tamoxifen for signs and symptoms of venous thromboembolism, cataracts, and uterine malignancy, and patients on aromatase inhibitors for the development of osteoporosis. **(A)**

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

Late last year, the US Preventive Services Task Force (USPSTF) sparked a nationwide controversy when it announced that it was recommending against routine screening mammography for women younger than age 50.¹ Indeed, that's a recommendation that many other organizations, including the American Cancer Society (ACS),² the American College of Obstetricians and Gynecologists (ACOG),³ and the National Comprehensive Cancer Network (NCCN),⁴ disagree with. But the age at which women should begin routine mammography isn't the only controversial question. Experts disagree on the benefits of breast self-examination, the optimal frequency of clinical breast exams, and the use of digital mammography—among other issues. This evidence-based review can help you cut through the confusion.

CASE ▶ Carrie, a 39-year-old woman who has never been pregnant, comes in for an annual Pap smear and gynecologic exam. She has a negative past medical history, but a positive family history for breast cancer—both her mother and 1 of her sisters had the disease. How would you assess Carrie's risk of breast cancer, and what preventive measures would you recommend?

Use this predictive model to pinpoint your patient's risk

When making decisions regarding primary prevention of and screening for breast cancer, an accurate assessment of risk is critical. Many predictive models have been developed with that in mind. The most widely studied, the Gail model, incorporates a number of important risk factors (TABLE 1), including age; race; family history; reproductive factors such as age of men-

TABLE 1

Risk factors for breast cancer^{5,29}

- Age (>50 years)
- Sex
- Ethnicity*
- Family history (≥1 first-degree relative diagnosed with breast cancer, particularly if diagnosed at <50 years of age)
- Early menarche (<12 years)
- Late menopause (>55 years)
- Late age at first full-term pregnancy (>30 years)
- Nulliparity
- Breast density
- History of breast biopsies
- Atypical hyperplasia or LCIS on prior biopsy
- History of radiation to chest wall
- Lack of breastfeeding
- Physical inactivity
- Obesity
- Alcohol use[†]
- Exogenous hormones (HRT)

*African American and Caucasian women are at higher risk compared with Asian, Hispanic, and Native American women.

[†]1 drink/day results in minimal increase in risk; 2-5 drinks/day result in 1.5 increased risk compared with nondrinkers.

HRT, hormone replacement therapy; LCIS, lobular carcinoma in situ.

arche, menopause, and first childbirth; and previous history of breast biopsy and atypical findings, to calculate a woman's 5-year risk.⁵

A risk calculator (the Breast Cancer Risk Assessment Tool) based on the Gail model is available on the National Cancer Institute's Web site, at <http://www.cancer.gov/bcrisktool>. Generally, a score ≥1.66%,⁵ which indicates that a patient has at least a 1.66% chance of developing breast cancer over the next 5 years, is considered high risk.^{6,7}

CASE ▶ Carrie's 2 first-degree relatives affected by breast cancer and her nulliparous status place her at increased risk. Further questioning reveals a particularly strong family history, as both relatives were diagnosed before the age of 50 (her mom at 45 years of age and her sister, at 39). Carrie's 5-year risk is 1.8%.

All women can benefit from these preventive measures

As primary care physicians, we have a re-

sponsibility to stress lifestyle modification as the mainstay of breast cancer prevention. Whether or not a woman is at high risk, advise her that maintaining a normal weight, exercising vigorously, limiting alcohol consumption, and breastfeeding are evidence-based methods of primary prevention. Diets low in fat and high in fiber may be associated with a lower risk of invasive breast cancer, but there is no conclusive evidence to support specific dietary interventions to reduce the risk.⁸⁻¹¹ Nor has a link between active or passive smoking, antioxidants, or fruit and vegetable intake been firmly established.¹²

■ **There is a clear association between prolonged estrogen exposure and breast cancer**, however. Many reproductive factors, such as early menarche, late menopause, later age at time of first full-term pregnancy, and nulliparity, increase a woman's exposure to endogenous estrogen—and her risk of developing breast cancer.^{12,13}

■ **Exposure to exogenous estrogen** is also linked to the development of breast cancer. In 2002, the Women's Health Initiative (WHI) was stopped early after a report was released stating that the risks of hormone replacement therapy (HRT)—a higher incidence of cardiovascular events, stroke, and venous thromboembolism, as well as breast cancer—outweighed the benefits.¹⁴ Subsequent analyses have found a relationship between the declining incidence of breast cancer and the marked decrease in HRT use prompted by the WHI report. While causality has not been firmly established, multiple studies strongly suggest it.^{15,16}

■ **The association between oral contraceptives (OCs) and breast cancer** is more controversial. Some studies have found an increased breast cancer risk among OC users, but both the relative risk and absolute risk were found to be very small and to dissipate 10 years after stopping OC use. More recent studies with newer formulations containing lower doses of estrogen have failed to show an increased risk.⁸

Breast cancer screening: The parameters have changed

Various organizations have published guidelines for breast cancer screening (TABLE 2),

TABLE 2

Guidelines for breast cancer screening for women with average risk

Organization	Age (years)	Breast self-exam	Clinical breast exam	Mammography exam
American Cancer Society ²	20-40	Optional	Every 3 y	NA
	>40	Encourages	Annually	Annually
American College of Obstetricians and Gynecologists ³	40-49	Encourages	Annually	1-2 y
	50-69	Encourages	Annually	Annually
Canadian Task Force on Preventive Health Care ¹⁸	40-49	Recommends against teaching	Insufficient evidence	Insufficient evidence
	50-69	Recommends against teaching	1-2 y	1-2 y
National Comprehensive Cancer Network ⁴	20-40	Encourages	1-3 y	NA
	>40	Encourages	Annually	Annually
US Preventive Services Task Force ¹	40-49	Recommends against teaching	Insufficient evidence	Not routinely recommended
	50-74	Recommends against teaching	Insufficient evidence	Every 2 y

NA, not addressed.

and all are somewhat different. Here's what you need to know.

■ **Breast self-examination (BSE)**, which women were previously advised to perform monthly, has not been shown to improve mortality in any age group, and is no longer routinely recommended.¹⁷ While both the USPSTF and the Canadian Task Force on Preventive Health Care recommend against teaching women BSE, the ACS, ACOG, and NCCN encourage self-examination—particularly among women older than 40 years.^{1-4,17,18}

■ **Clinical breast examination** has an average sensitivity of 50% and detects approximately 5% of mammographically occult cancers.¹⁹ It is still not clear whether clinical breast exams save lives, however—a finding that is reflected in the USPSTF's "I" (insufficient evidence to assess the benefits and harms) recommendation.¹ Other consensus

guidelines still recommend clinical breast examination, albeit at varying frequencies.

■ **Screening mammography** decreases mortality rates by anywhere from 28% to 65%, depending on the statistical model used.²⁰ The benefit is greatest in women between the ages of 50 and 69 years, however, and most groups agree that mammography every 1 to 2 years is advisable for this age group. (There is limited data on the value of mammography for women 70 years of age and older, and no consensus on the age at which to stop screening.^{1,21}) But because the mortality benefit from screening mammography is lower for women aged 40 to 49, guidelines for this age group are more controversial.

Mammography's sensitivity is affected by a variety of factors, including age and menopausal status, prior breast surgery or radiation, breast density, and the experience of the radiologist. Women in their 40s have denser breast



AT PRESSTIME, a new study reported that screening mammography in women 50 and older did little to reduce breast cancer deaths. See the September 23 edition of *The New England Journal of Medicine* for more.

➤ **October is National Breast Cancer Awareness Month. Refer patients to <http://www.nbcam.org> for more information about risk, screening, and treatment.**

tissue than older women, making mammography less sensitive for this age group. Because of that, and because the overall incidence of breast cancer is lower for women younger than 50, some argue that screening mammography for women between the ages of 40 and 49 years leads to unacceptably high false-positive rates (9.8% annually²²) and that the harm associated with mammography may outweigh the benefit. Others counter that tumors in younger women tend to be more aggressive and faster growing, making early detection even more critical than for older women.

What should you advise women in this age group? You might point out that the USPSTF recommends against routine screening, but indicates that the decision to begin (or defer) routine mammography before age 50 should be individualized, based on the needs and values of each patient.¹

■ **Digital mammography.** A recent study of more than 43,000 women demonstrated that digital mammography is more accurate than film—but only for certain groups: These include women <50 years of age, women with dense breasts, and pre- and perimenopausal women.²³ Because it is still not clear whether the increased accuracy will translate into a mortality benefit, more research is needed before digital mammography is widely adopted. The USPSTF maintains that there is insufficient evidence to assess the benefits and harms of using either digital mammography or magnetic resonance imaging (MRI) rather than film mammography to screen for breast cancer.¹

■ **MRI.** In 2007, the ACS published guidelines on the use of MRI as an adjunct to mammography for breast cancer screening in high-risk women.²⁴ According to ACS guidelines, screening MRI should be offered to patients with a known BRCA 1 or 2 mutation (5%-10% of all breast cancers are associated with a mutation in the BRCA 1 or BRCA 2 gene, which is transmitted in an autosomal dominant pattern⁶). It also should be offered to those with a strong family history, or a lifetime risk of developing breast cancer that is >20% to 25%. And finally, MRI should be offered to women who had chest wall radiation when they were between the ages of 10 and 30 years—another significant risk fac-

tor for breast cancer—and those with other genetic syndromes that increase their lifetime risk of breast cancer.²⁴

Evidence is insufficient for or against MRI screening for women with a personal history of breast cancer, atypical hyperplasia, or lobular carcinoma in situ, however, and neither breast ultrasound (which is generally used diagnostically, not for screening purposes) nor MRI has been shown to be helpful as a screening tool in women with <15% lifetime risk of developing breast cancer.^{24,25}

When to consider chemoprevention

For women like Carrie, who are at high risk of developing breast cancer, selective estrogen receptor modulator (SERM) therapy and surgical interventions may be options to consider. The Breast Cancer Prevention Trial demonstrated the efficacy of tamoxifen as a preventive agent. This landmark trial showed that for high-risk women older than 35, 5 years of tamoxifen therapy can reduce the incidence of invasive breast cancer by nearly 50%.²⁶

Women with the BRCA 1 or 2 mutation—all of whom should be offered genetic counseling—were included in the study. Tamoxifen reduced the incidence of breast cancer in BRCA 2 carriers by 62%, the researchers found, but did not reduce risk in carriers of the BRCA 1 gene. This is likely due to the high prevalence of estrogen receptor-negative breast cancers among BRCA 1 carriers.²⁶

More recently, the Study of Tamoxifen and Raloxifene (STAR) trial compared the efficacy of tamoxifen and raloxifene, a second-generation SERM, in high-risk postmenopausal women ages 35 and older. The drugs were found to be equally effective in reducing the risk of invasive breast cancer, but raloxifene had a better side effect profile, with a lower incidence of thromboembolism and cataracts.²⁷

■ **What the guidelines call for.** In 2003, the USPSTF recommended that clinicians discuss chemoprevention with women at high risk for breast cancer and low risk for adverse effects of SERMs.²⁸

The most recent update to the NCCN breast cancer risk reduction guidelines recommends that clinicians offer tamoxifen to

premenopausal women with a 5-year projected breast cancer risk $\geq 1.7\%$ and offer tamoxifen or raloxifene to high-risk postmenopausal women.²⁹ It is worth noting, however, that SERMs can have significant adverse effects, including venous thromboembolism, stroke, cataracts, uterine malignancy, and hot flashes, while lifestyle modifications and the avoidance of HRT have few, if any, negative effects.

CASE ▶ After consultation with a genetic counselor, Carrie underwent testing for both the BRCA 1 and BRCA 2 mutations. She tested negative for both. She declined chemoprevention and prophylactic surgery, opting for enhanced screening with yearly mammography and MRI and lifestyle modification instead.

When a mass is found

For women ages 30 or older with palpable masses or solid masses ≥ 2 cm found on imaging, core needle biopsy is recommended.^{30,31} Biopsy is indicated for women younger than 30 as well, if the mass is >2 cm or imaging is suspicious. In general, a needle biopsy read as benign is considered adequate for diagnostic purposes only if the lesion appeared benign on imaging.

For lesions shown to be cystic on imaging, recommendations for follow-up or additional testing are based on the characteristics of the cyst. For simple cysts, 2- to 4-month follow up for stability, followed by routine screening, is adequate.²¹ Additional evaluation of complex cysts is indicated, including aspiration for complicated cysts and biopsy for complex cysts. After aspiration, surgical excision of bloody aspirates or persistent masses is recommended.^{30,31}

Staging using the TNM system

The TNM (tumor, node, metastases) classification system is used for the staging of breast cancer:

- **T** refers to the tumor type, size, and extent of local involvement
- **N** describes regional lymph node involvement
- **M** refers to distant metastases.

The TNM classifications are also grouped by stage (I through IV).

■ **Lumpectomy and sentinel node mapping with excision** is the preferred method for staging of early-stage breast cancer without palpable lymphadenopathy—provided that the surgical team has documented experience with sentinel node biopsy.³² Sentinel node biopsy is preferred because of its safety, low ($<10\%$) false negative rate, and decreased morbidity compared with full axillary dissection, although dissection is recommended for patients with more advanced cancer or a positive sentinel node.³² The comparative effects of sentinel node biopsy vs axillary node dissection on tumor recurrence and patient survival are not known.³³

■ **Testing for tumor markers** such as estrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER2) expression status in biopsy-proven breast cancer is now the standard of care. Seventy percent of breast cancers are estrogen receptor-positive, with increasing frequency associated with older age.³⁴ Estrogen/progesterone receptor positivity is associated with a more favorable outcome, and multiple hormonal therapies can be aimed at these receptors.³⁴ While HER2 overexpression—which occurs in 15% to 30% of newly diagnosed breast cancers³⁵—is associated with more aggressive tumors, women with this type of tumor cell can benefit from trastuzumab, an anti-HER2 drug.³⁶

Key factors that affect prognosis

Important factors affecting prognosis and treatment of localized breast cancer are tumor size, age and menopausal status, tumor expression of hormone receptors and/or the HER2 protein, as well as the status of the draining axillary nodes. Factors that predict a greater chance of recurrence include the spread of disease to axillary nodes, larger tumor size, invasive histology, inflammatory pathology, lack of estrogen/progesterone receptors, and age <50 years or premenopausal status.

Treatment options include surgical resection, radiation, and systemic adjuvant therapy in the form of chemotherapy, en-

➤ **Digital mammography is more accurate than film—but only for women <50 years of age, women with dense breasts, and pre- and perimenopausal women.**

➤
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doctrine therapy, or anti-HER2 monoclonal antibodies.³⁷ (For more on treatment, see “Surgery, radiation, and systemic therapy: Making the most of what’s in our arsenal” at jfponline.com.)

Don't overlook quality-of-life issues

Follow-up of breast cancer patients should go beyond treatment and work-up for recurrence and metastatic disease to focus on health and lifestyle issues, such as stress reduction, mood, smoking cessation, diet and exercise, treatment of hot flashes, sexual dysfunction, and bone health. A recent study found both reduced recurrence and increased survival in women receiving psychological interventions to improve quality-of-life measures after an 11-year follow-up.³⁸

Refer women to targeted Web sites such as the National Breast Cancer Awareness Month organization (<http://www.nbcam.org/>), the National Breast Cancer Foundation (<http://community.nationalbreastcancer.org/>), and the Susan G. Komen Breast Cancer Foundation (<http://www5.komen.org/>). Offer treatment for bothersome symptoms. Hot flashes and depression, for example, often related to endocrine therapy, can be treated with selective serotonin reuptake inhibitors

(SSRIs). That said, some SSRIs decrease the active metabolite of tamoxifen by inhibiting CYP2D6 enzyme and must, therefore, be used with caution. However, venlafaxine and citalopram are less likely to alter tamoxifen metabolism than other SSRIs.³⁹

CASE ▶ When Carrie was 47, she had an abnormal MRI of the left breast. Core needle biopsy and pathology of the lesion revealed an estrogen and progesterone receptor-positive tumor that was negative for HER2 overexpression. She underwent lumpectomy, which revealed a 1.5 cm tumor, followed by a negative sentinel node biopsy, and was diagnosed with stage I (T1N0M0) breast cancer. Carrie had radiation after surgery; she did not require chemotherapy, but was told to take tamoxifen for 5 years. This adjuvant endocrine therapy led to hot flashes and depression, both of which were successfully treated with venlafaxine. Carrie is currently cancer-free and participates in a breast cancer survivor program that includes regular visits with her primary physician and her oncologist. **JFP**

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The dawn of a new era:
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Hepatitis B & C

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As many as 2 million Americans are infected with hepatitis B and 5 million are infected with hepatitis C. Despite this large patient population, standards for virus prevention, screening, and clinical care are currently inadequate, resulting in a major unmet medical need.

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Surgery, radiation, and systemic therapy: Making the most of what's in our arsenal

Breast cancer surgery has changed dramatically over the years. Multiple studies have shown that breast-conserving therapy (lumpectomy followed by radiation) for carefully selected women is comparable to mastectomy for local recurrence and survival. While there has been much interest in determining whether a subset of patients could forego radiation after lumpectomy, a meta-analysis by the Early Breast Cancer Trialists Collaborative Group demonstrated that radiation after lumpectomy provides an absolute local recurrence risk reduction of 19%, and a 5.4% absolute reduction in 15-year breast cancer mortality rates compared with lumpectomy without radiation.¹ Thus, radiation after lumpectomy remains the standard of care for all women undergoing breast-conserving therapy, regardless of tumor characteristics.

In certain women with a high risk of recurrence (≥ 4 positive nodes), radiation is also recommended after mastectomy. Women undergoing mastectomy have numerous options for immediate or delayed breast reconstruction. Consultation with a multidisciplinary team, including a plastic surgeon, prior to any surgical intervention is advised.²

Multiple systemic chemotherapy regimens have been shown to be beneficial in carefully selected patients with breast cancer. Systematic reviews have demonstrated that an anthracycline-based regimen can decrease annual breast cancer mortality by 38% in women <50 years old and by 20% in women ages 50 to 69 years.¹ In more recent randomized controlled trials, the addition of taxanes to anthracycline-based regimens has produced promising results.³

Numerous hormonal therapies benefit women with estrogen or progesterone receptor-positive breast cancer. Tamoxifen blocks the activity of estrogen on receptors located in breast cancer tissue, for example; aromatase inhibitors block the conversion of androgens to estrogen; and gonadotropin-releasing hormone (GnRH) analogs such as leuprolide and goserelin suppress ovarian production of estrogen.

For postmenopausal women, options include an aromatase inhibitor alone or tamoxifen followed by an aromatase inhibitor.

In premenopausal women, aromatase inhibitors are not very effective, as decreasing peripheral estrogen stimulates the ovaries to produce more estrogen. Thus, for these patients, adjuvant endocrine therapy consists of tamoxifen, with ovarian ablation (via surgery or radiation) or ovarian suppression with a GnRH analog. If the patient goes through menopause as a result of this therapy, she may benefit from aromatase inhibitors at that time.^{4,5}

Women with breast cancer that overexpresses the HER2 gene benefit from adjuvant treatment with trastuzumab, an anti-HER2 antibody.⁶ While current guidelines advise treatment for 1 year, multiple studies are evaluating dosing schedules and optimal duration of treatment. For now, patients should be monitored for signs of cardiotoxicity at baseline and every 3 months thereafter until completion of therapy.⁴

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